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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  
Arlington, Virginia 22202

October 9, 2007

8:39 A.M.

1 U.S. ENVIRONMENTAL PROTECTION AGENCY  
2 FIFRA SCIENTIFIC ADVISORY PANEL  
3 OPEN MEETING  
4 OCTOBER 9, 2007  
5 MR. BAILEY: Good morning everyone.  
6 We're a few minutes so I'd like to go ahead and get  
7 started here.  
8 My name is Joe Bailey and I'm serving as  
9 the designated federal official for this meeting.  
10 As you know this is a four day meeting  
11 on the Potential for Atrazine to Affect Amphibian  
12 Gonadal Development. And as the DFO for this meeting I  
13 serve to ensure that the provisions of the Federal  
14 Advisory Committee Act are met.  
15 The FIFRA SAP is a federal advisory  
16 committee that provides independent peer review to the  
17 Agency on pesticide related issues. No one provides  
18 recommendations and advice. It's up to the Agency to  
19 make the decisions and implement those decisions.  
20 Part of my responsibility is to ensure  
21 that all provisions of the Federal Conflict of Interest  
22 Laws are met, and to that end each of the panel members  
23 have filled out a standard government form and we have  
24 reviewed those forms and also the panel members have  
25 been briefed on the ethics requirements.

1 There is a public comment period  
2 established for the meeting and it will begin  
3 midmorning. And anyone who has not signed up for  
4 public comments, please see me. And if you have not  
5 made prior arrangements I would ask that you limit your  
6 comments to five minutes today.  
7 There is a public docket that's  
8 established for the meeting as well and all of the  
9 background materials that have been presented to the  
10 panel, as well as presentations that will be made today  
11 will be placed in that docket and the number is  
12 referenced on the agenda if you're interested in seeing  
13 what's in the docket.  
14 We will prepare final meeting minutes  
15 after this meeting is over. Within 90 days we will do  
16 that and the final meeting minutes will be posted on  
17 the website as well.  
18 If there are any press individuals here  
19 who have any questions or anything, I think we do have  
20 a press person who is supposed to be in the office,  
21 Dale Kemery. I haven't seen him yet this morning but  
22 he is supposed to be here. So if anybody from the  
23 press has any questions we will try to track him down  
24 and have him address any of your questions.  
25 One final note is, this meeting is being

1 audio recorded, so when you have a comment to make I  
2 would ask that you please give your name and  
3 affiliation so that we can have a clear recorded  
4 transcript of the meeting.  
5 That's all of my comments and at this  
6 time I am very pleased to introduce Doctor Heeringa to  
7 my left who will be serving as Chair for this meeting.  
8 DR. HEERINGA: Good morning everyone and  
9 welcome to this meeting of the FIFRA SAP on the topic  
10 of the Potential for Atrazine to Affect Amphibian  
11 Gonadal Development.  
12 I'm Steve Heeringa. As Joe said I am  
13 the current Chair of the FIFRA Science Advisory Panel.  
14 I am from the University of Michigan. I  
15 am an applied statistician who specializes in  
16 population based research. I hold no specific  
17 expertise on this topic. My job is primarily to see  
18 that the proceedings of this meeting move smoothly, and  
19 that we have a full and complete discussion of the  
20 topic at hand.  
21 But to support us here are certainly a  
22 panel of experts in this field and I'd like to have  
23 them introduce themselves at this point and I want to  
24 begin on my left with Doctor Ken Portier.  
25 DR. PORTIER: Good morning, I'm Ken

1 Portier, Director of Statistics at the American Cancer  
2 Society, National Office in Atlanta. My expertise is  
3 in environmental sampling and probabilistic risk among  
4 others.  
5 DR. CHAMBERS: I'm Jan Chambers with the  
6 College of Veterinary Medicine at Mississippi State  
7 University. I'm one of the members of the permanent  
8 SAP. My area of expertise is pesticide toxicology with  
9 emphasis on metabolism and neurotoxicology.  
10 DR. SCHLENK: My name is Dan Schlenk.  
11 I'm in the Department of Environmental Sciences at the  
12 University of California, Riverside. I'm also a member  
13 of the, a permanent member of the SAP. And my research  
14 interests are in aquatic ecotoxicology.  
15 DR. BUCHER: I'm John Bucher, I'm the  
16 Associate Director of the National Toxicology Program  
17 at NIEHS. My research interests are in carcinogenesis  
18 and of toxicology and I'm a member of the permanent  
19 panel.  
20 DR. HANDWERGER: I'm Stuart Handwerker  
21 from the Departments of Pediatrics and Cell Biology at  
22 the University of Cincinnati College of Medicine. My  
23 clinical expertise is in pediatric endocrinology. My  
24 research is in developmental and perinatal  
25 endocrinology.

<p style="text-align: right;">Page 6</p> <p>1 DR. ISOM: Good morning, I'm Gary Isom 2 from Purdue University. I'm a neurotoxicologist. My 3 area of interests include molecular mechanisms and 4 neurodegeneration. And I am a permanent member of the 5 panel. 6 MR. PAULI: Good morning, my name is 7 Bruce Pauli. I'm with Environment Canada. I'm a 8 wildlife biologist with a special interest in the 9 effects of pesticides on wildlife. I've been studying 10 the effects of pesticides on amphibians for the last 11 few years. 12 DR. SKELLEY: My name is David Skelley. 13 I'm a Professor of Ecology at Yale University and my 14 research interests include the ecology of amphibians 15 and notably developmental deformities in wild 16 populations. 17 DR. DENVER: Good morning, my name is 18 Robert Denver from the University of Michigan and I am 19 a Professor in the Department of Molecular, Cellular 20 Developmental Biology. I'm a neuroendocrinologist and 21 my research interests are in hormone action of the 22 developing brain and I study amphibians also. 23 DR. FURLOW: My name is David Furlow. 24 I'm with the University of California at Davis, Section 25 of Neurobiology, Physiology and Behavior. I'm an</p>	<p style="text-align: right;">Page 8</p> <p>1 DR. PATINO: I'm Reynaldo Patino with the 2 U.S. Geological Survey, Texas Cooperative Fish &amp; 3 Wildlife Research Unit. I'm a comparative 4 endocrinologist working mainly with fish and some with 5 amphibians as well. 6 DR. HEERINGA: Thank you very much. And 7 I'm sure you'll agree with me we have assembled I think 8 a fairly complete set of expertise to address the 9 questions at hand. And I want to express my 10 appreciation in advance to all of the panel members for 11 participating here this week on this very important 12 topic. 13 Just a few notes to add to Joe's 14 comments earlier with regard to the proceedings. 15 One thing that I'm going to try to do as 16 we get into conversation it's sort of easy just to come 17 to the mike. I'll try to acknowledge all speakers. 18 When you do begin to speak if you would just state your 19 name. Because of the transcription it'll make it a lot 20 easier to identify the speakers on the transcription if 21 you just state your name before making your comments. 22 So just a minor thing but it's important in terms of 23 the capturing of the proceedings. 24 So at this point I think we're prepared 25 to begin and I'd like to introduce Mr. Bill Jordan who</p>
<p style="text-align: right;">Page 7</p> <p>1 endocrinologist as well, also studying amphibians and 2 my expertise is in thyrohormone control of gene 3 expression. 4 DR. HEERINGA: And we'll move over to 5 Doctor Yeater. 6 DR. YEATER: I'm Kathy Yeater, I'm from 7 the Department of Agricultural and Agricultural 8 Research Service. I'm an applied statistician 9 specializing in biological and agricultural life. 10 DR. BAILEY: Ted Bailey from Iowa State 11 University. My interests are in statistical methods 12 and design of experiments. 13 DR. DELORME: Peter Delorme from Health 14 Canada, Pest Management Regulatory Agency. I'm with 15 the Environmental Assessment Division as a Senior 16 Science Advisor. I'm interested in environmental 17 toxicology. 18 DR. LEBLANC: I'm Gerry LeBlanc from 19 North Carolina State University. I'm a Professor in 20 Toxicology and Department Head in the Department of 21 Environmental and Molecular Toxicology with a research 22 interest in endocrine toxicology. 23 DR. MILLER: I'm Debra Miller from the 24 University of Georgia and I'm a veterinary pathologist 25 and I do work amphibians.</p>	<p style="text-align: right;">Page 9</p> <p>1 is the Senior Policy Advisor from the Office of the 2 Pesticide Programs at the EPA. Good morning, Bill. 3 MR. JORDAN: Good morning, Doctor 4 Handwerger excuse me, Heeringa 5 DR. HEERINGA: Good morning. 6 MR. JORDAN: and Doctor Handwerger and 7 all the rest of the SAP permanent members and ad hoc 8 members. 9 As Doctor Heeringa suggest, I'm bill 10 Jordan and I work in the Office of Pesticide Programs. 11 The Office Director, Deborah Edwards is on travel this 12 week and asked me to extend her best wishes to you and 13 to welcome you to EPA on her behalf. 14 And I want to add also my welcome and 15 say how much we appreciate the time that you are taking 16 to help us sort out some very important scientific 17 questions. 18 We understand that you have many other 19 things to do and that spending nearly a full week with 20 us represents a significant commitment of time, not to 21 mention the amount of time that you will spend also in 22 getting prepared for this session and in contributing 23 to the development of the report on the work that you 24 do collectively. 25 So we greatly appreciate the</p>

<p style="text-align: right;">Page 10</p> <p>1 contributions that you are making here.</p> <p>2 I also want to say a thank you to Steve</p> <p>3 Knott and Joe Bailey and the other members of the</p> <p>4 secretariat for the Scientific Advisory Panel. I know</p> <p>5 hard they have worked to get ready for this meeting for</p> <p>6 finding such a distinguished group of panel members,</p> <p>7 and then in helping us in the Office of Pesticide</p> <p>8 Programs get our materials ready and distributed to you</p> <p>9 for this meeting, setting up all the logistics and</p> <p>10 handling so many of the details. So Joe and Steve, we</p> <p>11 greatly appreciate your efforts as well.</p> <p>12 I'd like to extend a welcome also to the</p> <p>13 members of the public who have come to listen and some</p> <p>14 of them to make comments to this particular SAP</p> <p>15 meeting.</p> <p>16 We find that the engagement with our</p> <p>17 stakeholders across the full range of interest groups</p> <p>18 that are affected by and people who are interested in</p> <p>19 the regulation of pesticides to be a very helpful and</p> <p>20 constructive process. And we are delighted that we</p> <p>21 have a very full audience today.</p> <p>22 I have, I was sitting here talking with</p> <p>23 Artie Williams about old t.v. shows and I realized that</p> <p>24 I've been around here for a long, long time. In fact I</p> <p>25 was working at EPA back before there was an SAP. And I</p>	<p style="text-align: right;">Page 12</p> <p>1 controversy about the scientific underpinnings of EPA's</p> <p>2 regulatory decisions, and that there is still a lot of</p> <p>3 value to be had from going through a process of</p> <p>4 independent scientific peer review of the Agency's</p> <p>5 decisions.</p> <p>6 And so today we are bringing to you for</p> <p>7 your expert review and commentary, our assessment of a</p> <p>8 large body of information concerning the Affect of</p> <p>9 Atrazine on Amphibian Gonadal Development.</p> <p>10 We have found over the years, since the</p> <p>11 '70s when we began this process, that the SAP's that</p> <p>12 we've had on a wide variety of subjects have really</p> <p>13 made a valuable contribution to our understanding of</p> <p>14 the science and to the development of sound scientific</p> <p>15 positions underlying our regulatory process.</p> <p>16 And as a consequence of that I think</p> <p>17 that we have by and large at EPA made much better</p> <p>18 decisions, regulatory decisions about what is</p> <p>19 acceptable and what is not acceptable. That there has</p> <p>20 been a greater breadth of acceptance of those</p> <p>21 decisions, in no small measure because of the</p> <p>22 continuing good advice that folks like you have given</p> <p>23 us over the last thirty years.</p> <p>24 So we are looking forward eagerly with</p> <p>25 perhaps a little bit of nervousness about what you'll</p>
<p style="text-align: right;">Page 11</p> <p>1 was reflecting over the weekend about how the SAP came</p> <p>2 into existence.</p> <p>3 For those of you who have not been</p> <p>4 around this process as long as I have, I'd like to take</p> <p>5 just a couple of minutes and offer some observations.</p> <p>6 In the early '70s there was a lot of</p> <p>7 controversy about the regulation of pesticide products.</p> <p>8 There were actions being taken by the Agency that folks</p> <p>9 thought were motivated by political considerations and</p> <p>10 were not consistent with sound scientific analysis of</p> <p>11 the available information. And so the Congress, in an</p> <p>12 effort to make sure that the Agency didn't run amuck</p> <p>13 and do silly things, directed, passed a law that</p> <p>14 directed EPA when we were making important scientific</p> <p>15 decisions, important regulatory decisions that were</p> <p>16 grounded on controversial scientific propositions, to</p> <p>17 seek out the advice of the experts. They said that we</p> <p>18 needed to take our analysis to an independent</p> <p>19 scientific body, the SAP, who would review it and</p> <p>20 comment on it and then we had to think seriously about</p> <p>21 and address those comments before we went ahead.</p> <p>22 And I was thinking about that and I</p> <p>23 decided, you know, things don't change very much. We</p> <p>24 still find ourselves in a situation where there's a lot</p> <p>25 of controversy about pesticide regulation, a lot of</p>	<p style="text-align: right;">Page 13</p> <p>1 have to say about our quality of our scientific work.</p> <p>2 And we're also looking forward to having the input of</p> <p>3 public commenters as well so that you too will hear</p> <p>4 some of the kinds of concerns that are on their mind.</p> <p>5 With that I'll say thank you again for</p> <p>6 coming and I look forward to being here for the rest of</p> <p>7 today and hearing the beginning of the process.</p> <p>8 Thanks.</p> <p>9 DR. HEERINGA: Thank you very much, Mr.</p> <p>10 Jordan.</p> <p>11 At this point I'd like to introduce</p> <p>12 Director Jean Williams who is the Acting Division</p> <p>13 Director of the Environmental Fate and Effects Division</p> <p>14 of the Office of Pesticide Programs.</p> <p>15 MS. WILLIAMS: Thank you Doctor Heeringa</p> <p>16 and members of the panel for taking the time out of</p> <p>17 your schedules to be here and assist us with this</p> <p>18 important issue.</p> <p>19 On behalf of the Environmental Fate and</p> <p>20 Effects Division I would like to welcome you to the new</p> <p>21 facility that we have and hope you are finding it</p> <p>22 enjoyable and will continue to throughout the long week</p> <p>23 that we're all going to spend here.</p> <p>24 The FIFRA Scientific Advisory Panel</p> <p>25 serves as our primary scientific peer review mechanism</p>



<p style="text-align: right;">Page 14</p> <p>1 for the Office of Pesticide Programs. Its purpose is  2 to provide scientific advice, information and  3 recommendations to the Agency's administrator on  4 pesticides and pesticide related issues and regulatory  5 actions, and in particular, those that have impacts on  6 health and the environment.  7 As the title of this SAP indicates, we  8 are meeting this week to discuss the potential for the  9 pesticide Atrazine to affect amphibian gonadal  10 development.  11 As will be described in later  12 presentations, this is the second time that the Agency  13 has relied on the FIFRA Scientific Advisory Panel to  14 review our analysis and interpretation of data related  15 to this potential affect.  16 Also as will be reiterated throughout  17 the Agency's presentations, the specific focus on the  18 affects of Atrazine on amphibian gonadal development is  19 based on recommendations made by the FIFRA Scientific  20 Advisory Panel in 2003 when they initially addressed  21 this issue.  22 Based on those recommendations the  23 Agency required the technical registrant for Atrazine  24 to conduct studies to determine whether Atrazine  25 affects amphibian gonadal development.</p>	<p style="text-align: right;">Page 16</p> <p>1 concludes that no changes in its interpretation of  2 Atrazine's ecological risks are warranted at this time  3 based on the potential affects, based on this potential  4 affect of Atrazine.  5 As with all regulated pesticides, we'll  6 continue to review information as it becomes available  7 and we'll reevaluate our scientific position where that  8 is warranted.  9 The SAP members have been provided  10 copies as Joe mentioned, of the Agency's 2003 white  11 paper and our most recent 2007 white paper examining  12 the affects of Atrazine on amphibian gonadal  13 development. The SAP members have also been provided  14 copies of the full study conducted by the registrant in  15 response to recommendations made to the Agency by the  16 SAP in 2003.  17 Copies of open literature articles  18 reviewed in the 2007 white paper have also been  19 provided to the panel members. Unfortunately we were  20 unable to obtain permission from all of the relevant  21 journals to broadly distribute copies of all of the  22 open literature.  23 Over the remainder of this week the  24 panel members will have an opportunity to listen to  25 public comments as Joe mentioned regarding these</p>
<p style="text-align: right;">Page 15</p> <p>1 Additionally, research of this affect of  2 Atrazine on amphibian gonadal development has also  3 been  4 reported in the open literature since the 2003 review  5 that we conducted.  6 We have reviewed all of this information  7 in our 2007 white paper and concluded that across  8 multiple lines of evidence Atrazine does not affect  9 amphibian gonadal development.  10 Additionally since no affects could be  11 consistently demonstrated in laboratory studies using  12 the African Clawed Frog, a common amphibian in  13 laboratory tests, the Agency has concluded that testing  14 with other amphibian species is not warranted at this  15 time.  16 Consistent with the process identified  17 in the Agency's 2003 white paper and with the  18 recommendations made by the 2003 FIFRA Scientific  19 Advisory Panel, since no affects were demonstrated in  20 the laboratory studies, the Agency has also concluded  21 that no additional testing is required with respect to  22 the potential affects of Atrazine on amphibian gonadal  23 development.  24 Finally, since the multiple lines of  25 information do not provide evidence that Atrazine  affects amphibian gonadal development, the Agency</p>	<p style="text-align: right;">Page 17</p> <p>1 affects, followed by the Agency's analysis and  2 conclusions regarding the subject.  3 Afterwards we'll review specific charge  4 questions that the SAP has been asked to consider and  5 address regarding the Agency's analyses and  6 conclusions.  7 As stated earlier, the Agency relies on  8 the FIFRA Scientific Advisory Panel as a means of  9 scientific peer review. These public external peer  10 review meetings assist the Agency in making sound  11 scientific decisions.  12 We're looking forward to a candid and  13 open exchange as we proceed with this FIFRA SAP  14 meeting  15 and I thank you for the opportunity to address the  16 panel and for your efforts on behalf of the Agency and  17 the public that it serves.  18 Thank you.  19 DR. HEERINGA: Thank you, Director  20 Williams. And I will promise you that we will  21 certainly devote our full attention to the scientific  22 issues that are presented to us this week and we look  23 forward to it as well.  24 So at this point I think we're ready to  25 actually move into a presentation on the historical  perspective on the issue of the Potential for Atrazine</p>

<p style="text-align: right;">Page 18</p> <p>1 to Affect Amphibian Gonadal Development, and to 2 present 3 that is Doctor Thomas Steeger of the Environmental Fate 4 and Effects Division, Office of Pesticide Programs. 5 Doctor Steeger. 6 DR. STEEGER: Thank you very much. I'd 7 like to thank you for this opportunity to address the 8 FIFRA Scientific Advisory Panel regarding the Agency's 9 evaluation of recent data on the affects of Atrazine on 10 amphibian gonadal development. 11 As Doctor Heeringa mentioned, my name is 12 Tom Steeger, I'm a senior biologist in the 13 Environmental Fate and Effects Division and I've also 14 served as the coauthor of the 2003 and the 2007 white 15 paper. 16 During this presentation I will provide 17 a brief overview of the paradigm that the Agency uses 18 to conduct ecological risk assessments. Afterwards I 19 will discuss the factors leading up to the 2003 SAP, 20 the studies reviewed at that time regarding the affects 21 of Atrazine on amphibian gonadal development, and the 22 2003 white paper and FIFRA SAP recommendations. 23 And finally I will provide a brief 24 overview of what has occurred subsequent to the 2003 25 SAP that has led to the development of the 2007 white 26 paper and the affects of Atrazine on amphibian gonadal</p>	<p style="text-align: right;">Page 20</p> <p>1 In 2003 the Agency issued an interim re-registration 2 eligibility decision for Atrazine. In the interim re- 3 registration eligibility decision, the Agency concluded 4 that Atrazine may continue to be used provided that all 5 precautions are implemented to reduce risk to drinking 6 water. 7 The decision was based in part on an 8 analysis of both human health and ecological risks in 9 the currently registered uses of Atrazine as a 10 herbicide. 11 In response to a consent decree the 12 Agency considered the potential affects of Atrazine on 13 amphibian development. In 2003 the Agency reviewed 14 studies on the affects of Atrazine on amphibian 15 development that had been conducted up to that point in 16 time. 17 The Agency's review was summarized in 18 the 2003 white paper and was presented to the SAP in 19 June 2003. At that time the studies focused primarily 20 on the affects of Atrazine on amphibian gonadal 21 development. 22 In 2003 the Agency reviewed a total of 23 seventeen studies that were submitted as of February 24 28th of that year. Twelve of the studies were 25 sponsored by the registrant and five were drawn from</p>
<p style="text-align: right;">Page 19</p> <p>1 development. 2 This figure depicts the ecological risk 3 assessment paradigm followed by EPA in assessing risks 4 to non-target animals from stressors such as 5 pesticides. 6 The process consists of three major 7 phases, the problem formulation, analysis and risk 8 characterization. The process is intended to be, as 9 more information becomes available, it is integrated 10 with the existing information, the problem formulation 11 including its conceptual model may change. As a 12 result, the additional data may be required for 13 estimating either exposure or affects. 14 In turn the Agency's assessment of 15 potential risks may change. 16 In the slides that follow, various 17 components of the risk assessment paradigm are 18 depicted. Although many of the arrows appear to be 19 unidirectional, in practice the process is iterative as 20 data analysis informs both problem formulation and risk 21 characterization. 22 Whether additional information is 23 required depends on the risk management decisions under 24 consideration. 25 Atrazine was first registered in 1958.</p>	<p style="text-align: right;">Page 21</p> <p>1 the open literature. 2 Registrant submitted studies received 3 more scrutiny during the Agency's review since more 4 detailed information was available. Although none of 5 the studies were fully compliant with good laboratory 6 practices or their standards, many of the studies had 7 standard operating procedures and some level of quality 8 assurance in place. 9 Additionally, for studies where raw data 10 were available the Agency conducted an independent 11 statistical analysis of those data. 12 Since most of the published studies 13 reviewed in 2003 did not have standard operating 14 procedures, nor were raw data available for review for 15 the majority of the open literature studies, the open 16 literature studies were evaluated at face value with 17 the understanding that these published studies would 18 have been subject to some degree of scrutiny already 19 through the normal journal peer review process. 20 In 2003 as well as today, formal Agency 21 guidelines are not available for specifically examining 22 the affects of Atrazine on gonadal development in 23 amphibians. As a result the Agency relies on other 24 aquatic and terrestrial animal tests for which there 25 are guidelines to serve as surrogates for estimating</p>

<p style="text-align: right;">Page 22</p> <p>1 risks to amphibians.</p> <p>2 Additionally many of the measurement end</p> <p>3 points such as inter-sex, sex ratio, laryngeal muscle</p> <p>4 area examined in previous studies differ from those</p> <p>5 regularly utilized by the Agency to estimate acute</p> <p>6 and/or chronic risks.</p> <p>7 However the Agency is not confined to</p> <p>8 using the study requirements to identify potential</p> <p>9 hazards.</p> <p>10 As part of 158 of the Code of Federal</p> <p>11 Regulations which outlines data requirements for the</p> <p>12 registration of pesticides, if data are insufficient to</p> <p>13 permit the Agency to evaluate the potential risks of a</p> <p>14 pesticide to cause unreasonable adverse affects,</p> <p>15 additional data requirements above those required by</p> <p>16 the Code of Federal Regulations can be imposed.</p> <p>17 In determining whether additional data</p> <p>18 are required the risk assessment team relies on the</p> <p>19 professional judgement and available lines of evidence</p> <p>20 to determine whether toxicological end points can be</p> <p>21 linked to assessing end points in a reasonable and</p> <p>22 transparent manner.</p> <p>23 As I said, in 2003 a total of seventeen</p> <p>24 studies were submitted for review. Seven of the</p> <p>25 studies were conducted in the laboratory exclusively</p>	<p style="text-align: right;">Page 24</p> <p>1 Although most of the laboratory studies</p> <p>2 relied on tadpoles, field studies examined both larval</p> <p>3 and adult animals.</p> <p>4 End points measure in the laboratory and</p> <p>5 field studies included time to metamorphosis, growth in</p> <p>6 terms of length and weight, presence of gonadal</p> <p>7 abnormalities, laryngeal muscle area, sex ratios,</p> <p>8 plasma steroid concentrations and brain/gonad aromatase</p> <p>9 activity.</p> <p>10 As stated previously the majority of</p> <p>11 studies reviewed in 2003 focused on activity and</p> <p>12 gonadal development.</p> <p>13 Each of the studies evaluated in 2003</p> <p>14 contained uncertainties or inconsistencies in the way</p> <p>15 data were collected. Evaluation focused primarily on</p> <p>16 the methodological issues rather than on statistical</p> <p>17 analysis of the data.</p> <p>18 In other words, there were sufficient</p> <p>19 uncertainties in how the data were collected and it</p> <p>20 made it difficult to put the data into any perspective.</p> <p>21 As mentioned previously there were seven</p> <p>22 laboratory studies and ten field studies. Most of the</p> <p>23 field studies included some laboratory analysis.</p> <p>24 Collectively the following issues were</p> <p>25 identified in the laboratory studies. Atrazine</p>
<p style="text-align: right;">Page 23</p> <p>1 while ten of the studies were conducted in the field.</p> <p>2 Field studies included Florida, Indiana, Iowa,</p> <p>3 Illinois, Michigan, Nebraska, Utah, Wyoming and South</p> <p>4 Africa.</p> <p>5 Consistent with the Agency's process for</p> <p>6 evaluating the studies, each of the seventeen studies</p> <p>7 were evaluated using the following criteria.</p> <p>8 Experimental design, study protocols and quality</p> <p>9 assurance mechanisms, the strength and shape of the</p> <p>10 cause and effect relationship, whether there was a dose</p> <p>11 response, whether the observed affects have a plausible</p> <p>12 mechanism of action that is consistent with what is</p> <p>13 known about the chemical, and finally, whether the</p> <p>14 measured affects are ecologically relevant.</p> <p>15 A range of amphibian species were tested</p> <p>16 in the studies. While the sum of the laboratory</p> <p>17 studies relied on non-native species, each of the field</p> <p>18 studies examined species within their native or</p> <p>19 introduced ranges.</p> <p>20 Thus, cane toads in Florida, bullfrogs</p> <p>21 were studied in Iowa, norther leopard frogs were</p> <p>22 studied in Wyoming, Utah, Nebraska, Indian, green frogs</p> <p>23 were studied in Michigan, cricket frogs were studied in</p> <p>24 Illinois and African clawed frogs were studied in South</p> <p>25 Africa.</p>	<p style="text-align: right;">Page 25</p> <p>1 contamination of the controls, poor water quality, poor</p> <p>2 growth development and survival of the test species,</p> <p>3 high variability in end point measurements, a lack of</p> <p>4 reproducibility and unresponsive positive controls.</p> <p>5 With respect to the field studies, the</p> <p>6 Agency recognizes that field studies can be difficult</p> <p>7 to conduct since researchers are not able to control</p> <p>8 environmental conditions. Also the Agency recognizes</p> <p>9 the difficulty in identifying sampling sites that can</p> <p>10 be considered true replicates of one another and/or</p> <p>11 devoid of factors that can potentially confound</p> <p>12 analysis.</p> <p>13 Of the field studies submitted there was</p> <p>14 considerable variability between the sampling sites.</p> <p>15 Similar to some of the laboratory studies, Atrazine</p> <p>16 parent compound and/or its derivatives was present in</p> <p>17 reference groups, the reference sites.</p> <p>18 Additionally other trizine herbicides</p> <p>19 and chemicals, other pesticides were present but not</p> <p>20 always well characterized.</p> <p>21 Where pesticides were characterized the</p> <p>22 concentrations were in some cases relatively high and</p> <p>23 it's unclear what impact they may have had on the</p> <p>24 study.</p> <p>25 In some studies there was unusual</p>



<p style="text-align: right;">Page 26</p> <p>1 environmental conditions that may have impacted the 2 study, such as unusually high rainfalls and increased 3 depredation due to introduced species were problematic 4 in some of the studies.</p> <p>5 In spite of all the issues identified in 6 the available studies, the Agency believed that the 7 laboratory and field studies provided some useful 8 information in terms of how to improve study designs. 9 The studies provided sufficient information with which 10 to formulate a hypothesis on the potential affects of 11 Atrazine on amphibian development.</p> <p>12 They provided insight on the potential 13 sources of variability and they provided insight on 14 future test species and study conditions.</p> <p>15 Although many of the studies did not 16 demonstrate any affect of Atrazine on amphibian 17 development, there were sufficient data to suggest that 18 Atrazine alone may be affecting developmental and more 19 specifically, amphibian gonadal development.</p> <p>20 Thus the hypothesis was that Atrazine 21 exposure may result in affects on amphibian gonad that 22 may ultimately impact secondary sexual characteristics 23 and reproductive fitness.</p> <p>24 However there were not sufficient data 25 to refute or confirm the hypothesis that Atrazine alone</p>	<p style="text-align: right;">Page 28</p> <p>1 tested. Therefore the lines of evidence suggested that 2 Atrazine exposure did not impact gonadal development.</p> <p>3 However there were lines of evidence 4 from the laboratory and field studies that supported 5 the formulation of a plausible hypothesis that Atrazine 6 exposure may result in developmental affects in 7 amphibians.</p> <p>8 The studies also provided useful 9 information of the potential sources of variability. 10 This information will be critical to the design of 11 future studies.</p> <p>12 Because there were insufficient data to 13 refute or confirm the affects of Atrazine on 14 amphibians, the Agency recommended and the SAP 15 concurred that additional studies be initiated and that 16 these studies build on the body of information 17 available in 2003.</p> <p>18 The Agency proposed, and the SAP 19 concurred that a tiered approach be used to examine the 20 cause/affect, dose response, mechanistic plausibility 21 and ecological relevance of any affects observed 22 following the exposure of Atrazine to amphibians.</p> <p>23 As will be discussed in later 24 presentations, the white paper identified an analysis 25 plan where the initial tier of testing focused on first</p>
<p style="text-align: right;">Page 27</p> <p>1 may cause gonadal affects in amphibians because of the 2 collective uncertainties associated with the studies.</p> <p>3 Uncertainties included whether the 4 cause/affect is real and can be readily repeated in 5 different laboratories, a lack of a clear and 6 consistent dose reponse relationship, the mechanistic 7 plausibility of Atrazine exposure causing a given 8 affect, the inability to readily extrapolate laboratory 9 affects to the field and the uncertain ecological 10 relevance of the measurement end points.</p> <p>11 Without addressing these uncertainties 12 it was not possible for the Agency to determine whether 13 a particular affect could be consistently expected to 14 occur at a particular exposure level, whether the 15 affect, if real, could be expected to occur in other 16 animals, and whether the affect were likely to reverse 17 the affect in animals' reproductive fitness.</p> <p>18 In 2003 the Agency concluded that none 19 of the studies fully accounted for the environmental 20 and husbandry factors capable of influencing 21 measurement end points.</p> <p>22 Based on all seventeen studies the 23 Agency concluded in its 2003 white paper and the SAP 24 concurred that Atrazine exposure did not produce 25 consistent reproducible affects across all species</p>	<p style="text-align: right;">Page 29</p> <p>1 establishing whether Atrazine exposure results in 2 affects on amphibian gonadal development.</p> <p>3 As of the 2003 SAP, or after the 2003 4 SAP the Agency required the technical registrant for 5 Atrazine to conduct studies to examine the potential 6 affects of Atrazine on amphibian gonadal development.</p> <p>7 In November of 2004 the Agency issued a 8 data call in requiring the Agency requiring the 9 registrant to conduct the tier one amphibian studies. 10 In response to the data call in, the registrant 11 provided the Agency with a study protocol that 12 incorporated all the design elements identified in the 13 2003 white paper.</p> <p>14 The Agency provided comments on the 15 protocol and the registrant adjusted the protocol to 16 reflect the Agency's input.</p> <p>17 Additionally, during the course of the 18 studies, EPA inspected the laboratories to verify that 19 the protocols were being followed and that quality 20 assurance and quality control procedures were 21 operational. As part of the inspection EPA verified 22 the data were accurately recorded.</p> <p>23 In June 2007 the registrant provided the 24 Agency with a complete final report of the tier one 25 amphibian studies.</p>

<p style="text-align: right;">Page 30</p> <p>1 In addition to the registrant's 2 submitted studies that were responsive to the DCI, the 3 Agency reviewed open literature studies completed after 4 the 2003 SAP. 5 A total of nineteen studies have been 6 reviewed since 2003 and white paper has been developed, 7 summarizing the Agency's interpretation of the 8 available data. 9 Including the studies reviewed for the 10 2003 SAP, a total of thirty-six documents representing 11 both interim reports, final reports and published open 12 literature have been reviewed examining the affects of 13 Atrazine on amphibian development. The vast majority 14 of these studies examined amphibian gonadal 15 development, primarily in the African clawed frog. 16 While other potential affects of 17 Atrazine have been reported in the open literature, the 18 Agency's focus with regard to the current white paper 19 and this SAP meeting is on the affects of Atrazine 20 alone on amphibian development alone. 21 This week the Agency will present its 22 analysis of the open literature and the registrant 23 submitted studies in response to the data call in and 24 the Agency will ask the SAP to comment on its analysis 25 and conclusions.</p>	<p style="text-align: right;">Page 32</p> <p>1 advance, and there are two speakers. 2 What I would like to recommend to the 3 public commenters is that we will begin your public 4 comments but I would plan to take a break about halfway 5 through. So if there's a logical breaking point and 6 that's acceptable, I think with an hour and a half we 7 have to probably permit that. So that would be my plan 8 at this point. 9 So before we invite the presenters for 10 the first public speaker to the podium here, or to the 11 table, I'd like to turn to the Designated Federal 12 Official, Joe Bailey for some initial comment on the 13 MR. BAILEY: Thank you, Doctor Heeringa. 14 Joe Bailey here. During today's public comment period 15 we anticipate hearing about Syngenta's sponsored study 16 that was conducted by Doctor Vern Klaus who is a former 17 SAP member. And some of the written public comments 18 for this meeting have addressed Doctor Klaus' role in 19 the conduct of the study. And I just wanted to make a 20 couple of comments regarding post-employment 21 restrictions for former SAP members. 22 First, once an SAP panel has completed 23 its work, former panel members are free to engage in 24 any outside employment they desire, with one exception. 25 And that is, under certain circumstances former SAP</p>
<p style="text-align: right;">Page 31</p> <p>1 DR. HEERINGA: Thank you very much, 2 Doctor Steeger. Recognizing that Doctor Steeger and 3 the scientific staff of the EPA will have extensive 4 presentations tomorrow morning in support of their 5 white paper and its findings, are there any comments or 6 questions for Doctor Steeger on this historical 7 perspective on the problem at hand? 8 Okay, we are actually ahead of schedule 9 but I think this will be a floating agenda. We're 10 schedule to follow the printed agenda through Friday, 11 but we will progress at a pace which covers all of the 12 issues but also means that we will float a little bit 13 with regard to time. 14 At this point in a little bit of a 15 difference from past SAP meetings we have placed the 16 public comment period up front and we've done that more 17 recently in another SAP meeting and it worked quite 18 well I think in terms of stimulating the conversation 19 and sort of setting the tone for the meeting. 20 And so I'd like to enter at this point 21 the public comment period. And before we do that 22 though I want to take a quick look. I think our first 23 public commenter will be Syngenta Crop Protection and 24 they're scheduled for approximately an hour and a half, 25 and that was negotiated with the DFO, Joe Bailey in</p>	<p style="text-align: right;">Page 33</p> <p>1 members may not represent a third party back to the 2 U.S. government on the same issue that they addressed 3 as a member of the SAP. 4 And I understand from discussions that 5 to avoid raising questions regarding this restriction, 6 Doctor Klaus will not be present this morning at the 7 meeting to participate in any of the public comments. 8 Thanks very much. 9 DR. HEERINGA: Okay, at this point then 10 I'd like to begin the public comment period and welcome 11 the representatives from Syngenta Crop Protection, 12 Doctor Keith Solomon and Doctor Glen Van Der Kraak. 13 MR. OSMER: Mr. Chairman and panel 14 members, good morning. I'm Alan Osmer with Syngenta 15 Crop Protection and I served as the GOP Study Director 16 for the two studies that are the subject of the 17 scientific evaluation and we appreciate this time this 18 morning. 19 In the function as Study Director it was 20 my responsibility to assemble and coordinate a team of 21 scientific experts capable of delivering the data 22 required to address the question of Atrazine's 23 potential to affect gonadal development amphibians. 24 Also present is Doctor Keith Solomon, 25 University of Guelph and Doctor Glenn Van Der Kraak,</p>

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1 University of Guelph. Both of these gentlemen have  
2 served on the Atrazine ecological endocrine panel and  
3 in addition Doctor Van Der Kraak was the scientific  
4 advisor on the current study.

5 We'd like to provide two fairly brief  
6 presentations, the first by Doctor Solomon to provide  
7 some additional results of work that Syngenta has  
8 funded since 2003, but work that is not being  
9 considered by this panel at this time.

10 Then Doctor Van Der Kraak will present  
11 findings of the current studies.

12 These two studies have evolved over  
13 eighty scientists and technicians in multiple locations  
14 and we have a number of people here today to address  
15 the questions which you may have concerning the  
16 studies.

17 And these also include Doctor Jeff  
18 Wolfe, a certified veterinary pathologist from  
19 Experimental Pathology Laboratories. This is the  
20 gentleman that did one hundred percent of the histopath  
21 work for both of the studies.

22 We have Doctor Tim Springer, aquatic  
23 toxicologist from Wildlife International.

24 Doctor Ilga Lutz, comparative  
25 endocrinologist from IGB in Berlin.

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1 MR. OSMER: Okay. I appreciate that.

2 MR. BAILEY: Excuse me, Joe Bailey here,  
3 just a quick note, for the panel we are going to get  
4 copies of these slides for you. We thought we'd have  
5 them but we're a little ahead of time so as soon as  
6 they get there we'll get the presentations to you, hard  
7 copy.

8 MR. OSMER: Okay, very good. With that  
9 then I will turn it over to Doctor Solomon.

10 DR. SOLOMON: Thank you very much, Alan.  
11 Mr. Chairman, members of the panel and members of the  
12 audience, I am Keith Solomon, I'm a Professor and the  
13 University of Guelph where I do research on  
14 environmental toxicology and risk assessment.

15 And what I'm going to present is an  
16 overview which will be, or has been made available to  
17 you in written form that summarizes a large number of  
18 studies, including many of them that have been  
19 conducted under the purview of a group of us that  
20 formed a panel to address this issue.

21 To introduce the panel and acknowledge  
22 the members, it's sort of kind of like an orchestra  
23 when you're on one of these panels, everybody plays a  
24 different instrument, you all have your own expertise,  
25 I've served on many of these in my life and it's been a

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1 Doctor Bob Silken who performed of  
2 Silken & Associates, who did the statistical analyses.

3 And also present and involved in the  
4 studies, present in the room is Doctor Larry Holden of  
5 Silken & Associates.

6 And Doctor Hank Kruger, terrestrial  
7 toxicologist with Wildlife International.

8 And Doctor Robert Yopeley, an analytical  
9 chemist with Syngenta and responsible for all of the  
10 Atrazine analyses, the water samples.

11 So Mr. Chairman, depending upon the  
12 nature of the questions from the panel I would request  
13 that the appropriate people be permitted to come as  
14 needed to address those questions.

15 DR. HEERINGA: We'll certainly permit  
16 that and I'll allow you to sort of moderate that if you  
17 would.

18 MR. OSMER: Thank you.

19 DR. HEERINGA: Again, what we would like  
20 to do is throughout the public comment period for all  
21 of the public commenters I will give the panel time for  
22 exchange to pose questions for clarification or  
23 additional insight into the presentation, so we'll  
24 handle it that was and between you and I we'll keep  
25 track of time and progress.

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1 wonderful experience.

2 But I would certainly acknowledge our  
3 Chair and then also the key members of the panel on the  
4 left side of the screen. Some of these individuals are  
5 here today, including Doctor Louis Dupree from South  
6 Africa who would be able to answer and all of these  
7 individuals would be able to answer additional  
8 questions should they be needed.

9 I'd also point out that a number of  
10 students have been participating in this project.  
11 Several of them now are actually professors in their  
12 own right and there are a large number of reports that  
13 have been written and an equally large number I think  
14 of publications have been published in the literature.  
15 And some ancillary studies have been done that really  
16 have nothing to do with Atrazine, but have helped us  
17 illuminate some of the issues that we're dealing with  
18 here.

19 To put this in a larger context, and  
20 I'll come back to this later, we took what we call the  
21 guidelines for causality that were developed from some  
22 of the old principles as espoused by Koch, Hill, Dahl  
23 and more recently in the IPCS document on endocrine  
24 disruptors.

25 But looking here at temporality,

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1 strength of association, consistency biological  
 2 plausibility of recovery, these are all essentially  
 3 similar issues that were pointed out by Doctor Steeger  
 4 in his introductory comments.  
 5       So this is the way we've looked, or  
 6 we've tried to look at this data.  
 7       We've also looked at a large range of  
 8 end points and I don't have the time to go through all  
 9 of these but they are in written form that we made  
 10 available to you, ranging from the basic principles of  
 11 acute toxicity, developmental tests such as the FETAX  
 12 test on Xenopus, things through limb deformity, sex  
 13 ratio, sexual development of the testes, aromatase,  
 14 which I'll deal with in a bit more detail and some  
 15 other issues, all the way up to the level of the  
 16 population.  
 17       This is probably the most scientifically  
 18 appropriate to look at an issue such as we are dealing  
 19 with here, because obviously affects on reproduction  
 20 can have affects all the way up to the population  
 21 level.  
 22       I'd like to spend a little bit of time  
 23 on what I call the aromatase theory. Aromatase is the  
 24 enzyme that converts testosterone to estradiol and the  
 25 ratio of these hormones and related hormones depends,

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1 at least in amphibians, results in the expression of  
 2 female or male characteristics, depending on the ratios  
 3 and concentrations of these hormones.  
 4       And one of the theories that's being put  
 5 forward, that to explain some of the results that we  
 6 observed with Atrazine in terms of gonadal development,  
 7 have been based on the early work of Sanderson and  
 8 others which showed that you could induce aromatase in  
 9 cancer cell cultures, both Atrazine and a number of  
 10 related trizines.  
 11       A couple of important points to notice  
 12 here in this study. This was seen only in cell  
 13 cultures. They looked at tissue slices from fish and  
 14 didn't find any affects. The EC50's are, occurred in  
 15 relatively concentrations and as is typical with all  
 16 induction responses, it's a monotonic concentration  
 17 response, not an inverted view. So any downstream  
 18 affects of this would most likely follow the same  
 19 monotonic dose response.  
 20       In other studies, not in this one that  
 21 I'm referencing here, these affects have not been seen  
 22 in all animals, but certainly it's been reported in  
 23 tissue culture systems.  
 24       To go into that in some detail, this is  
 25 work from Katie Cody of Michigan where she looked a

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1 aromatase activity in Xenopus laevis and obviously  
 2 large differences, pink for females and blue for males,  
 3 the females have much higher innate aromatase activity.  
 4 And this is responsive to estradiol exposures because  
 5 it's a study with a regulated process. And that's the  
 6 reason for the significant difference on the left side  
 7 of the screen.  
 8       But as you see on the right side of the  
 9 screen, both in males and females where it's not easy  
 10 to measure, there's no concentration response to  
 11 Atrazine and no significant differences as well in this  
 12 particular study.  
 13       The result of aromatase activity would  
 14 be expressed in estradiol and you can see from the same  
 15 study the results with plasma estradiol, there were  
 16 significant differences but again no concentration  
 17 response from a range .1 to 25 micrograms per liter of  
 18 Atrazine.  
 19       One of the downstream affects of  
 20 androgens and estrogens and interactions between these  
 21 is the development of sexual characteristics such as  
 22 the laryngeal muscle in humans as well as in  
 23 amphibians. And what you see here are results from a  
 24 laboratory study where the laryngeal muscle, at least  
 25 an area was measured, and again you can see affects of

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1 DHT which stimulates the development of the larynx and  
 2 the or then what's consistently significant but the  
 3 affects of estrogen that decrease it as well in other  
 4 studies.  
 5       But the important message here is no  
 6 significant responses in terms of Atrazine exposure  
 7 through that range of concentrations.  
 8       We were fortunate enough to be able to  
 9 study Xenopus in the field. Xenopus is a native of  
 10 Africa and it is found widely through southern Africa  
 11 where it occurs in ponds and cornfields where it has  
 12 been exposed to Atrazine over many decades now of mace  
 13 production in southern Africa. So these were frogs,  
 14 adult frogs collected from field sites across the  
 15 reference areas where no corn growing was taking place  
 16 in the watershed where no Atrazine was being  
 17 historically used and the corn growing areas where  
 18 Atrazine had been used for many years and the  
 19 concentrations were measured in these systems.  
 20       And again you see the difference between  
 21 males and females in the sense of larynx size, but no  
 22 significant differences between the reference sites,  
 23 either between the males or the females.  
 24       The bottom line of this I guess is that  
 25 based on the response of aromatase and the lack of any



<p style="text-align: right;">Page 42</p> <p>1 significant downstream affects, there seems to be  2 little support for the aromatase hypothesis.  3 Another issue that's come up certainly  4 in some publications has been that of uptake and  5 bioconcentration. And given its water solubility and  6 particularly its optimal water partition coefficient,  7 one would not expect Atrazine to bioconcentrate to any  8 great extent in aquatic or terrestrial organisms.  9 But this has implications for static  10 renewal and flow through type studies.  11 So in order to further eliminate this  12 issue a study was conducted where the uptake and  13 elimination of labeled Atrazine was studied in <i>Xenopus</i>  14 <i>laevis</i>, this had not been done before in this  15 particular species.  16 Now this is work of Etington and Neuro  17 and what you see here is the results for Atrazine. The  18 uptake is indicated by the red bar and the depuration  19 phase when the animals were moved to clean water, this  20 was in Stage 66, is shown by the green bar. And you  21 will see rapid equilibration between the solution and  22 then a very rapid depuration once the animals were  23 removed to fresh water.  24 Atrazine residues were not detectable in  25 the frogs after 22 hours and when you used the uptake</p>	<p style="text-align: right;">Page 44</p> <p>1 you to count and quantify the disintegrations in a  2 particular area and so you can actually do numerical  3 evaluations here.  4 If you enlarge that you can see here  5 that the radio label, which of course is a mixture of  6 Atrazine and any of its metabolites, is present in the  7 gallbladder and the GI tract. So this is consistent  8 with metabolism and also excretion via the bile.  9 There was no concentration observed, or  10 no untoward concentration observed in tissues or other  11 tissues of the organism. We can see the eye and the  12 brain up in the top there.  13 So this was I think very useful  14 information in terms of understanding exposures in  15 these organisms and how to interpret them.  16 Another issue that's come up is a  17 testicular ovarian follicle. This is perhaps a new  18 term to some of you. We ourselves have recently  19 realized that this is the more correct terminology. We  20 used to call these testicular oocytes which is a little  21 bit easier to say, but an abbreviation of TOF or TOF's  22 might be appropriate.  23 What are these? It's basically a female  24 tissue in the testes, you can see the testes tissue  25 surrounding this testicular ovarian follicle with a</p>
<p style="text-align: right;">Page 43</p> <p>1 and depuration kinetics to estimate the BCF it was 1.5.  2 In other words the concentration in the animals would  3 be one and a half times that of the surrounding water.  4 The half life of Atrazine was 48 minutes and it was  5 also shown in this study to be rapidly metabolized to  6 several known metabolites as well as some unknown  7 metabolites.  8 So it is not a chemical that would  9 accumulate over time. The animals are in very rapid  10 equilibrium with their environment and the exposure to  11 the environment are probably the most important ones in  12 terms of assessing any affects.  13 In this same study we were able to also  14 look at the distribution radio label within the tissues  15 of the frogs. The top two pictures here show sections  16 of whole animals done using freezing sections so that  17 the location of the radio label was not disturbed by  18 solid extraction in the normal procedures. And this  19 allowed us to identify the various organs and tissues  20 that could then be studied using radioautography  21 techniques where the intensity or the amount of radio  22 label is indicated by increasing color. And you can  23 see a scale on the bottom here to give you some  24 representation of that.  25 Now this process also actually allows</p>	<p style="text-align: right;">Page 45</p> <p>1 nucleus and you can also see the epithelial cells  2 associated with it, which is the reason for calling it  3 a follicle.  4 These have been commonly observed in the  5 literature in all sorts of situations. They've been  6 seen in fish. There was a recent study published that  7 looked at control fish, Japanese Padica and it was seen  8 in unexposed control animals with some indication of  9 specificity to the strains for the labs that were doing  10 these studies. It's been seen in reptiles, in snapping  11 turtles, either exposed or unexposed to Atrazine, there  12 was no concentration response.  13 It's also been reported in laboratory  14 studies with frogs. They're either absent, depending  15 on where the study is done or there is no concentration  16 response observed at concentrations as you'll hear  17 later on up to 100 micrograms per liter.  18 We've not even seen a concentration  19 response in the generational study that I will focus on  20 shortly.  21 One study reported an occurrence of  22 these in the field sorry, in the lab and the field at  23 concentrations less than .1 microgram per liter  24 Atrazine.  25 There have also been a number of field</p>

<p style="text-align: right;">Page 46</p> <p>1 studies and again no concentration response was  2 observed in the field studies.  3       This sort of led us to wonder if the  4 testicular ovarian follicles are really a natural  5 phenomenon. We've seen them in exposed/unexposed  6 organism without a concentration response. They've  7 also been observed historically in a number of frog  8 species listed here.  9       And just to focus in on one of those  10 studies by Amy Reader from the University of Illinois,  11 this was inter-sex incidents in cricket frogs from  12 museum specimens. It was kind of an interesting study  13 to go back almost on an archeological hunt to look for  14 this. And what you can see, this represents deviation  15 from expected which is the mean of the entire data set,  16 that these occurred well before the introduction of  17 Atrazine and which occurred roughly there. And in fact  18 one might argue that there's been a decrease. I don't  19 know if that's significant or not.  20       With this background and with  21 differences in studies reported on the <i>Xenopus laevis</i>,  22 we were interested in seeing if we could find <i>Xenopus</i>  23 <i>laevis</i> in South Africa that were truly removed far  24 enough from the use of Atrazine in mace production that  25 they would be true reference sites.</p>	<p style="text-align: right;">Page 48</p> <p>1 no testicular ovarian follicles in any of the animals  2 collected from there.  3       So this begged the question is, were  4 there physiological and perhaps genetic differences  5 between these species. But we were very fortunate to  6 have at our disposal at the University of Guelph, a  7 program called the Bar Code of Life which uses  8 mitochondrial DNA to type species in a very rapid way.  9       And working with these people we were  10 able to develop a mitochondrial DNA fingerprint which  11 was  12 also confirmed with nuclear DNA as well to look at the  13 distribution of the various <i>Xenopus</i> species. You'll  14 see at the bottom, <i>tropicalis</i>, <i>muelleri</i> and <i>gilli</i>,  15 which separate out quite distinctly from a large group  16 that is traditionally known <i>Xenopus laevis</i>.  17       These as you know are distributed all  18 the way through south of the Sahara down to the Cape.  19       But what was most interesting was that  20 there was a very clear genetic difference between the  21 animals from the Cape region southwest of the Cape Fold  22 Mountains and the animals from the region northeast of  23 the Cape Fold Mountains.  24       Just to focus in a little bit on there,  25 these organisms here from the Cape are the source of  26 importations of test organisms in <i>Xenopus</i> One and</p>
<p style="text-align: right;">Page 47</p> <p>1       So with this in mind Louis Dupree, a  2 colleague from South Africa conducted a study where he  3 collected frogs from the major mace producing area  4 where much of the previous work had been done, this is  5 very close to Doctor Dupree's university, through down  6 towards Cape Town and then also across the Cape Fold  7 Mountains to several sites on the other side in what we  8 call the Cape sites to differentiate it from the  9 northeast sites by the Cape Fold Mountains.  10       So this is the area of mace production  11 and where Atrazine might be used and in these areas  12 Atrazine and mace, this is a semi-desert area where  13 Atrazine is not used because the mace is not grown.  14 And this is also upwind of these sites. The prevailing  15 winds are from the southwest.  16       We also measured concentrations in these  17 sites. At the time of collection of these specimens  18 there was Atrazine present in this site but not in any  19 of the other sites.  20       We found testicular ovarian follicles in  21 all of these sites, although Atrazine was not present  22 in three of them and there was no indication of a  23 spatial trend in terms of the numbers, although it's  24 only really four sites.  25       When we went to the Cape sites we found</p>	<p style="text-align: right;">Page 49</p> <p>1 <i>Xenopus</i> Express and we also tested those strains from  2 American, samples from the American distributors and  3 they also have fitted into this group. Whereas the  4 other group were a distinct type that is quite  5 different.  6       These were used in the studies you'll  7 hear about later which I've called the Osmer, et al  8 studies, and these were used in the Dupree and other  9 studies conducted in the northwest province. Atrazine  10 is not used in the Cape so we can't study the other  11 species under field conditions. But they obviously  12 have been studied in the laboratory.  13       This really begs the question about, you  14 know, what about <i>Xenopus</i> used in other studies? What  15 is the provenance of cultures? And I know there have  16 been some recent issues around leeches and the  17 provenance of leeches that are used in various  18 physiological and neurophysiological studies as well,  19 for the same reason that they may be the same type or  20 species.  21       We don't see any relationship to  22 Atrazine exposure. The background incidence of these  23 seems to be genetically determined. We feel this has  24 serious implications for the use of certainly  25 testicular ovarian follicles as a marker of endocrine</p>

<p style="text-align: right;">Page 50</p> <p>1 modulated responses and OECD is proposing that this be  2 the protocol and this species be used in the protocol  3 for this type of response.  4 And we also feel that at best, studies  5 may be confounded unless we know the genetic  6 background  7 of the frogs being used.  8 The last study I'd like to focus on is  9 the Growout study because this addresses an issue  10 related to population and other issues. A paper  11 published in 2005 in Environmental Science &amp;  12 Technology  13 looked at a microcosm study where frogs were taken from  14 four days old through Stage 66 and through to ten month  15 old juveniles.  16 These animals were used to look at the  17 end point of testicular ovarian follicles as well as  18 other developmental affects and they were exposed to a  19 range of concentrations of Atrazine in these field,  20 semi-field microcosms. We extended through the lab in  21 South Africa and Doctor Dupree's department took these  22 animals out to 24 months with continued exposure. So  23 the F1 generation in this study was exposed to Atrazine  24 all the way through 24 months.  25 And then we used these animals to assess  26 reproduction and development. We did this by crossing</p>	<p style="text-align: right;">Page 52</p> <p>1 with testicular ovarian follicles, there were, this is  2 the total number of frogs out of the 40 that were  3 randomly selected from the pairings for histological  4 analysis, you see certainly no significant, at least no  5 clear concentration response and no significant  6 difference here but quite a bit of variability in the  7 number of testicular ovarian frogs sorry, ovarian  8 follicles per frog.  9 So we see general conclusions from this.  10 No evidence to suggest any trans-stimulation of relay  11 affects in terms of and also development of the young  12 Xenopus. This is consistent with robust populations in  13 the areas where Atrazine was used in southern Africa.  14 It's also consistent with most other studies where no  15 affects have been found associated with exposure to  16 Atrazine and it doesn't support hypothesis that  17 Atrazine affects reproductive fitness development in  18 frogs.  19 To go back to the temporality, strength  20 of associations and other guidelines that we started  21 with, we see in terms of temporality, no correlation  22 between occurrence of gonadal affects and introduction  23 of the use of Atrazine.  24 In terms of strength of association  25 there's no clear concentration response. If you</p>
<p style="text-align: right;">Page 51</p> <p>1 of the responses we had seen earlier had been seen in  2 males, we focused mainly on those and we crossed,  3 exposed males to referenced females, but we also did  4 one cross between the high concentration males and the  5 high concentration females.  6 And we took the progeny of the F2  7 generation, looked at numbers of eggs hatched,  8 development, various size parameters, and also  9 testicular ovarian follicles.  10 This was done, these animals moved  11 indoors during the wintertime and exposures were  12 continued as they were in the field, the same water  13 source and the same concentrations of Atrazine. You  14 can see the tanks with the adults on the left and the  15 tanks for the larvae on the right.  16 Looking at a number of end points,  17 hatch, time to metamorphosis, first metamorphosis, last  18 metamorphosis, survival, there were some statistically  19 significant differences here in some of these, but no  20 concentration responses in relation to exposures of the  21 parental generation, the F2 generation who were not  22 exposed to Atrazine in these studies.  23 If you look at some more parameters  24 related to size there were no significant differences.  25 In terms of the F2 generation, frogs</p>	<p style="text-align: right;">Page 53</p> <p>1 convert the postulate to address chemicals we see no  2 evidence of causality there. The incidence in wild  3 populations is very inconsistent and in many cases  4 other confounders have not be specifically addressed.  5 We don't know what all of those might be but there may  6 be some other ones out there.  7 In terms of consistency, the outcomes  8 were inconsistent between one laboratory and another  9 and from laboratory to the field.  10 In terms of biological plausibility  11 there is no evidence of affects to the estrogenic and  12 androgenic mechanisms.  13 And in terms of recovery which is one of  14 the postulates, we've not been able to address that  15 because we have not been able to produce consistent and  16 robust responses from which we can see the recovery.  17 So our final conclusion if you want to  18 think of this as a symphony is environmentally  19 irrelevant concentrations of Atrazine are not  20 demonstrated to affect growth, sexual development,  21 reproduction and survival in amphibians.  22 And with that I'd like to thank you. I  23 believe it might be better if we held the questions  24 until Doctor Van Der Kraak has made his presentation if  25 that's your wish, Mr. Chairman.</p>

<p style="text-align: right;">Page 54</p> <p>1 DR. HEERINGA: I was going to ask you the 2 same question and you seem to have given the response 3 already. I will accept that. 4 We are at ten minutes of ten and I would 5 like to if we could, use this opportunity to take a 6 break. And we'll return to hear Doctor Van Der Kraak's 7 presentation and then we'll entertain questions and 8 comments from the panel. 9 Is that acceptable. I guess the full 10 team will be there. 11 MR. OSMER: I believe that works fine. 12 DR. HEERINGA: Okay. Let's take a 13 fifteen minute break. I have 9:48, we'll reconvene 14 here at let's say 10:05. 15 (WHEREUPON, there was a recess.) 16 DR. HEERINGA: Prepare to start again in 17 a minute or so. Photocopies of the presentation 18 materials are being circulated to the panel members and 19 for the audience and the public those will be available 20 on the docket for this particular panel meeting. 21 Okay, welcome back everyone to the 22 second half of our first morning session on the 23 Potential for Atrazine to Affect Amphibian Gonadal 24 Development, FIFRA Science Advisory Panel Meeting. 25 At this point we are in the process of</p>	<p style="text-align: right;">Page 56</p> <p>1 of those were such that the results were inconclusive 2 as a result of issues associated with design 3 deficiencies and uncertainties, questions about water 4 quality and husbandry and inconsistent procedures 5 across the various studies. 6 However these studies established that 7 <i>Xenopus laevis</i> was an appropriate model to move 8 forward 9 with additional tests to evaluate the affects of 10 Atrazine on gonadal development. 11 Part of the EPA requirements and through 12 the data call in instructions to the sponsor, Syngenta, 13 there was the need for the development of the standard 14 operating procedures to do these tests in flow through, 15 to meet ASTM water quality and testing standards, to 16 verify exposure, to deal with the terminology and make 17 it standardized with respect to gonadal structures and 18 to conduct the study under good laboratory practice 19 standards with quality assurance. 20 Now, in order to achieve this, and part 21 of this has been introduced, there was a large study 22 team that was assembled. The in-life studies which 23 were conducted at Wildlife International and IGB Labs 24 in Germany and Doctors Springer, Klaus and Lutz as the 25 principal investigators. Jeff Wolfe who is at the table was with,</p>
<p style="text-align: right;">Page 55</p> <p>1 beginning our period of public comment. We've heard 2 from Doctor Solomon on the conclusions drawn from a 3 series of additional studies and I think, Mr. Osmer, at 4 this point we're going to hear from Doctor Van Der 5 Kraak and then I'd like to stop to give the panel a 6 chance to pose some questions on these presentations. 7 So if you'd like to go ahead at this 8 point. 9 MR. OSMER: That would be fine and for 10 your time management we anticipate that Doctor Van Der 11 Kraack's presentation would be about 25 to 30 minutes 12 and then use the remainder of our time to address any 13 questions from the panel. 14 DR. HEERINGA: That will be fine. 15 MR. OSMER: So I'll turn it over to 16 Doctor Van Der Kraack. 17 DR. VAN DER KRAAK: Thank you, Alan and 18 Mr. Chair. I'm very pleased to have the opportunity to 19 present the results of two studies that have assessed 20 the potential affects of Atrazine on growth, 21 metamorphosis and sexual differentiation of <i>Xenopus</i> 22 <i>laevis</i>. 23 To put this in context and to summarize 24 if you will what Doctor Steeger spoke of this morning, 25 in 2003 seventeen studies were evaluated and the result</p>	<p style="text-align: right;">Page 57</p> <p>1 or is with EPL Labs and he was the principal 2 investigator responsible for the zoological evaluation 3 of the gonads. 4 Larry Holden who is here along with Bob 5 Silken from Silken Associates were responsible for the 6 statistical analysis. 7 Alan Osmer on my left was the GLP study 8 director. 9 And I had a role, a very minor role 10 throughout the project as a scientific advisor to this 11 group. 12 In terms of restating the objectives, 13 the objectives were to evaluate the potential affects 14 on gonadal development in <i>Xenopus laevis</i> and this was 15 conducted over two parts. 16 And the first part was conducting 17 estradiol pre-exposure studies to address design and 18 method deficiencies, to confirm the appropriateness of 19 the test systems and to identify the concentration of 20 estradiol that would be used as a positive control 21 level for the studies evaluating the affects of 22 Atrazine. 23 And then specifically the main study was 24 to determine whether a wide range of exposures to 25 Atrazine during early development would affect aspects</p>



<p style="text-align: right;">Page 58</p> <p>1 of survival, growth, metamorphosis or sexual 2 differentiation of <i>Xenopus laevis</i>. 3 Now, this slide comes with the title 4 that <i>Xenopus laevis</i> is the standard model for sexual 5 differentiation in amphibians, and that certainly is 6 the case. There is much that's known about primary sex 7 differentiation in this species, including the affects 8 of steroids. There's much that's know about many of 9 the genes involved in steroid hormone biosynthesis and 10 in other genes as well as information on secondary sex 11 differentiation, including the affects of the major 12 steroid hormones. 13 To put this in a little bit of a 14 different context, sexually undifferentiated tadpoles 15 will mature to males or females and they do so under 16 the appropriate hormonal environment. 17 Much is know about how hormones affect 18 sexual differentiation in <i>Xenopus</i>, such that there is 19 information on a sensitive window or a sensitive stage 20 over which hormones can direct sexual differentiation. 21 And then beginning about Stage 55 through to Stage 60, 22 one starts to identify and be able to very clearly 23 morphologically distinguish the ovary and the testes. 24 In terms of this particular experiment, 25 the exposure periods spanned from days 46 or pardon</p>	<p style="text-align: right;">Page 60</p> <p>1 at a governmental level and these occurred as I 2 mentioned previously at all of the major laboratories 3 through the EPA Office of Enforcement and Compliance 4 Assurance, the EPA Office of Research and Development, 5 and by the German GLP Federal Bureau which was 6 associated with their Institute for Risk Assessment. 7 There were also a series of audits that 8 were conducted by the internal quality assurance units 9 in each of the major laboratories, including people 10 coming from the registrant, Syngenta Crop Protection. 11 In all, there were 90 quality assurance 12 audits that evaluated various phases of the study 13 conduct and reporting. 14 So in terms of the experimental designs 15 for the Atrazine studies at the two laboratories you're 16 going to hear more about the treatments. This included 17 a positive control which was 17 beta estradiol at .2 18 micrograms per liter, a negative control which was 19 untreated and Atrazine in 5 different dose 20 concentrations spanning a ten thousandfold difference 21 in concentration. 22 The number of tanks were 8 per treatment 23 for Atrazine. There were 8 tanks for the positive 24 controls and 16 negative controls at each of the 25 laboratories.</p>
<p style="text-align: right;">Page 59</p> <p>1 me, from Stage 46 through to the end of Stage 66 which 2 is the time in which there is the final resorption of 3 the tail. 4 In terms of putting this in chronology, 5 if we start back here in 2003 there was the EPA 6 Amphibian SAP which Doctor Steeger talked about and 7 following that the registrant worked extensively on 8 method development and lab selection for these 9 definitive studies. 10 Wildlife International and the IGB Labs 11 were selected and they went through a estradiol study 12 in both locations where there was much work on protocol 13 refinement and review of the procedures by the U.S. 14 EPA. 15 This led to the definitive studies with 16 estradiol as a positive control and Atrazine conducted 17 at the two laboratories again and these were also 18 subject to review, both in terms of the EPA Atrazine 19 Protocol Review and quality assurance inspections by 20 the EPA at the three major laboratories involved in the 21 studies, IGB, Wildlife International and at EPL where 22 the histology evaluations were conducted. 23 In terms of the good laboratory practice 24 inspections and study audits, these were very 25 extensive. There were inspections that were conducted</p>	<p style="text-align: right;">Page 61</p> <p>1 The number of larvae that were put into 2 these tanks were 25 and it's written here that the sex 3 was unknown because they were put in before they were 4 sexually differentiated. They were put in at a loading 5 rate that met ASTM standards. And the exposure began 8 6 days post-fertilization and it ended at Stage 66 at 7 tail resorption or up to 83 days post-fertilization. 8 Now, the Atrazine concentrations as I've 9 mentioned, spanned four orders of magnitude from .01 10 through to 100 micrograms per liter. These bracketed 11 the Atrazine concentrations for which affects were 12 previously reported. And they included and exceeded 13 environmentally relevant concentrations for chronic 14 exposure. 15 They also covered potential low dose 16 response or concentrations that would be appropriate 17 for looking at potential low dose responses to 18 Atrazine. 19 Now in terms of 17 beta estradiol, it 20 was determined experimentally that .2 micrograms per 21 liter would be the concentration of estradiol that 22 would cause approximately an EC50 response for 23 feminization of males. And this would mean that one 24 would predict that this would be a concentration that 25 resulted in about 75 percent females in the treatments.</p>

<p style="text-align: right;">Page 62</p> <p>1 This was taken in part again as a  2 positive control and the intent was to increase the  3 likelihood of intermediate responses such as mixed sex  4 individuals and inter-sex individuals. In fact, with  5 going quickly to some data, the .2 microgram per liter  6 was very close to the predicted response in terms of  7 achieving 71 percent and 65 percent females in the two  8 trials that we're going to report on, again very close  9 to this EC50 concentration.  10 Now in developing and validating the  11 test procedures the study design I think went well  12 beyond some of the requirements laid out by the EPA.  13 Much effort was made in the design of the experiment  14 and in terms of making sure that the appropriate  15 statistical power was achievement. The pre-studies  16 which I've mentioned were important in establishing the  17 methods that would be used. It also enabled inter-  18 laboratory harmonization and verification of the  19 experimental design.  20 A unique feature was the repeated  21 independent experiments that were conducted at the two  22 site. And there was considerable work that was  23 expended in refining the methods for assessing both  24 gross morphology and gonadal histology.  25 And in the process of doing this</p>	<p style="text-align: right;">Page 64</p> <p>1 control two and control one which was pardon me,  2 control two and control one, control two and control  3 one, these were also completely randomized so that the  4 experimenters would not know which tanks were  5 associated with those particular treatments.  6 In terms of the design, so there was  7 clusters of four tanks each for each treatment except  8 for the negative controls which had four clusters.  9 These clusters as I've mentioned were color coded and  10 randomly positioned.  11 Now, in the course of the experiment and  12 the monitoring of the levels of Atrazine, it turned out  13 that one of the control tanks had recurring low levels  14 of Atrazine contamination and the maximum  15 concentration  16 that was observed was below .013 micrograms per liter.  17 But given that Atrazine was detected in these tanks,  18 which it turned out were sandwiched between two of the  19 highest concentrations of Atrazine in the treatment  20 because of the randomization procedures, those tanks  21 were removed from the analysis.  22 In the process of doing the study there  23 were also microbial blooms which were identified in the  24 two sets of tanks associated, one tank here  25 specifically, tank six in the low group of Atrazine,  26 that was removed as was this entire cluster of control</p>
<p style="text-align: right;">Page 63</p> <p>1 experiment there were recommendations that were put  2 forward by the OECD and in fact and this was  3 specifically for an amphibian metamorphosis assay and  4 this study met the relevant water quality parameters.  5 To describe a little bit about the  6 experimental set up, the experimental set up was such  7 that it was a standard flow through system which is  8 commonly used in aquatic testing. The tanks were  9 glass, the tubing was such that it was selected to  10 minimize the exposure to potentially, or to compounds  11 that had previously been identified as ones that  12 interfere with endocrine function. Any test solutions  13 were made weekly and they were delivered to a mixing  14 chamber and then these were delivered to the tanks such  15 that there were 7 tank volume exchanges per day. The  16 treatments, as you'll see in the next couple of slides  17 were conducted blinded and they were, the tanks were  18 distributed in a random fashion.  19 Now this is a picture of what the  20 experimental layout looked liked at the labs at  21 Wildlife International. If you look across the picture  22 you'll see various different colors and they represent  23 the concentrations of various test compounds. If  24 you'll note very quickly, there were two sets of  25 control tanks shown here and it's pair was up here,</p>	<p style="text-align: right;">Page 65</p> <p>1 tanks shown here. So those were removed.  2 This still left at the end additionally,  3 additional control tanks so that at the end of the  4 experiment, two negative control cluster were omitted  5 from the analysis. However the robust study design  6 permitted continuation of the study and there were  7 eight tanks that were included for all treatments.  8 Now, the experimental layout at the IGB  9 Labs was similar. There was the same pardon me, the  10 layout was different in terms of the structure of the  11 room, but the tanks that were included or the  12 treatments that were included stayed the same.  13 There was an issue that was identified  14 in this that Atrazine rather than estradiol was  15 inadvertently used to prepare the estradiol stop  16 solution on day 49 post-fertilization during the course  17 of this study. Now this occurred after the sensitive  18 developmental window closed for the species, that is to  19 say this was occurring at Stage 56, and there were  20 consistent results with what was seen in these tanks  21 with what was evident at the Wildlife International  22 studies. And this indicated there was no impact on the  23 study and these tanks were included in the study.  24 Now this is a real important slide and  25 what this shows is the measured concentrations of</p>

<p style="text-align: right;">Page 66</p> <p>1 Atrazine at both the laboratories of Wildlife 2 International and IGB. You'll not here that dosing 3 started at day negative 5, so 5 days before, and then 4 continued until the end of the experiment. 5 Now you'll notice that in some of these 6 cases monitoring continued for longer time intervals 7 and that relates to the times, or whether there was 8 frogs in those tanks that hadn't completed 9 metamorphosis. So if there were no frogs there was no 10 point in further sampling the fish not the fish, the 11 frogs. 12 In terms of the concentrations of 13 Atrazine, there was a clear delineation and very close 14 agreement with nominal concentrations, such that there 15 was no overlap in concentrations of Atrazine over the 16 four orders of magnitude of the concentration response. 17 In terms of the control tanks the levels of Atrazine 18 that were detected are listed as non-detectable and 19 they were lower than the level of detection which was 20 .005 micrograms per liter. 21 In terms of placing these data in a 22 different context, one could comment on them in 23 relation to the nominal concentrations and one could 24 look at these in relation to what was the study mean 25 over the course of the entire study and what was the</p>	<p style="text-align: right;">Page 68</p> <p>1 analytes at the highest treatment group turned out to 2 be less than 1 percent, well less than 1 percent of the 3 measured Atrazine concentrations. 4 Now, to get to some actual results of 5 what happened in the experiment in terms of the 6 biological end points, there were a suite of primary 7 end points, and these related to survival, body weight, 8 snout to vent length as a measure of gross development, 9 time to metamorphosis as a key developmental measure. 10 And then a series of the responses within the gonad, 11 including sex ratio, the incidence of mixed sex 12 individuals, inter-sex individuals and the testicular 13 ovarian follicles which Doctor Solomon mentioned. As 14 well there were gross gonad, liver and kidney features 15 that were monitored. 16 Now, this slide, I'm going to just take 17 a second because many of the slides will follow this 18 same pattern. This is reported as the various 19 treatment groups going from the positive control, the 20 negative control to the various concentrations of 21 Atrazine for Wildlife International and for IGB. This 22 is the survival and it turns out that there were no 23 significant differences in mortality between 24 treatments. 25 And if you focus on the y axis, the</p>
<p style="text-align: right;">Page 67</p> <p>1 concentration during the critical window of survivor 2 the critical window for sexual differentiation. 3 Again there was a high degree of 4 congruence between the levels that were nominal and the 5 levels that were actually measured. As well there was 6 measurement of estradiol concentrations and these again 7 were, levels were achieved with high reproducibility 8 across the study. 9 An issue that came up was whether there 10 should be an analysis of Atrazine degradants. This was 11 not part of the protocol per se and in part it wasn't 12 there because under static conditions negligible 13 amounts of the degradates would be expected based on 14 EPA standard fate studies for aqueous photolysis, 15 aerobic aquatic degradation or hydrolysis. 16 Now the study was in fact, you know, 17 conducted under flow through conditions which would 18 produce even less opportunity for degradate formation. 19 As well, Atrazine stocks were prepared weekly and 7 20 exposure, or 7 tank volume exchanges occurred per day. 21 Nevertheless there was an analysis made 22 of degradates in 6 of the tanks from the 100 microgram 23 per liter samples taken from the IGB and Wildlife 24 International studies. The analytes that were listed 25 here were measured, but the concentration of these</p>	<p style="text-align: right;">Page 69</p> <p>1 survival was very high across the treatment, ranging 2 from about 93 percent to above 98 percent for all 3 treatments. 4 One of the other parameters that were 5 evaluated was mean body weight at metamorphosis and in 6 terms of the studies at Wildlife International for 7 males in blue and females in this burgundy type color, 8 there were no significant differences between body 9 weight across the various treatments. 10 By comparison, in the studies at IGB 11 there were some significant differences that were 12 reported in some of the Atrazine treated groups, but 13 only for females. 14 But again if you focus on the y axis the 15 range of biological variability across those treatment 16 groups was in fact very tight. 17 In a similar manner, snout to vent 18 length was measured at the time of metamorphosis and 19 again there were no significant differences from the 20 negative control across the various treatment groups at 21 Wildlife International. 22 Again, no affects in males but the same 23 groups that appeared that were significant on the 24 previous graph were also significant for snout-vent 25 length for those groups treated with Atrazine at these</p>

<p style="text-align: right;">Page 70</p> <p>1 varied concentrations.</p> <p>2 Now, just to remind you a little bit</p> <p>3 about what this study was looking at, and one of the</p> <p>4 key factors was metamorphosis, and so as I had</p> <p>5 mentioned that tadpoles were initiated to the tanks, in</p> <p>6 fact even earlier than the stage depicted here which</p> <p>7 was Stage 48, and the experiment terminated at complete</p> <p>8 tail resorption at Stage 66. And in this example this</p> <p>9 would have been the progression of over 55 days of</p> <p>10 treatment.</p> <p>11 This slide is a bit complicated and it</p> <p>12 reports cumulative numbers of individuals that had</p> <p>13 completed metamorphosis. And so this axis shows the</p> <p>14 composite number of individuals having completed</p> <p>15 metamorphosis and you'll note that this essentially</p> <p>16 goes to 100 percent, in that throughout the entire</p> <p>17 study, only 3 individual frogs did not complete</p> <p>18 metamorphosis.</p> <p>19 Now, you'll notice this and of course if</p> <p>20 I was looking at my students having presented this I</p> <p>21 would be critical, and I would say I can't make out</p> <p>22 those lines. I don't think that's important in this</p> <p>23 situation, in that this represents the control</p> <p>24 individuals and the Atrazine treated individuals. And</p> <p>25 in males there was one group that was an outlier and</p>	<p style="text-align: right;">Page 72</p> <p>1 be experts by now and realize that this would be female</p> <p>2 with a normal ovary. This would be a normal testis and</p> <p>3 this would be a mixed sex individual and you'd very</p> <p>4 quickly recognize that there was an ovary there and a</p> <p>5 testis there on one of the gonads and a testis there</p> <p>6 and an ovary there on the other gonad.</p> <p>7 These individuals though with these</p> <p>8 mixed sex conditions were ones that were treated with</p> <p>9 estradiol.</p> <p>10 Now throughout the study the reliance on</p> <p>11 scoring gonadal development was not made on the basis</p> <p>12 of gross morphology, but rather was made on the basis</p> <p>13 of histological evaluation of the gonad. So all of the</p> <p>14 individual frogs were trimmed and embedded and then</p> <p>15 they were sectioned. And they were sectioned from the</p> <p>16 ventrum to the dorsum. And if you look at the bottom</p> <p>17 slide there you can see the sectioning occurring.</p> <p>18 And then there were four micron sections</p> <p>19 and slides or sections at 12 micron intervals were</p> <p>20 evaluated. It turns out that all of the histological</p> <p>21 sections, that is to say greater than 100,000 of these</p> <p>22 were evaluated in a blinded manner by one board</p> <p>23 certified veterinary pathologist. And to add a little</p> <p>24 of humor to the day, Jeff who did this work in fact had</p> <p>25 hair when he started.</p>
<p style="text-align: right;">Page 71</p> <p>1 that was the group that was treated with estradiol.</p> <p>2 If you look at this, the slope of this</p> <p>3 line parallels the other lines. What this is</p> <p>4 suggesting is that estradiol is delaying the onset of</p> <p>5 metamorphosis.</p> <p>6 In a similar fashion you see this at IGB</p> <p>7 for males. And if we look in females it turns out that</p> <p>8 the group that would be the far right hand group was</p> <p>9 also the estradiol treated group.</p> <p>10 To put these data in a different context</p> <p>11 if you will to look at the mean age at metamorphosis,</p> <p>12 if one looks at the negative controls and the Atrazine</p> <p>13 treated groups, whether it's at Wildlife International</p> <p>14 or at IGB, there are no significant differences across</p> <p>15 these treatments.</p> <p>16 There is however at both locations a</p> <p>17 significant increase in the age at metamorphosis in</p> <p>18 both males and females that were treated with</p> <p>19 estradiol.</p> <p>20 Again though you'll not that there is</p> <p>21 particularly within the negative controls and the</p> <p>22 Atrazine treated frogs, a very tight range in terms of</p> <p>23 this parameter of age at metamorphosis.</p> <p>24 Now, a major focus in this study was to</p> <p>25 look at gonadal differentiation and so you all should</p>	<p style="text-align: right;">Page 73</p> <p>1 Now, these are standard protocols for</p> <p>2 this type of analysis, but one might want to ask the</p> <p>3 question, having done this gonad sectioning and</p> <p>4 evaluation procedure, would significant findings have</p> <p>5 been missed using the methodology? And the answer to</p> <p>6 that is, I'm going to say no, things would not be</p> <p>7 missed. And I say that because the estrogenic</p> <p>8 responses that one would see in terms of a sex reversal</p> <p>9 and mixed sex gonads are obvious as I showed you a</p> <p>10 couple of slides back in terms of the gross morphology.</p> <p>11 And the testicular leukocytes or</p> <p>12 testicular ovarian follicles as described earlier by</p> <p>13 Doctor Solomon, the smallest of these are 29 microns in</p> <p>14 diameter. And by taking 12 micron step sections, these</p> <p>15 are less than half of the diameter of the follicle.</p> <p>16 And so there's a high degree of confidence that one</p> <p>17 would not miss these should they be present.</p> <p>18 So, having said that let's go to what</p> <p>19 was actually found.</p> <p>20 And this is just what one of the</p> <p>21 histological slides would have looked like in terms of</p> <p>22 showing kidney, normal testis. In a similar fashion if</p> <p>23 one looks at the ovary one would have seen normal</p> <p>24 ovarian structure. But if one looks at what happens in</p> <p>25 those frogs that are treated with estradiol, one sees a</p>



<p style="text-align: right;">Page 74</p> <p>1 series of different types of phenotype and this ranges  2 from a normal ovary to very obviously altered ovarian  3 structure that's associated with these large vacuolated  4 areas to those individual frogs with normal testis  5 structure to those with dilated tubules showing an  6 obvious altered structure, and including those  7 individuals that have a mixed sex gonad phenotypes.  8 In treating with estradiol we see that  9 there is a increase in the proportion of individuals  10 that have the ovarian phenotype and as you'll see in a  11 few moments, an increase in the proportion of  12 individuals that have the mixed sex phenotype.  13 So, this slide is a real key one because  14 this slide reports the percentage of male, female and  15 mixed sex frogs at the two locations. And if you focus  16 in first of all on the Atrazine treated individuals  17 there was no affect on the proportion of males or  18 females at any of the Atrazine concentrations that were  19 evaluated.  20 So looking here from the negative  21 control through the high concentration of Atrazine, and  22 again female in burgundy, male in the blue coloration.  23 If one continues on and looks at what  24 happens with the estradiol exposure at this  25 concentration that was selected to cause 50 percent</p>	<p style="text-align: right;">Page 76</p> <p>1 And so here in this case there were a suite of end  2 points that were characterized and evaluated in this  3 study.  4 Now, a question that came up in previous  5 discussions associated with the EPA was the question of  6 whether there should be differential gonad cell  7 counting that evaluated cell types in these frogs. And  8 that was not performed because the immaturity of Stage  9 66 gonads was such that there a very limited number of  10 cell types that are available to enumerate.  11 These histological features though were  12 ones that were selected and they represent the best  13 effort to evaluate, is there something going on within  14 the gonad that is remarkable and should be categorized?  15 Now, let's look at this. So, this  16 figure shows statistical differences that were seen  17 between estradiol treated and negative control frogs,  18 and the corresponding results that were taken for  19 Atrazine treated frogs.  20 Now, in terms of estradiol treated at  21 both IGB and Wildlife International, I've already  22 reported to you that there was a decreased percentage  23 of males, an increased percentage of mixed sex  24 individuals with estradiol treatment, and using this  25 histological evaluation, there were clear affects of</p>
<p style="text-align: right;">Page 75</p> <p>1 feminization, there was a significant increase in the  2 proportion of females here, and there was an increased  3 number of individuals that were of the mixed sex  4 phenotype.  5 Now I'm sure you're asking were any  6 mixed sex individuals seen in the Atrazine treated  7 groups? Yes, there was one individual frog that was of  8 mixed sex, and that was in the 25 microgram per liter  9 Atrazine treatment seen only at the IGB labs. And so  10 this represents one individual out of approximately  11 2,400 Atrazine and negative treated control frogs.  12 In terms of other major or primary end  13 points that were looked at, there were no testicular  14 ovarian follicles and this was expected based on the  15 data that Doctor Solomon had talked about in that frogs  16 from Xenopus One which were the supplier of these  17 frogs, come from the western Cape.  18 There was also no evidence of inter-sex  19 and that is the left and right gonads being of the  20 opposite sex, so no inter-sex were observed in this  21 study in any treatment.  22 Now, in addition to the primary end  23 points that were evaluated, and we've already talked  24 about, there were a number of other histological that  25 were reported. And this was the work of Doctor Wolfe.</p>	<p style="text-align: right;">Page 77</p> <p>1 estradiol on the testes in terms of dilated tubules,  2 dividing leukocytes, internal melanophores and in the  3 ovary in terms of increased ovarian cavity size.  4 By comparison, if you look at the  5 responses that were seen with Atrazine, all of these  6 responses were non-significant.  7 So, the conclusion from this is that the  8 findings associated with estradiol exposure were not  9 observed in Atrazine exposed frogs and as such there is  10 no evidence of feminization in the Atrazine exposed  11 frogs.  12 Now, as I mentioned there were a suite  13 of these other histological descriptors that were  14 evaluated and so one should ask, what happened with  15 these? So in terms of Atrazine treatments the  16 incidence of these histological descriptors was low and  17 it was low irregardless of the treatment.  18 There were sometimes inconsistent, or  19 inconsistent and sometimes contradictory findings  20 between laboratories for Atrazine, but none of these  21 responses were significant in paralyzed comparisons.  22 Further analysis showed that only one of  23 the end points, that being the fused kidneys, was  24 significant at both IGB and Wildlife International in  25 monotonic trend tests, and only when all of the doses</p>

<p style="text-align: right;">Page 78</p> <p>1 were included.</p> <p>2 The real take home message from this is</p> <p>3 that there was a lack of concentration response to</p> <p>4 Atrazine over four orders of magnitude in that Atrazine</p> <p>5 concentration.</p> <p>6 So, let me just make a point here. In</p> <p>7 terms of the histological evaluation of the gonad of</p> <p>8 Stage 66 Xenopus, the evaluation that was conducted in</p> <p>9 this experiment was in my estimation far more extensive</p> <p>10 than anything that has been done in the past.</p> <p>11 And the take home message from that was</p> <p>12 that the histological descriptors were not consistently</p> <p>13 significant across Atrazine treatments in the two</p> <p>14 studies. And the biological significance of those</p> <p>15 histological changes in gonad structure is truly not</p> <p>16 known.</p> <p>17 So, to sum this up in terms of key</p> <p>18 findings, this study established a standardized</p> <p>19 procedure and protocol for evaluating sexual</p> <p>20 differentiation in Xenopus laevis and it was done in a</p> <p>21 manner that enabled a flow through exposure system.</p> <p>22 The studies evaluated key end points,</p> <p>23 growth, metamorphosis, sexual differentiation and it</p> <p>24 was shown in these studies that all of these were</p> <p>25 highly responsive to the positive control, estradiol,</p>	<p style="text-align: right;">Page 80</p> <p>1 Yes, Doctor Skelley?</p> <p>2 DR. SKELLEY: Doctor Solomon, one of the,</p> <p>3 this is David Skelley, one of the study results you</p> <p>4 reported had to do with how rapidly Atrazine is cleared</p> <p>5 from amphibians and you mentioned that within 22 hours</p> <p>6 it could be undetectable, is that correct?</p> <p>7 DR. SOLOMON: Yes, that's when you move</p> <p>8 them from an exposure situation to an unexposed</p> <p>9 situation.</p> <p>10 DR. SKELLEY: Okay. So</p> <p>11 DR. SOLOMON: Sorry, it's Keith Solomon</p> <p>12 for the record.</p> <p>13 DR. SKELLEY: One of the studies that was</p> <p>14 submitted by the registrant is titled, Characterization</p> <p>15 of Atrazine Exposure and Potential Affects for</p> <p>16 Amphibians Inhabiting Sugarcane dominated</p> <p>17 Ecosystems in</p> <p>18 Florida", and the primary author is Timothy Gross.</p> <p>19 And I'd like to just read one sentence</p> <p>20 out of the summary. The basic finding in the study was</p> <p>21 that 28 percent of the male frogs in sugarcane field</p> <p>22 associated locations had abnormal development of the</p> <p>23 Bidder's organ and this was about a fourfold increase</p> <p>24 over nonagricultural context.</p> <p>25 And the sentence in the summary that I'd</p> <p>like to read is, "although the incidence of developed</p>
<p style="text-align: right;">Page 79</p> <p>1 affects of estradiol on all of these end points.</p> <p>2 Whereas, treatment with Atrazine over</p> <p>3 four orders of magnitude, .01 to 100 micrograms per</p> <p>4 liter had no affect on these primary end points.</p> <p>5 One of the charge questions and one of</p> <p>6 the discussion points was, what was the mechanism by</p> <p>7 which Atrazine was disrupting gonadal development?</p> <p>8 Well, I'd like to leave you with the</p> <p>9 comment that in the absence of affects, we can report</p> <p>10 on a mechanism by which Atrazine disrupts gonadal</p> <p>11 development in Xenopus laevis.</p> <p>12 Thank you, Mr. Chairman.</p> <p>13 DR. HEERINGA: Thank you very much,</p> <p>14 Doctor Van Der Kraak. At this point Mr. Osmer, I think</p> <p>15 that I'm going to entertain comments but I would</p> <p>16 anticipate quite a few comments, and to keep some order</p> <p>17 to this we're going to hear about this data again</p> <p>18 tomorrow from the EPA and we'll have chances at that</p> <p>19 point to ask questions and I presume your team will be</p> <p>20 here if the EPA would like to call on you.</p> <p>21 So what I'd like to do is I'd to return</p> <p>22 to the first presentation by Doctor Solomon and ask,</p> <p>23 are there any questions on the panel about the</p> <p>24 aromatase hypothesis and the results that were</p> <p>25 presented there?</p>	<p style="text-align: right;">Page 81</p> <p>1 Bidder's organs was greatest in cane sites in the</p> <p>2 current study, results should be interpreted as an</p> <p>3 association between Atrazine exposure and the increased</p> <p>4 incidence of males with developed Bidder's organs since</p> <p>5 plasma Atrazine concentrations were not correlated with</p> <p>6 this anomaly at any site".</p> <p>7 And I'd just like to ask you to comment</p> <p>8 on that conclusion relative to the statement you made.</p> <p>9 DR. SOLOMON: Well first of all we have</p> <p>10 not studied the clearance of Atrazine from Bufo Marinus</p> <p>11 so I don't have actual data on the half life in those</p> <p>12 organisms.</p> <p>13 It would depend on the most recent</p> <p>14 exposure, given that these are terrestrial and also</p> <p>15 aquatic, they share that habitat. Whereas the Xenopus</p> <p>16 is totally aquatic.</p> <p>17 And our original study was designed to</p> <p>18 look at Xenopus as a model organism to see what</p> <p>19 clearance rates were in that. The, to do that kind of</p> <p>20 study, and I can't speak for Tim Gross personally</p> <p>21 because he's, I don't know enough of the detail of the</p> <p>22 study, but I would suspect that it would depend on the</p> <p>23 time of collection in relation to when the animals were</p> <p>24 last in the water and the sensitivity of the technique</p> <p>25 of analysis which is based on immunoassay and the</p>

<p style="text-align: right;">Page 82</p> <p>1 possible issues with immunoassays, and given the other  2 kinds of pesticides used in sugarcane production and in  3 those agricultural areas.  4 I don't know that it's possible to draw  5 any real conclusions about an Atrazine affect in that  6 kind of mixed exposure situation.  7 DR. HEERINGA: Any other questions  8 related either to the aromatase theory or to the uptake  9 retention?  10 Yes, Doctor LeBlanc?  11 DR. LEBLANC: Gerry LeBlanc. Again  12 Keith, regarding the accumulation of Atrazine, the  13 information you presented which I assume was for  14 Atrazine, or perhaps it was for radio labeled, and I  15 just wondered if you could clarify that? Can we look  16 at the information and conclude that Atrazine and its  17 metabolites have a half life of about 22 hours?  18 DR. SOLOMON: In fact the paper which is,  19 you can obtain from Environmental Science &amp;  20 Technology,  21 the Atrazine was cleared quickly because it was  22 metabolized as well as excreted. And the metabolites  23 formed were also excreted from the animals and the half  24 lives ranged for the metabolites, ranged from about the  25 same time as Atrazine, roughly an hour, to around eight  26 hours or something like that.</p>	<p style="text-align: right;">Page 84</p> <p>1 Is that sort of consistent that you'd  2 see such a low turnover rate and how does that compare  3 to other species?  4 DR. SOLOMON: Keith Solomon. I would  5 actually defer to people with more expertise in that  6 area. Perhaps Doctor Van Der Kraak would be prepared  7 to try that one.  8 DR. VAN DER KRAAK: It's Glen Van Der  9 Kraak. The specific comparison, let me answer the  10 question in two ways. The values that were reported  11 for amphibians were consistent with other literature  12 values for aromatase activity.  13 In terms of the cross species  14 comparison, it becomes a little bit complicated as you  15 move across species and particularly if you go to  16 tissues like the brain and you do that in fish for  17 example. The concentrations of aromatase in the brain  18 there are very, very high.  19 The other issue is, is that you have a  20 range of developmental stages across obviously groups  21 of organisms.  22 And again I would come back to the fact  23 that the values that were reported for the amphibians  24 made biological sense as one looked across stage, so  25 there was some consistency with what one would expect</p>
<p style="text-align: right;">Page 83</p> <p>1 But total radio activity was cleared  2 relatively quickly as well, although there was some  3 residual activity and one never knows, you know, it's  4 bowel residue whatever that is, it could be EC14  5 incorporated into protein or unextractable conjugants,  6 although they were hydrolyzed to see if they could be  7 identified.  8 But we did identify several of the  9 common metabolites but there were some unknown ones  10 as  11 well. That was done using chromatography  12 radiotography.  13 DR. HEERINGA: Doctor Schlenk and then  14 Doctor Isom.  15 DR. SCHLENK: Dan Schlenk, UCR. A  16 question about the aromatase assays. We've done a lot  17 of work with P450 assays and the turnovers that you  18 normally see with those assays are usually in the peak  19 omoles, or hundreds of and this is in fish mostly, in  20 mammals it's much higher, but the turnover rates are  21 normally in the hundreds of peak omoles per minute per  22 milligram. But yet your assays are femtomoles per hour  23 per milligram and I'm kind of curious how that relates  24 to say activity in the sinus which you also have  25 activity there as well and how that compares to what  26 you would see in say a rat or other organisms.</p>	<p style="text-align: right;">Page 85</p> <p>1 to see.  2 In terms of the femtomoles per milligram  3 of protein and making comparisons with what happens in  4 other species is that you also need to recognize, and  5 you do, for the gonadal tissue that you're looking at  6 an oviparous species, so the relative amount of tissue  7 that is actually going to be the stereogenic tissue in  8 an ovary of an oviparous species is much lower than it  9 is in, you know, a mammal for example.  10 So I suspect that those are some of the  11 reasons why there may be species differences but I  12 think that I'm confident that the values that were  13 reported for amphibians were, you know, appropriate  14 with what's seen in the literature.  15 MR. OSMER: Mr. Chairman, Alan Osmer.  16 DR. HEERINGA: Yes, Mr. Osmer.  17 MR. OSMER: If there is additional  18 interest in Atrazine and aromatase I would like to ask  19 Doctor Jim Simkins to come to the table.  20 DR. HEERINGA: Let me turn to the panel.  21 I guess I want to make sure that we proceed through the  22 question period here within the allocated time.  23 Panel members, are there any other  24 questions? Doctor Isom, you had a question regarding  25 the aromatase?</p>

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1 DR. ISOM: Well, Doctor Solomon, I'd just  
2 like to revisit your slide 29 and 30 and perhaps you  
3 could explain part of it in a little more detail than  
4 the conclusions on the slides. So that would 29.  
5 DR. SOLOMON: Just give me a moment to  
6 get to that.  
7 DR. ISOM: The upper right on survival?  
8 DR. SOLOMON: Correct.  
9 DR. ISOM: It appears to me that at least  
10 on the 1 microgram per liter exposure you did see a  
11 reduction?  
12 DR. SOLOMON: Yes, there was a  
13 statistically significant decrease in survival there.  
14 And I guess under pressure of time, during the  
15 presentation this particular permit me to use other  
16 pointer so everybody can see it in this particular  
17 data set we had a significant difference at this  
18 concentration of exposure, that it did not show a  
19 concentration response which was what I was referring  
20 to down here.  
21 In some of the other studies there was  
22 no significance in terms of the treatments and there  
23 was also no significant concentration response.  
24 DR. ISOM: Okay. On the next slide, 30,  
25 again on the right side it seems that we do see some

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1 significance. And I think you said there were no  
2 significant differences?  
3 DR. SOLOMON: There was no significant  
4 difference on this side and there was no significant  
5 difference here either.  
6 You can see this rather high variance in  
7 the number of testicular ovarian follicles per frog.  
8 And I guess the other important message here was no  
9 concentration response.  
10 This paper by the way is accepted in  
11 Chemosphere and I believe a copy has been made  
12 available to the panel. It's just been accepted so it  
13 was not circulated prior to this meeting.  
14 DR. ISOM: In the upper right there's no  
15 indication of  
16 DR. SOLOMON: No.  
17 DR. ISOM: of variation in the  
18 DR. SOLOMON: No, we took in sequence out  
19 of the tanks a total of 40 frogs because the  
20 histological work up is quite intensive.  
21 So what I've just presented there is the  
22 number of frogs out of 40 that had testicular ovarian  
23 follicles in one or more of the testes. So I don't  
24 have any variance there.  
25 Obviously if you count individual

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1 follicles in testis you can get some idea of variance  
2 which is in the lower panel.  
3 DR. HEERINGA: Doctor Bailey?  
4 DR. BAILEY: Yeah, Ted Bailey. I'm  
5 interested in are those error bars coming up from the  
6 heights of those?  
7 DR. SOLOMON: Keith Solomon again, yes,  
8 these are standard errors of the mean.  
9 DR. BAILEY: And do standard errors of  
10 the mean depend on the treatment?  
11 DR. SOLOMON: Well, possibly. We did not  
12 actually look at that response.  
13 DR. BAILEY: I would have expected a pool  
14 there, I would have expected those bars to be the same  
15 across all treatments unless you had evidence of  
16 heterogeneity in your error turn.  
17 DR. SOLOMON: I will differ to  
18 statistical advice later on that if you don't mind.  
19 DR. HEERINGA: We, may we revisit that  
20 unless we're prepared at this point. We can revisit  
21 when we have a little more time.  
22 Doctor Denver, please.  
23 DR. DENVER: Bob Denver. I noticed in  
24 reading the papers on the aromatase activity that the  
25 assays were conducted at a temperature of 37 degrees

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1 and the frogs, *Xenopus laevis* has a thermal optimum  
2 that's around 25 degrees.  
3 So I wonder if you can comment on that?  
4 And also there were a couple of papers  
5 that were published this year by Fan and colleagues  
6 that looked at the affects of Atrazine on aromatase  
7 activity in these cancer cells and propose a mechanism  
8 whereby it might be interacting with a transcription  
9 factor SF-1 and you didn't mention this, so I'd just  
10 like to hear what you have to think about it.  
11 DR. SOLOMON: If I can, Keith Solomon  
12 again, those studies are actually addressed in the  
13 overview document, the Fan study and some of the other  
14 studies.  
15 In terms of temperature, as an appointed  
16 senior citizen to make the presentation I'll hand over  
17 to one of my younger compatriots if you don't mind.  
18 DR. HEERINGA: Absolutely. Mr. Osmer, if  
19 you'd like to comment.  
20 MR. OSMER: I don't know if I can answer  
21 that question directly in the sense that in part with  
22 the relatively low activity of aromatase in amphibians,  
23 some of the tests were done, or the tests were done at  
24 37 degrees.  
25 And these were done consistently across



<p style="text-align: right;">Page 90</p> <p>1 all treatment groups so that if there was a bias, the 2 bias would have been such that it was comparable across 3 treatment groups. 4 As those particular studies that you're 5 referring to were conducted in Doctor Gesey's 6 laboratory at Michigan State University, I'd like to 7 defer to trying to get some information about it from 8 Doctor Gesey as to whether he did a thorough evaluation 9 of responses at that range of temperature. 10 DR. GESEY: I'll just comment that given 11 the Q10 affects that, you know, temperature has on 12 enzyme activity, I would predict that the amphibian 13 enzymes would be very unstable at that temperature. 14 MR. OSMER: Mr. Chairman. 15 DR. HEERINGA: Mr. Osmer. 16 MR. OSMER: Alan Osmer, it does seem that 17 there is continued interest in aromatase. 18 DR. HEERINGA: Absolutely. 19 MR. OSMER: And if Doctor Simkins could 20 join us 21 DR. HEERINGA: He may. 22 MR. OSMER: I would appreciate it. 23 DR. HEERINGA: He may, yes, I agree. 24 Just to remind everybody too, we have probably 25 approximately 30 minutes additional for this. But,</p>	<p style="text-align: right;">Page 92</p> <p>1 So once again as Glen has pointed out, 2 looking or trying to determine a mechanism in mammals 3 for a response that doesn't exist doesn't make a great 4 deal of sense to us. 5 And those papers are all peer reviewed 6 and published. 7 With regard to the Fan observations, you 8 are correct, those studies are out there, they're 9 reported and he describes what he believes, that is in 10 the Fan papers is described a specific interaction of 11 Atrazine with SF-1 transcriptional factor, those 12 studies are being certainly reviewed. And secondly 13 there are now attempts to replicate those studies. 14 Beyond that I would just comment that 15 the affects of Atrazine on aromatase in vitro has been 16 seen now in three cell types. Two of them are 17 transformed cells, one is the transfected cell that Fan 18 and colleagues used. It has not been seen in five 19 other cell types that have been looked at. 20 The other observation I think is 21 interesting is, over the entire dose range of Atrazine 22 that's been tested, the magnitude of the aromatase 23 response appears to be about a twofold increase which I 24 find fairly remarkable in the lack of induction of 25 aromatase in those cell types that respond.</p>
<p style="text-align: right;">Page 91</p> <p>1 Doctor Simkins. 2 DR. SIMKINS: Jim Simkins. I'm a 3 Professor and Chair of the Department of Pharmacology 4 and Neuroscience, University of North Texas Science 5 Center. I am here on behalf of Syngenta. 6 With regard to two issues that came up, 7 one was cross species comparison, I certainly am not 8 qualified to talk about the aromatase assays in frogs, 9 but am in mammals. 10 We have done those kinds of assays and I 11 will report, or would like to point out to you that 12 Ralph Cooper's spent a great deal of effort looking at 13 the affects of aromatase, excuse me, of Atrazine on 14 aromatase activity in a variety of tissues using both 15 enzyme assays as well as message levels, and simply was 16 not able to find affects of dosing up to 21 days in 17 adult male rats at doses as high as 200 milligrams per 18 kilogram. 19 And because of that we've come to the 20 conclusion and that was looking at brain, adrenal, 21 liver and testes we concluded that Atrazine was not 22 affecting aromatase in animals. 23 And that's very consistent with a 24 variety of livelong exposures to Atrazine in which no 25 evidence of feminization of animals were seen.</p>	<p style="text-align: right;">Page 93</p> <p>1 We currently are working on the 2 hypothesis that the response seen in cell types that 3 are capable of steroidogenesis may be a rather 4 nonspecific response to the stress of Atrazine at or 5 exceeding its solubility limits. We know well, at in 6 the mammalian species that Atrazine is induced when 7 cells are under stress and we think that may be what's 8 being observed in some of those cell types. 9 DR. HEERINGA: Thank you, Doctor Simkins. 10 Doctor Schlenk I believe had another question. 11 DR. SCHLENK: Yeah, it just occurred to 12 me, I wonder why do people actually look at the gonadal 13 aromatase and not the CNS if there's greater CNS 14 activity? I mean it seems like all the studies that 15 I've seen have focused on the gonadal aromatase, at 16 least in this particular docket that we've seen. 17 Is there any relationship to the CNS 18 levels or is that not even part of the equation? I'm 19 just curious. 20 DR. SIMKINS: As to the relationship with 21 CNS levels we know that at least ovarian steroids 22 induce expression of brain aromatase. So there is a 23 connection. 24 When it has been looked at, and agin 25 I'll refer you to the Cooper papers, no affects of very</p>

<p style="text-align: right;">Page 94</p> <p>1 high doses of Atrazine. These are doses that cause  2 weight loss in rats. There was no affect on brain  3 aromatase activity.  4 So again it's asking questions about  5 mechanisms when no affect is seen.  6 DR. HEERINGA: Thank you, Doctor Simkins.  7 Doctor Van Der Kraak?  8 DR. VAN DER KRAAK: There were, Glen Van  9 Der Kraak, there were two papers that were published  10 that deal with aromatase message and this was a paper  11 by Parke, et al which described the methodology. And  12 there was a second paper by Ecker, et al that looked at  13 aromatase activity and that included evaluation in the  14 brain.  15 And while I don't have in front of me  16 the dose response relationship, as I recall there was  17 no affect of Atrazine on the induction of aromatase in  18 the message or expression, the messenger RNA  19 expression.  20 DR. HEERINGA: Doctor Chambers?  21 DR. CHAMBERS: Doctor Solomon, with  22 respect to the uptake in depuration studies that you  23 reported that appears to be for adults, has something  24 similar been done in tadpoles?  25 DR. SOLOMON: Just to clarify that, thank</p>	<p style="text-align: right;">Page 96</p> <p>1 difference, the hapla typing was done after, long after  2 the study had started at Wildlife International and  3 IGB. So we did not know that at the time.  4 But at the current time those animals  5 from the western Cape, the Cape sites are the source of  6 exports of Xenopus laevis from South Africa to the rest  7 of the world. And, but of course in cultures that have  8 been in existence for many years such as is true in  9 some laboratories, the actual provenance of those  10 cultures is uncertain at this time.  11 Although this does offer a mechanism to  12 ascertain what hapla type A might be.  13 MR. OSMER: Mr. Chairman, Alan Osmer,  14 could I  15 DR. HEERINGA: Yes.  16 MR. OSMER: add to that that while  17 those as Doctor Solomon said the hapla type, the  18 genetic knowledge of the frogs that were used in the  19 definitive studies was unknown at the time, and while  20 they may be less sensitive to testicular oocyte, they  21 certainly demonstrated sensitivity to feminization in  22 the presence of estradiol.  23 DR. HEERINGA: Thank you. At this point  24 I'd like, and we can return if there is another issue,  25 but I'd like to return to Doctor Van Der Kraak's</p>
<p style="text-align: right;">Page 95</p> <p>1 you, Keith Solomon, it was done in Stage 66 metamorphs.  2 We wanted to, or one of the questions we were  3 attempting to address there was not only the uptake in  4 depuration in a size of aquatic organism that was  5 reasonably easy to work with.  6 We also wanted to see if there was any  7 accumulation in specific tissue such as the gonads and  8 we needed to have animals that had at least  9 differentiated gonads at that point. So we went for  10 Stage 66. This was not adults.  11 DR. CHAMBERS: But still nothing in the  12 younger tadpoles then?  13 DR. SOLOMON: No, there was no, we didn't  14 do any work in the younger tadpoles.  15 DR. HEERINGA: Doctor Bucher?  16 DR. BUCHER: Doctor Solomon, it seems  17 like based on the work done to distinguish the two  18 populations of Xenopus and South Africa, the frogs that  19 were chosen for the Syngenta studies were those from a  20 lower background for testicular ovarian follicle  21 populations.  22 Is that correct and would that have a  23 did you think had any affect on the results?  24 DR. SOLOMON: I guess we can't both talk  25 at the same, I apologize. We actually did not know the</p>	<p style="text-align: right;">Page 97</p> <p>1 presentation specifically in terms of the description  2 of the experimental design, experimental outcomes and  3 statistical analysis of the two trials.  4 Members of the panel, yes, Doctor  5 Patino?  6 DR. PATINO: I had a question if you  7 could put your slide number 6, Doctor Van Der Kraak.  8 I thought there was an indication there  9 on the sensitive period?  10 DR. VAN DER KRAAK: Sorry, Doctor Patino,  11 this doesn't, I need to go to the slide show in order  12 to show that. Yes?  13 DR. PATINO: Yes, the question I had or  14 just a reaction or a comment, elicit a comment from you  15 is, according to that sensitive period the sensitive  16 stage or the period begins at Stage 42 of development  17 and the experimental design has the exposure starting a  18 little later than that somewhere between Stage 46 and  19 48 and I was just wondering if you had a comment on  20 that?  21 DR. VAN DER KRAAK: I do have a comment  22 on that and the, starting the experiment here in this  23 Stage 46 is well within that window for which one could  24 affect a 100 percent sex change, given the appropriate,  25 you know, concentrations.</p>

<p style="text-align: right;">Page 98</p> <p>1 In terms of how does this compare to the 2 exposures that have been done in other labs, this falls 3 right within what would be called the typical or normal 4 exposure period that's been reported in the literature. 5 So the study group, and they may wish to 6 comment more specifically on this, was well aware of 7 this range of time for the sensitive window and they 8 were confident that that was an appropriate to initiate 9 the exposure. 10 DR. PATINO: And so you would expect a 11 decline in sensitivity, say to a low dose as you wait 12 during that window and start later? 13 DR. VAN DER KRAAK: Yes, we would expect 14 that there would be a decline in sensitivity if we were 15 to have extended this to have the exposure start at a 16 later time interval. 17 And so if this declining component of 18 this graph that I'm showing with the pointer here is 19 saying that if you were to initiate the exposure here 20 at Stage 54 or 55, you would have got a zero sex 21 reversal. And if you were to start here you would have 22 proportional up to 100 percent sex reversal. 23 DR. PATINO: Okay, so to make sure I 24 understand, so if you start the exposure anywhere 25 between 42 and probably 51</p>	<p style="text-align: right;">Page 100</p> <p>1 origin of the distinction in influence of Atrazine on 2 growth to metamorphosis might be? 3 And I'd just be interested in what your 4 conclusion is with regard to the affect of Atrazine on 5 growth? 6 DR. VAN DER KRAAK: I'd like to make a 7 comment and then I'd like to also pass this to some of 8 the investigators. 9 In terms of the response to Atrazine I 10 would certainly say what these data show to me is that 11 the response is not a very robust one, in the sense 12 that the studies that were conducted at Wildlife 13 International showed no significant difference across 14 treatments over a very wide range of Atrazine 15 concentrations. 16 The response in terms of the snout-vent 17 length certainly in males did not show any significant 18 differences with the treatment. 19 There were these affects that were seen 20 in the Atrazine treated groups. And I guess that when 21 I looked at these, one of the aspects that was struck 22 by was how very tight the data points were. 23 And it occurred to me that I was having 24 difficulty trying to understand what in a biological 25 sense was a significant biological difference when some</p>
<p style="text-align: right;">Page 99</p> <p>1 DR. VAN DER KRAAK: 52. 2 DR. PATINO: it doesn't matter. I mean 3 the sensitivity doesn't decline? 4 DR. VAN DER KRAAK: That's correct. 5 DR. HEERINGA: Presumably there's a 6 Steve Heeringa presumably there's a distribution 7 underlying this figure 2 in terms of actual individual 8 exposure periods? 9 DR. VAN DER KRAAK: Yes, there would be a 10 distribution. This is a cumulative figure that was 11 prepared by Doctor Klaus who presented 12 DR. HEERINGA: Sure. 13 DR. VAN DER KRAAK: -- this at a recent 14 conference on, you know, on aspects of sexual 15 differentiation in amphibians. 16 DR. HEERINGA: Okay. Are there questions 17 yes, Doctor Skelley? 18 DR. SKELLEY: This is David Skelley. 19 Doctor Van Der Kraak, I wondered if you could show 20 your 21 slide number 20. 22 So it appears that your groups went to 23 great lengths to conduct virtually interchangeable 24 experiments in two locations. 25 And I have a two part question. First, I wondered if you could comment on what you think the</p>	<p style="text-align: right;">Page 101</p> <p>1 of these differences were measured in, you know, .1 or 2 .2 of a gram. And similarly, when you looked at 3 aspects of snout to vent length on the next slide they 4 were also incredibly narrow in terms of differences 5 that were in many cases much less than a millimeter, 6 very much less than a millimeter. 7 So I wonder personally whether these 8 magnitude of changes were ones that were, I would call, 9 you know, great responses and question their, if you 10 will, the global biological outcome that might result 11 from these changes. 12 That's not withstanding that there are 13 statistically significant differences within those 14 groups. 15 But perhaps, and if you'd like an 16 additional comment on that I could pass that to Doctor 17 Springer perhaps. 18 DR. HEERINGA: Doctor Skelley, are you 19 DR. SKELLEY: David Skelley, an 20 additional comment would be fine please. 21 DR. HEERINGA: Doctor Springer. 22 DR. SPRINGER: This is Tim Springer from 23 Wildlife International. My interpretation of those 24 figures is that there is probably a little bit of a 25 variation between the groups that shows up here in the</p>

<p style="text-align: right;">Page 102</p> <p>1 control group at IGB, it's a slight increase that 2 occurred by chance. 3 And because the control is high you see 4 that in comparison across all of the other groups, and 5 the reason that I, I believe that is because you don't 6 see that in the Wildlife International figure. 7 So if you consider that one group being 8 one that varies, then that's the way I've interpreted 9 those slides. 10 DR. HEERINGA: Doctor Skelley, please. 11 DR. SKELLEY: David Skelley, just one 12 follow up question, I want to make sure I got this 13 right. 14 The WLI control, you ended up with eight 15 containers. Is it the case that the IGB treatment 16 there is based on sixteen containers? 17 DR. SPRINGER: This is Tim Springer 18 again. Yes, you're absolutely correct. 19 DR. HEERINGA: Doctor LeBlanc. 20 DR. LEBLANC: Gerry LeBlanc for Doctor 21 Van Der Kraak. Just some clarification with respect to 22 experimental design. 23 If I understand correctly, each 24 treatment consisted of eight tanks divided into two 25 clusters.</p>	<p style="text-align: right;">Page 104</p> <p>1 studies, nor probably the outcomes here. 2 It was really the tight variability and 3 you got a little bit of statistical significance, but 4 not biological significance. That's not too 5 surprising. 6 We did look at the idea of the grouping 7 of four tanks together. This was something that we 8 raised at the time of the design and said, well, why 9 don't we have, you know, each tank separately. It just 10 really wasn't practically possible to manage a separate 11 pumping system for each of the individual tanks. 12 And we also looked at the issue of, 13 well, if you're going to have eight feeds for the same 14 concentration, the variability in getting those feeds 15 all the same is probably a greater danger than having 16 two sets. 17 We did nevertheless consider the 18 question of whether there would be an affect between 19 the two clusters, whether we needed to consider a 20 cluster affect. 21 We did test for those affects and only 22 on one occasion out of 160 tests did we find any 23 evidence at all of a cluster affect. So we did look 24 for one. We didn't find one. If there would have been 25 a cluster affect it would have tended to increase the</p>
<p style="text-align: right;">Page 103</p> <p>1 DR. VAN DER KRAAK: Yes. 2 DR. LEBLANC: Were the clusters 3 themselves treated as replicates in the analysis? 4 DR. VAN DER KRAAK: I have knowledge 5 about that but I would really like to pass that on to 6 Doctor Silken who has considered that very question and 7 he may be better positioned to give you a specific 8 answer to that question. 9 DR. HEERINGA: Doctor Silken. 10 DR. SILKEN: This is Robert Silken, I'm a 11 statistician with Silken &amp; Associates and we were 12 responsible for the statistical analyses of all four 13 aspects, the two gross and the two histo analyses. 14 With respect to the issue of the design 15 of the experiment, we did follow a robust design based 16 upon the estradiol studies and the earlier studies and 17 we did allow for sixteen control tanks just in case 18 anything should happen, and as it turns out it did 19 happen. 20 I heard Doctor Skelley ask a question 21 about whether this was due to the fact that IGB ended 22 up with sixteen controls and Wildlife International 23 ended up with only eight. The power of those two 24 studies is very comparable. The impact of going from 25 sixteen to eight did not affect the power of those</p>	<p style="text-align: right;">Page 105</p> <p>1 false positive rate and hence increase our chance of 2 finding differences. 3 DR. LEBLANC: So just a clarification, 4 typically when we're looking at statistical 5 significance, tanks are the replicates, not the 6 clusters, is that correct? 7 DR. SILKEN: Yes, throughout this 8 analysis for Atrazine the tank was always the unit of 9 observation. When there was extreme feminization which 10 only occurred in the E2 portion, estradiol portion, for 11 males there was only a very few males for the E2 12 treated tanks. Then we had to fall back to individual 13 frog levels. 14 But everywhere else, and including all 15 the Atrazine, it was all done at the tank level. 16 DR. LEBLANC: And I would go back to 17 Doctor Van Der Kraak. Three of the clusters in one of 18 the experiments was eliminated at some point in the 19 course of the experiment due to problems. 20 And my question is, were they eliminated 21 during the experiment or were they taken to completion 22 and then the decision was made to not include them? 23 DR. VAN DER KRAAK: Glen Van Der Kraak, 24 there were two clusters that were removed and one 25 individual tank.</p>



<p style="text-align: right;">Page 106</p> <p>1 DR. LEBLANC: Okay, so could you clarify</p> <p>2 which clusters and which individual tanks?</p> <p>3 DR. VAN DER KRAAK: On the slide, this</p> <p>4 cluster was removed and this cluster was removed. And</p> <p>5 DR. LEBLANC: Okay.</p> <p>6 DR. VAN DER KRAAK: and it's tank</p> <p>7 number 6 in this situation here that was removed.</p> <p>8 DR. LEBLANC: Okay. And these were never</p> <p>9 taken to completion?</p> <p>10 DR. VAN DER KRAAK: I'll let Alan respond</p> <p>11 to that please.</p> <p>12 MR. OSMER: And I was going to ask Doctor</p> <p>13 Springer, who was the principal investigator at that</p> <p>14 lab to respond.</p> <p>15 DR. HEERINGA: Doctor Springer.</p> <p>16 DR. SPRINGER: This is Tim Springer. The</p> <p>17 control tank cluster to the left and also the well,</p> <p>18 the two control tank clusters, the animals from those</p> <p>19 were actually processed and taken through histology and</p> <p>20 the information from those is available, okay?</p> <p>21 The control tank, or rather the tank</p> <p>22 from the 1 microgram per liter Atrazine group was</p> <p>23 terminated at the time that that bloom was observed in</p> <p>24 that. We just terminated it immediately at that point.</p> <p>25 We decided to keep those frogs in the</p>	<p style="text-align: right;">Page 108</p> <p>1 cluster of four tanks that has the microbial bloom, is</p> <p>2 that correct?</p> <p>3 DR. SPRINGER: Initially the bloom showed</p> <p>4 up in the tank number 6 in the 1 microgram per liter</p> <p>5 Atrazine group, that tank was terminated. And in a</p> <p>6 couple of days it showed up in the control 2 cluster</p> <p>7 that's circled there.</p> <p>8 And so those five tanks were affected by</p> <p>9 it. It wasn't seen in any of the other tanks.</p> <p>10 DR. BAILEY: It seems like the tanks are</p> <p>11 not acting independently, I mean as a cluster they were</p> <p>12 taken out of the study? Not independent tanks around</p> <p>13 the room?</p> <p>14 DR. SPRINGER: You are correct, the</p> <p>15 observation was that that cluster of tanks, notice what</p> <p>16 we did for example, in the 1 microgram per liter tank</p> <p>17 it was detected because we walked into the room and the</p> <p>18 tank was cloudy, so it was obvious what was going on.</p> <p>19 DR. BAILEY: Thank you.</p> <p>20 DR. HEERINGA: Yes, Doctor Yeater.</p> <p>21 DR. YEATER: This is Kathy Yeater. I</p> <p>22 think my question probably applies to Doctor Silken as</p> <p>23 far as the choice of statistical analysis of the data.</p> <p>24 I was wondering if you could comment on</p> <p>25 the use of age to metamorphosis as a continuous</p>
<p style="text-align: right;">Page 107</p> <p>1 process flow at that time, but we decided at that time</p> <p>2 that they would not be used in the value or excuse</p> <p>3 me, the statistical evaluation. So the decision to</p> <p>4 exclude them from the statistical evaluation was made</p> <p>5 when we discovered in the case of the control 2 tank</p> <p>6 that's circled, when we discovered the bloom in those</p> <p>7 we had to treat them differently and try to clean them</p> <p>8 up to try to stop the bloom.</p> <p>9 So at that point they were no longer</p> <p>10 comparable and we made the decision at that time to</p> <p>11 exclude them from statistical analysis. But, we were</p> <p>12 afraid to not take the animals through because</p> <p>13 questions could come up about, well, what about those</p> <p>14 animals, you know?</p> <p>15 So if you look in the report the raw</p> <p>16 data is there but they're not included in the</p> <p>17 statistical analysis.</p> <p>18 DR. LEBLANC: Thank you.</p> <p>19 DR. HEERINGA: Before we turn to Doctor</p> <p>20 Bailey, just a comment, my plan is to continue this</p> <p>21 discussion until a logical break for out noon lunch and</p> <p>22 then return to public comment, starting with the next</p> <p>23 public commenter after lunch.</p> <p>24 So Doctor Bailey please.</p> <p>25 DR. BAILEY: Ted Bailey. It was a</p>	<p style="text-align: right;">Page 109</p> <p>1 variable as opposed to using it as a time to event</p> <p>2 response and perhaps applying, and being able to use</p> <p>3 the time dependent variable such as the snout length</p> <p>4 and body weight that were also recorded at the time of</p> <p>5 metamorphosis in terms of Kaplan-Meier estimation</p> <p>6 which</p> <p>7 would be more commonly used in the survival analysis,</p> <p>8 but it can still be used for a time to event data.</p> <p>9 DR. SILKEN: This is Doctor Silken. Yes,</p> <p>10 well it's true the Kaplan-Meier is a standard procedure</p> <p>11 for analyzing a time to response event.</p> <p>12 Here we did not of course a timed series</p> <p>13 of body weights or snout to vent length. We really</p> <p>14 only had one observation and not a timed series for</p> <p>15 those.</p> <p>16 The only thing that we did have was one</p> <p>17 observation on the time to metamorphosis that a</p> <p>18 continuous variable as you point out, and it was</p> <p>19 treated in an analysis of variance context.</p> <p>20 DR. YEATER: And so the body weights and</p> <p>21 measurements, were those taken at metamorphosis or at</p> <p>22 the end of the time frame of the study? Anyone?</p> <p>23 MR. OSMER: This is Alan Osmer. All</p> <p>24 measurements of the frogs were taken at Stage 66, at</p> <p>25 termination of the individual frog.</p> <p>DR. SILKEN: This is Doctor Silken, let</p>

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1 me add on to my earlier comment.  
 2 We were also working with the tanks  
 3 means, so we had tank means for age too, time to  
 4 metamorphosis, or age at metamorphosis, so that was a  
 5 tank means.  
 6 DR. HEERINGA: Doctor Chambers.  
 7 DR. CHAMBERS: Jan Chambers, I have two  
 8 questions.  
 9 One is, was the same batch or lot number  
 10 of Atrazine used throughout the entire experiment and  
 11 at both locations?  
 12 MR. OSMER: This is Alan Osmer. Yes, the  
 13 answer is yes for Atrazine, estradiol and any other  
 14 parameter that we could harmonize between the two.  
 15 DR. CHAMBERS: And the second question to  
 16 clarify, each of the four tanks in a cluster received  
 17 the same solution out of the mixing tank, is that  
 18 correct, so they were all the same water?  
 19 MR. OSMER: Alan Osmer again. That is  
 20 correct. For each of the treatments there one stock  
 21 solution that was then fed to a pump, went into a  
 22 mixing cup that fed the four tanks in that cluster.  
 23 DR. HEERINGA: Steve Heeringa. A  
 24 question maybe to Doctor Silken or Doctor Springer or  
 25 Doctor Lutz with regard to the frogs themselves. There

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1 were a number of breeding pairs, I want to say sixteen.  
 2 How were they allocated to sites and  
 3 then to tanks within, in terms of their prodigy, in  
 4 terms of the tanks within sites?  
 5 MR. OSMER: This is Alan Osmer, let me  
 6 begin an answer and then ask others to expand upon it.  
 7 All of the frogs originated in Michigan,  
 8 Xenopus One.  
 9 DR. HEERINGA: About twelve miles from my  
 10 home.  
 11 MR. OSMER: They were approximately ten  
 12 breeding paid from that source. They were not the same  
 13 pairs that went to Germany and Maryland. They were,  
 14 many thousand were spawned and held at Xenopus One  
 15 for  
 16 a period of five days perhaps and then shipped.  
 17 And so they were essentially randomized  
 18 at the supplier but the different spawn were kind of  
 19 randomly mixed and then shipped.  
 20 DR. HEERINGA: So the spawn of the  
 21 breeding pairs were randomized, there were different  
 22 breeding pairs that were used at both sites, but the  
 23 spawn was randomized within the site across tanks as  
 24 best could be done?  
 25 MR. OSMER: Correct, yes. There was no  
 process to try to randomize them but just in the

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1 procedure I think they were fairly random.  
 2 DR. SPRINGER: I think there were  
 3 different levels of randomization that occurred. At  
 4 Xenopus One they had their own procedures which, you  
 5 know, I don't know the details of, but once they  
 6 arrived at our laboratory, when they were allocated to  
 7 tanks there was a randomization procedure occurring at  
 8 that point in time too, which I can describe if you  
 9 like.  
 10 DR. HEERINGA: I think the comment that  
 11 I'll make, it appears that at least to the best of the  
 12 ability there was no specific co-occurrence of breeding  
 13 pairs with individual tanks or individual treatments.  
 14 I figured that was the case but I just wanted to hear  
 15 that.  
 16 Doctor Schlenk.  
 17 DR. SCHLENK: Yeah, Dan Schlenk. This is  
 18 actually a twofold question.  
 19 The first relates I think to one of the  
 20 biological aspects and the second relates more to the  
 21 exposure chemistry, so I think there was somebody that  
 22 you wanted to bring in with the analytical aspects.  
 23 But first of all I'll deal with the  
 24 biological aspects. I notice in the report that was  
 25 given to us that there, an affect was noted in males at

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1 the point 1 dose as gonadal hypoplasia and it was only  
 2 seen at the WFI site if my notes are correct.  
 3 And I was just curious, the reason why  
 4 that was not considered significant was because it was  
 5 only seen at one location and not the other, would that  
 6 be fair I guess?  
 7 MR. OSMER: Maybe I could make sort of a  
 8 general comment on  
 9 some of these other morphological features and  
 10 DR. SCHLENK: Sure.  
 11 MR. OSMER: and what the motivation  
 12 was.  
 13 The EPA's white paper and the SAP's  
 14 recommendations in 2003 were to examine the, what were  
 15 referred to as apical end points, so sex ratio, inter-  
 16 sex, mixed sex, the more overt findings.  
 17 The team met and decided that to be all  
 18 inclusive, that if we were going in we would look for  
 19 any and all morphological attributes that might be  
 20 associated with estrogenic affects or Atrazine. And  
 21 that is a question that I've had posed to me from the  
 22 Syngenta folks for a long time, why are you looking  
 23 there?  
 24 So it is the, our motivation was  
 25 scientific in nature.

<p style="text-align: right;">Page 114</p> <p>1 And then I think over the course of the</p> <p>2 study we were reevaluating the significance or lack of</p> <p>3 significance of those other findings.</p> <p>4 And I guess with that I might ask Jeff</p> <p>5 Wolfe to comment on his perception of some of the</p> <p>6 secondary end points. And then I believe the other</p> <p>7 question was really more to the statistical</p> <p>8 significance of it.</p> <p>9 DR. SCHLENK: No, the chemistry, but</p> <p>10 that's</p> <p>11 MR. OSMER: Okay, I will take that.</p> <p>12 DR. SCHLENK: Yeah.</p> <p>13 DR. HEERINGA: Doctor Wolfe.</p> <p>14 DR. WOLFE: This is Jeff Wolfe, EPL out</p> <p>15 of Sterling, Virginia, I'm the study pathologist.</p> <p>16 When I was asked to actually perform the</p> <p>17 histopathological evaluation of this study, I did not</p> <p>18 limit myself to any specific end points, even though we</p> <p>19 were aware of what those apical or primary end points</p> <p>20 were. I was not, I did not feel it appropriate and I</p> <p>21 was not asked by Syngenta to limit myself to only a few</p> <p>22 end points.</p> <p>23 So I was looking for any possible</p> <p>24 abnormality that I could find.</p> <p>25 Now, I'm not sure whether you were</p>	<p style="text-align: right;">Page 116</p> <p>1 gonadal hypoplasia, if that was something that was</p> <p>2 biologically significant or not and maybe that was why</p> <p>3 is was not included, or not, you know, highlighted as</p> <p>4 an affect. And that wasn't an Atrazine treatment, it</p> <p>5 was in the .1 treatment.</p> <p>6 And the second question I had was</p> <p>7 related to the chemistry. If you want to go to slide</p> <p>8 15 on Glen's presentation. So the table that I have,</p> <p>9 at least in the report that I was given doesn't have</p> <p>10 the actual amounts that are listed as far as the</p> <p>11 concentrations, particularly in the two lower doses.</p> <p>12 And what I have in the report is a graph</p> <p>13 that shows the percent nominal verus the study days.</p> <p>14 And one of the things I found when I was going through</p> <p>15 this, and this relates more to study question 4 I think</p> <p>16 we'll get to during the week, was the exposure regime</p> <p>17 and whether or not the concentrations were hitting the</p> <p>18 mark as far as nominal versus measured.</p> <p>19 And one of the things that was shown in</p> <p>20 the report that was given was that if it was, I think</p> <p>21 your LOQ was 10 nanograms per liter at .01 which is</p> <p>22 your low dose. Is that correct?</p> <p>23 MR. OSMER: Yeah, that is correct.</p> <p>24 DR. SCHLENK: Yeah.</p> <p>25 MR. OSMER: This is Alan Osmer.</p>
<p style="text-align: right;">Page 115</p> <p>1 referring the gross finding of segmental hypoplasia or</p> <p>2 the histological finding of segmental hypoplasia.</p> <p>3 DR. SCHLENK: It's table 7 on the report,</p> <p>4 whatever that is.</p> <p>5 DR. WOLFE: Well just one comment I will</p> <p>6 make as I think it was stated before, that we</p> <p>7 considered a priority, the histopathological assessment</p> <p>8 to be the gold standard. As in most toxicological</p> <p>9 bioassays, the gross observations were more in terms of</p> <p>10 pointing out places to look in terms of</p> <p>11 histopathological evaluation.</p> <p>12 And we did try to correlate all of the</p> <p>13 gross findings, or not correlate, but associate the</p> <p>14 gross findings with a histological diagnosis whenever I</p> <p>15 could.</p> <p>16 So the biological relevance of some of</p> <p>17 these other findings such as segmental hypoplasia is</p> <p>18 really not very well known, not very well characterized</p> <p>19 and I think the important thing in my estimation is the</p> <p>20 fact that we had certain primary end points and</p> <p>21 secondary end points that were positive in the</p> <p>22 estradiol treated animals, and we just did not see any</p> <p>23 of that in the Atrazine treated animals.</p> <p>24 DR. SCHLENK: Yeah, I just, not being a</p> <p>25 pathologist I just wonder what the relevance was of</p>	<p style="text-align: right;">Page 117</p> <p>1 DR. SCHLENK: Yeah, and then your level</p> <p>2 of detection is half of that, basically it's .005?</p> <p>3 MR. OSMER: Correct.</p> <p>4 DR. SCHLENK: So, and anything that was</p> <p>5 below that was considered 50 percent?</p> <p>6 MR. OSMER: If it was below the LOQ</p> <p>7 DR. SCHLENK: It was condiered 50</p> <p>8 percent.</p> <p>9 MR. OSMER: 50 percent of that.</p> <p>10 DR. SCHLENK: So when I went through the</p> <p>11 tables in the back to look at the actual amounts that</p> <p>12 were listed there was no measured value, it just had</p> <p>13 less than 10 nanograms per liter out of a majority</p> <p>14 actually of the water samples that were taken.</p> <p>15 So I'm just wondering, is the figure</p> <p>16 here actually the one on the left or right, are those</p> <p>17 actual values then that were because that was, none</p> <p>18 of those actual values were actually in the report that</p> <p>19 I saw? They were all considered less than the ten.</p> <p>20 MR. OSMER: That is, I believe that is</p> <p>21 correct and I believe this figure was, because of the</p> <p>22 software used we were creating values to plot on there.</p> <p>23 But the information in the report is correct.</p> <p>24 DR. SCHLENK: Okay, so if it's just so</p> <p>25 that I know, the, so these values then, because if 5 is</p>

<p style="text-align: right;">Page 118</p> <p>1 your MDL then you basically are above 50 percent on a  2 lot of these then roughly? Because if that's 5 that  3 would be half of that but does that make sense? Do you  4 see what I'm saying?  5 MR. OSMER: I think I, I think I do but I  6 guess at this point I should try to have a chemist come  7 up here and give you the correct answer.  8 DR. SCHLENK: Well the point is, is that,  9 and if you look at the table that was presented, I  10 think it's the next slide maybe, if you go to the next  11 slide, that basically you're only getting 50 percent at  12 the IGB site which by the way is not where you didn't  13 see the hypoplasia by the way, so that's kind of the  14 relationship between the two, you're only seeing 50  15 percent of your official critical window mean.  16 Now that percentage is based on an  17 arbitrary number, so you don't really know that that's  18 not 50 percent of .01, that would be .09, .08, .07,  19 right? Or it could be .01 or .02, .03, right? Because  20 that's my, that's my question because in the table, if  21 you go through the actual tabular things, and maybe I  22 can show you this, you know, in the break or something,  23 in the tabular break it only shows less than ten, it  24 doesn't give you an actual number.  25 MR. OSMER: Uh-huh (nodding)</p>	<p style="text-align: right;">Page 120</p> <p>1 otherwise if we can take the time outside to work it  2 out maybe Dan can speak with him and we can come back  3 to the full group with the result.  4 MR. OSMER: Okay, we'll do that, we'll  5 work this out and bring it back to you.  6 DR. HEERINGA: I think that's to  7 everybody's benefit because then the question is  8 clearly understood and the response is clearly  9 understood too.  10 MR. OSMER: Yeah, that's fine, thank you.  11 DR. HEERINGA: Okay, panel members, Mr.  12 Pauli, you had a question before?  13 MR. PAULI: I was actually, I was going  14 to go back to something that Doctor Bucher it's Bruce  15 Puali, Environment Canada we heard something that, I  16 don't know if we have time for it, something that  17 struck me during Doctor Van Der Kraak's talk was that  18 there was no differential cell counts done in the  19 gonads because of the immaturity of Stage 66 of Xenopus  20 laevis gonads.  21 I have wondered, maybe with Doctor Wolfe  22 here, if he might care to comment on whether or not he  23 feels that might influence the overall judging of  24 developmental abnormalities? If they're not  25 differentiated at 66, would there be an advantage to</p>
<p style="text-align: right;">Page 119</p> <p>1 affirmatively).  2 DR. SCHLENK: And, you know, is it less  3 than 10, is it 9, is it 8, is it 7 or is it 1 or 2?  4 Because, do you understand what I'm saying? I mean  5 because it could be less than your LOD but not less  6 than your LOQ.  7 MR. OSMER: I do understand the question  8 and I think there's an easy answer if I could ask  9 Robert Yokeley to quickly join, just to  10 DR. HEERINGA: Okay.  11 MR. OSMER: clarify this.  12 DR. HEERINGA: The plan, I wanted to  13 amend my statement before. We will go until 12 o'clock  14 on this discussion. We can revisit some of these  15 points but I want to get in another public commenter  16 who is unable to be here later. So if you would like  17 to do that, otherwise I know there are other questions  18 on the panel, please go ahead though.  19 MR. OSMER: Okay, then I would  20 DR. HEERINGA: If it's just a matter of  21 computation I'd rather have it worked out and then  22 brought back to us for a statement.  23 MR. OSMER: That's fine, that's what  24 we'll do.  25 DR. HEERINGA: If it's very clear,</p>	<p style="text-align: right;">Page 121</p> <p>1 take some older animals and look for affects?  2 DR. WOLFE: Yeah, this is Jeff Wolfe  3 again. You are correct in that at Stage 66 the testis  4 essentially is comprised of, the germ cell population  5 is primordial germ cells and spermatagonia which really  6 are very difficult to even differentiate  7 histologically. And in the ovary there are primordial  8 germ cells and oogonia and in occasional animals you'll  9 see some oocyte, so it's correct that at Stage 66 it  10 would be and this is really one of the challenge  11 questions to come up it would be impractical and  12 probably of very little value to do any type of  13 differential type of counting.  14 I have actually done myself,  15 differential counting of germ cells in fish and adult  16 animals, in fact in minnows and it probably would be  17 more appropriate for adult animals.  18 MR. PAULI: Bruce Pauli, Environment  19 Canada, would that influence then do you think your  20 ability to identify TOF's?  21 DR. WOLFE: Back to me again? This is  22 Jeff Wolfe again. I think there might be a little bit  23 of sometimes a confusion between mixes sex and  24 testicular, TOF's, or testicular oocytes.  25 My interpretation, and this is not easy</p>



<p style="text-align: right;">Page 122</p> <p>1 to find in the literature anywhere, is that a lot of  2 the difference between whether you find mixed sex in  3 testicular oocytes is one of age or stage of gonadal  4 development.  5 In younger animals you're more likely I  6 believe to find mixed sex whereas in older animals  7 you're more likely to see testicular oocytes.  8 Now when I'm talking about older, I'm  9 not talking so much about relative to stage of  10 metamorphosis, I'm talking about chronological age and  11 reproductive age, because that seems to be a little bit  12 unhinged from metamorphosis and that's been shown in  13 previous literature and also in some of our early  14 estradiol work.  15 Does that answer your question?  16 MR. PAULI: Yeah, I think it does. I  17 think Doctor Solomon wants to jump in.  18 DR. SOLOMON: We did, Ernest Smith did a  19 study in South Africa where he looked at adults and  20 testicular cell types in reference and Atrazine exposed  21 sites, and found no difference between them in adults.  22 So Paul, that is published in the literature.  23 DR. WOLFE: There is one more thing I can  24 add. We did, even though we didn't do differential  25 cell counting per se, we did some semi-quantitative</p>	<p style="text-align: right;">Page 124</p> <p>1 I'd like to invite our second public commenter to the  2 podium, and that is Doctor Jennifer Sass who is here on  3 behalf of the Natural Resources Defense Council.  4 Doctor Sass, please. Doctor Sass has  5 requested twenty minutes and please take that twenty  6 minutes. Whatever you need. Doctor Sass has prepared  7 written comments for the panel. They've been  8 distributed to the panel and they will be part of the  9 docket as will all public comments from this session.  10 DR. SASS: Thank you, Doctor Heeringa.  11 And thanks for accommodating me. I am going to be  12 rapid but my written comments should be distributed and  13 they're more complete.  14 I'm Jennifer Sass, I'm a senior  15 scientist with the Natural Resources Defense Council,  16 which is an environmental nonprofit. I'm a senior  17 scientist in the health program and I'm based here in  18 Washington.  19 First of all, in summary, just to let  20 you know, the reason why this meeting is happening is  21 because after the '03 Scientific Advisory Panel, NRDC  22 negotiated with EPA to have a re-review of this issue  23 along with the cancer issue related to Atrazine when  24 more data was available and when a full and informed  25 review would be possible.</p>
<p style="text-align: right;">Page 123</p> <p>1 work.  2 So for example in the females where I  3 could differentiate between animals that had just  4 oögonia and animals that had oögonia and perinuclear  5 phase oocytes we did actually separate those two groups  6 out and look at those.  7 So there was some semi-quantitative  8 analysis done.  9 We also did semi-quantitative analysis  10 of germ cell density in both males and females which I  11 think was a lot more practical than doing differential  12 cell counting in this case.  13 DR. HEERINGA: Thank you, Doctor Wolfe.  14 At this point what I'd like to do is to  15 bring this period of the public comment to a close. We  16 can revisit questions that arise from the panel with  17 the Syngenta group during the public comment period if  18 they come up.  19 I want to make sure we have a full  20 discussion of all these issues and that the panel  21 members have all of their questions answered. But I  22 also want to keep the flow too of the public comment  23 period.  24 So at this point in time I'd like to  25 thank the public commenters representing Syngenta and</p>	<p style="text-align: right;">Page 125</p> <p>1 So what happened in the intervening  2 three years is the studies that you're going to look at  3 now.  4 Unfortunately we are extremely  5 disappointed that EPA chose to narrow the charge  6 questions so severely. And not only that, but to limit  7 the studies that are presented to you so severely that  8 you're asked to provide expert advice on a very narrow  9 charge question which is the affect of Atrazine on  10 gonads in amphibians during development.  11 The question that we had wanted looked  12 at, which is a more regulatory relevant question is  13 data pertaining to Atrazine impacts on wildlife and  14 human health, particularly its potential affects on  15 endocrine destruction.  16 That was the issue that was left over in  17 '03 and that's the issue that essentially EPA would be  18 informed on in order to regulate Atrazine better  19 according to its environmental statutes, to protect  20 human health and the environment.  21 EPA is not statutorily authorized to  22 protect gonads in amphibians from Atrazine during  23 development specifically.  24 And some of the authorities that EPA  25 uses to regulate pesticides that are relevant here are</p>

<p style="text-align: right;">Page 126</p> <p>1 listed on the back of my comments.  2 So in summary, NRDC would look forward  3 to a fair and complete review of all the available  4 literature, with greatest consideration given to those  5 studies that are robust and well designed and  6 preferably published in the peer reviewed literature.  7 We're disappointed by the narrow task that has been  8 assigned to the experts of this panel.  9 NRDC also asks EPA that all scientific  10 data relevant to Atrazine as an endocrine disruptor be  11 evaluated, including mammalian, aquatic and mechanistic  12 studies. And again, we're disappointed that the  13 experts have been hamstrung by the arbitrarily narrow  14 charge.  15 NRDC asks the Scientific Advisory Panel  16 to either consider providing broader and more relevant  17 advice to EPA or to ask EPA to convene a meeting in the  18 future when it can answer a question that's more  19 relevant to the regulation of Atrazine so as to protect  20 wildlife and human health.  21 And in particular, to go to NRDC's  22 response to the charge questions, which is how I've  23 laid out my comments so hopefully it will be easy for  24 you read when you skim it in your spare time, I know  25 you have a lot to look at.</p>	<p style="text-align: right;">Page 128</p> <p>1 you've already heard, even going so far as to inspect  2 the lab according to the white paper that actually  3 conducted the histological analysis as we've heard here  4 today.  5 So the idea that EPA is unable to get  6 the information it needs in order to make a clear  7 evaluation from all the other authors of all the other  8 studies, because somehow it can't pick up the phone and  9 talk to them, but in this particular study they were  10 able to work so closely with the authors in order to  11 get the information they needed, to me represents not  12 only a glaring inconsistency, but I think biases the  13 Agency towards unfairly considering what ends up being  14 one study set which EPA then uses to hinge its  15 conclusions on for the white paper.  16 Another charge question you're asked to  17 look at is how EPA considered the open literature  18 studies.  19 For this I am responding that EPA failed  20 to consider many studies in the open literature that  21 would have been relevant to a broader and more  22 important question.  23 For example, EPA failed to include  24 scientific evidence of neuroendocrine effects in  25 amphibians associated with Atrazine. And I list some</p>
<p style="text-align: right;">Page 127</p> <p>1 Most relevant I think is what I consider  2 to be a really glaring inconsistency in the way that  3 EPA has developed criteria for evaluation, not a priori  4 but in fact a posteriori to the studies. And then  5 secondarily apply those criteria in its white paper.  6 So I'm only going to pick on one for  7 these oral comments, but I have a few more in my  8 written comments, which is that there are numerous  9 occasions, and I, I think reference a table in the  10 white paper on page 35 where EPA says that it was  11 unable to determine or that there was not enough  12 information provided in the report or that the report  13 was not clear enough to somehow get the information  14 that it needed to evaluate all of the other studies,  15 except for the WLI/IGB studies, what it's calling the,  16 what it had from the data call in in the last three  17 years.  18 For that study, I'm going to call it one  19 because it was two labs but they coordinated together,  20 for that study EPA actually worked very closely with  21 the labs during the study, while it was being carried  22 out. And the white paper says they conducted  23 inspections of each of the laboratories, including  24 extensive review of the raw data, collection sheets and  25 data summary tables by AWEEKA and OPP personnel as</p>	<p style="text-align: right;">Page 129</p> <p>1 of those studies in my written comments.  2 EPA also failed to include scientific  3 studies of long term or pertinent effects resulting  4 from amphibians associated with Atrazine when they were  5 exposed during early life stages. And that would the  6 kinds of effects that would impact later life outcomes,  7 including susceptibility to subsequent infection. And  8 again in my written comments I list some of those  9 studies.  10 EPA also failed to consider scientific  11 evidence of nonlinear or nonmonotonic relationships.  12 This is disastrous when one is considering an endocrine  13 disruptor like Atrazine and again unfairly biases  14 towards studies that fail to find an affect. And I  15 list a number of studies in my written comments that  16 are relevant to this issue, including some that are  17 published by the registrant as well.  18 The severe limits placed on the SAP  19 review are likely to bias the outcome in my opinion.  20 EPA's scientific review failed to include studies that  21 demonstrate adverse endocrine effects of Atrazine in  22 mammals and evidence of hormone disruption activity in  23 amphibians and reports of destructive normal  24 progression of sexual development in rats. And I list  25 a number of those in my public comments, effects on</p>

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1 delayed puberty, effects on sperm count and motility,  
2 effects on testosterone production. And some of those  
3 are strain specific as you may know from the  
4 literature. And some of those are timing specific.  
5 But they're all relevant when wildlife and humans may  
6 be exposed.  
7 In my final point as far as the  
8 published literature goes is that EPA failed to  
9 consider evidence of impacts of mixtures and co-  
10 contaminants on Atrazine. This is sort of a failure of  
11 the regulatory system in general, but it is not a  
12 failure that EPA needs to accept when it's regulating  
13 pesticides. There's a lot of published literature  
14 showing that the effects of multiple pesticides  
15 together may have more than additive effects. And in  
16 addition we have USGS data showing that streams are  
17 contaminated with more than one pesticide at any given  
18 time.  
19 So it's both relevant from an exposure  
20 perspective and from a toxicology perspective. And I  
21 list some of the information in my written comments.  
22 Concerning the data call in studies I  
23 have no specific comments on them at this time.  
24 And so finally we believe that the  
25 agency has intentionally and unfairly hamstrung the

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1 Scientific Advisory Panel by developing a series of  
2 charge questions that clumsily avoid asking relevant  
3 regulatory questions about whether or not Atrazine  
4 poses a risk to human health and wildlife, in  
5 particular through its activity as an endocrine  
6 disruptor.  
7 And NRDC asks the experts on this panel  
8 to move beyond this limited set of charge questions and  
9 request that a meeting be reconvened in the future to  
10 review the more relevant questions related to Atrazine  
11 as an endocrine disruptor and its potential impacts on  
12 wildlife and human health.  
13 Thank you.  
14 DR. HEERINGA: Thank you very much,  
15 Doctor Sass. Are there any questions from members of  
16 the panel for Doctor Sass?  
17 Doctor Isom.  
18 DR. ISOM: Doctor Sass, I was wondering  
19 if perhaps you could provide us with the full citations  
20 on those papers. They just list the names.  
21 DR. SASS: Would it be okay if I emailed  
22 those this afternoon to Joe Bailey and he could  
23 distribute them?  
24 DR. HEERINGA: That would be just fine.  
25 DR. SASS: Okay.

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1 DR. HEERINGA: I think throughout this  
2 three or four day period there are going to be pieces  
3 of information which will be requested and I think we  
4 would handle that way, that they would be supplied to  
5 Joe Bailey and they would be provided to the panel and  
6 put on the docket.  
7 DR. SASS: That's fine, thank you.  
8 DR. HEERINGA: Additional questions from  
9 the panel? Not seeing any at this point I'm going to  
10 thank Doctor Sass for her comments.  
11 And we are at 12 noon. I would like to  
12 call a break for an hour and fifteen minutes.  
13 Experience has shown that sixty minutes doesn't allow  
14 everybody to get back here.  
15 So let's plan to reconvene at 1:15 and  
16 we will continue with the period of public comment at  
17 that point in time.  
18 My intent would be to take that  
19 commenters who have registered with Joe Bailey first.  
20 We may return to additional questions from the panel  
21 for the Syngenta group because of the complexity of  
22 that presentation.  
23 But any other public commenters who have  
24 had an interest in making a short, five minutes or  
25 less, comment at this point, we encourage to please see

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1 Joe Bailey during the break to arrange to be added to  
2 the agenda.  
3 Thank you very much. See everyone at  
4 1:15. I'll tell you what, let's make it 1:20, you'll  
5 get a little extra time.  
6 (WHEREUPON, the morning session was adjourned.)  
7 DR. HEERINGA: I'd like to welcome  
8 everyone back to the  
9 afternoon session for the first day of our multi-day  
10 meeting of the FIFRA Science Advisory Panel on the  
11 topic of the Potential for Atrazine to Affect Amphibian  
12 Gonadal Development.  
13 We are in the middle of our public  
14 comment period for this meeting and we've heard this  
15 morning from representatives of Syngenta Crop  
16 Protection. Also from Jennifer Sass or the Natural  
17 Resources Defense Council.  
18 And we're ready now to move on to our  
19 third public commenter. And that would be Rebecca  
20 Adcock of the American Farm Bureau Federation.  
21 And Rebecca, are you here?  
22 MS. ADCOCK: Good afternoon and thank you  
23 to the members of the SAP here today. The members that  
24 I represent are glad that you're here and seeking the  
25 review and looking into these matters that are very

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1 important to farmers, to agriculture and to the  
 2 environment.  
 3 My name is Rebecca Adcock and I am the  
 4 Congressional Relations and Government Relations  
 5 Director for the American Farm Bureau and I'm here  
 6 today to speak to you on behalf of our members, farming  
 7 and otherwise who believe that the registration of  
 8 safety and understanding the environmental effects of  
 9 all pesticides and all the chemicals we use are very  
 10 important.  
 11 The American Farm Bureau Federation is  
 12 the nation's largest general farm organization. It  
 13 represents farm families across this country and for  
 14 Atrazine it's the most important herbicide used in soil  
 15 saving conservation tillage and non-till farming.  
 16 Farmers depend on the safe and effective use of  
 17 Atrazine to control weeds on about two-thirds of the  
 18 country's corn and soy acreage, and 90 percent of its  
 19 sugarcane.  
 20 Atrazine is effective against the  
 21 toughest weeds. It's cost effective and it improves  
 22 crop yields.  
 23 Benefits it achieves for an estimated  
 24 \$28 per acreage advantage over other herbicides and  
 25 that is an EPA quote.

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1 AFBF is pleased that for more than 12  
 2 years or review EPA has completed another milestone in  
 3 establishing the safety of this important crop  
 4 protection product. As a result of this most review  
 5 EPA has determined that Atrazine does not adversely  
 6 affect amphibian gonadal development and believes that  
 7 there is no compelling reason to pursue additional  
 8 testing of Atrazine for amphibian gonadal affects.  
 9 AFBF does recognize that uncertainties  
 10 were identified in 2003 by the EPA SAP and that a need  
 11 to examine both field and laboratory studies on the  
 12 purported affects of Atrazine on amphibians was needed.  
 13 Because of these uncertainties EPA did require that the  
 14 registrant, Syngenta, conduct these studies and test  
 15 the potential for Atrazine to affect amphibian  
 16 development.  
 17 EPA has now reviewed 19 laboratory and  
 18 field studies, including the registrant's studies and  
 19 the research available in the public literature. And  
 20 according to EPA only two studies, the two that you've  
 21 heard from, submitted by the registrant incorporated  
 22 all of the necessary design elements and fully  
 23 accounted for experimental and environmental conditions  
 24 that could influence the results.  
 25 These two identical studies were

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1 performed separately by independent laboratories with a  
 2 third laboratory doing the pathology evaluations. Both  
 3 showed that Atrazine does not have an affect on the  
 4 development of the sexual organs in frogs at ranges  
 5 from very high to very low.  
 6 AFBF believes that this objective  
 7 research clearly reinforces the safety and supports the  
 8 continued availability of Atrazine for American  
 9 farmers.  
 10 AFBF and our counterparts in the crop  
 11 protection industry support extensive thorough research  
 12 and testing of the products relied upon to protect the  
 13 world's food and fiber production.  
 14 However there are some people who are  
 15 still critical and continue to condemn studies that are  
 16 sponsored by anyone other than the government or  
 17 perhaps themselves.  
 18 Relevant to all stakeholders is the fact  
 19 that no federal rules or policies suggest or should  
 20 suggest or require that quality controlled objective  
 21 scientific work be ignored or given lesser weight based  
 22 solely on who may have paid for it.  
 23 The simple truth is, studies conducted  
 24 to support registration of pesticides must and should  
 25 meet the extremely stringent standards of GLP audits in

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1 submission for all raw data so that EPA can reconstruct  
 2 the study from the ground up.  
 3 Atrazine has undergone the most  
 4 extensive safety testing, both in time and volume, ever  
 5 conducted on an herbicide. Our farming members  
 6 appreciate and support EPA's extensive review and  
 7 continue to support the safety of Atrazine in crop  
 8 production.  
 9 Thank you.  
 10 DR. HEERINGA: Thank you very much,  
 11 Rebecca. Any questions of this particular public  
 12 comment? Not seeing any, I'd like to thank Rebecca for  
 13 her comments and invite up the next scheduled public  
 14 commenter and that is Scott Slaughter and he's  
 15 representing the Center for Regulatory Effectiveness.  
 16 Mr. Slaughter has submitted comments in  
 17 writing in advance and those will be posted on the  
 18 docket.  
 19 MR. SLAUGHTER: Hi, I'm Scott Slaughter  
 20 and I'm presenting the comments on behalf of the Center  
 21 for Regulatory Effectiveness and I want to thank you  
 22 for this opportunity. The mike's now on.  
 23 CRE agrees with EPA's recommendation  
 24 that the higher tiers of testing proposed in the 2003  
 25 white paper are not needed at this time that's a



<p style="text-align: right;">Page 138</p> <p>1 quote from EPA.  2 The data call in tests are dispositive,  3 Atrazine does not harm frogs.  4 CRE commented in the 2003 amphibian SAP  5 that there were no test for Atrazine gonadal affects  6 that were accurate, reliable and reproducible.  7 CRE recommended that EPA develop a valid  8 test before reaching a conclusion on this issue. EPA  9 and the SAP agreed with CRE. They rejected all prior  10 tests as unreliable and following guidance from the  11 2003 SAP, EPA and the Atrazine registrant developed a  12 new laboratory test that is accurate, reliable and  13 reproducible.  14 The DCI tests show, and I quote EPA, "no  15 affects of Atrazine on amphibian gonadal development".  16 We do not believe there is any need for EPA to explore  17 this issue further.  18 CRE does wish to comment on charge  19 question 8B which asks about the potential value of  20 having the gross morphology and histopathological  21 sections from studies published in the open literature,  22 to potentially be volunteered by the authors for a  23 pathologist's review.  24 CRE does not believe that any data  25 considered in this manner should be CRE believes that</p>	<p style="text-align: right;">Page 140</p> <p>1 MR. SLAUGHTER: Thank you.  2 DR. HEERINGA: Thank you very much. I  3 should also mention that Rebecca Adcock's written  4 comments are also available for panel members and will  5 be posted on the docket too later. I neglected to say  6 that before.  7 I'm consulting with Doctor Portier here.  8 Mr. Slaughter, you had introduced a few additional  9 comments on the I think charge question number 8 and  10 Doctor Portier was suggesting you may want to amend  11 your written comments to reflect that.  12 MR. SLAUGHTER: Okay, so you me to just  13 add it? Okay.  14 DR. HEERINGA: Just add that and send it  15 in to Joe Bailey. We appreciate it.  16 MR. SLAUGHTER: Can I send it tomorrow?  17 DR. HEERINGA: Anytime.  18 MR. SLAUGHTER: Thank you.  19 DR. HEERINGA: Thank you very much. Our  20 next public commenter is Doctor Richard Fossett who is  21 here on behalf of the Triazine Network. Doctor  22 Fossett.  23 (WHEREUPON, there was a discussion off the record.)  24 DR. FOSSETT: Sorry I took a little time.  25 My name is Richard Fossett with Fossett Consulting and</p>
<p style="text-align: right;">Page 139</p> <p>1 any data considered in this manner should be documented  2 with raw data and with regard to the chain of custody  3 and audited and verified by good laboratory practice  4 standards as have the DCI studies that you're reviewing  5 now.  6 Additionally, any study submitted for  7 this purpose, the open literature pathology review,  8 must meet the standards of the Information Quality Act  9 as does the DCI test which you're reviewing now.  10 CRE commends the 2003 SAP, EPA and the  11 registrant for their integrity, effort and commitment  12 to answering the questions of Atrazine's affects on  13 amphibians. The 2003 SAP and the DCI test developed  14 and performed pursuant to the 2003 SAP, are a model for  15 how government regulatory science should be conducted.  16 CRE is confident that this SAP will be  17 conducted in accordance with the same high ethical and  18 scientific standards.  19 Once again, thank you for the  20 opportunity to submit these comments and we thank the  21 members of this SAP and the members of the 2003 SAP  22 for  23 their service.  24 DR. HEERINGA: Thank you very much, Mr.  25 Slaughter. Comments or questions from the members of  the panel for Mr. Slaughter and his comments?</p>	<p style="text-align: right;">Page 141</p> <p>1 I am appearing on behalf of the Triazine Network. And  2 I appreciate the opportunity this afternoon to meet  3 with the panel and very briefly share some background  4 and perspectives on the use of Atrazine and some  5 changes the farmers have made in management to try to  6 reduce the chances of Atrazine entering surface and to  7 protect aquatic environments. Next slide please.  8 Atrazine remains the most widely used  9 corn and soy herbicide in the U.S. and it's the most  10 widely used herbicide because it provides farmers with  11 value, effective weed control at low cost. And that  12 effective weed control results in increased yields.  13 An analysis of 20 years of university  14 weed control trials across the midwest, almost 250  15 different trials, treatments that contained Atrazine  16 yielded on average 5.7 bushels per acre more than  17 comparable treatments of combinations of herbicides  18 that lacked Atrazine.  19 What's interesting is that in recent  20 years that yield benefit from Atrazine remained very  21 similar to what it was 10 or 15 or 20 years ago,  22 despite the introduction of many new compounds, many  23 of  24 those used in combination with Atrazine, there still is  25 that yield benefit.  One of the attributes of Atrazine is it</p>

<p style="text-align: right;">Page 142</p> <p>1 very much facilitates farmers in converting to what we  2 call conservation tillage where farmers make fewer  3 trips across the field to till and may make no tillage  4 at all in order to protect the soil from soil erosion  5 and to produce other environmental benefits.  6 Atrazine is used more frequently by  7 conservation tillage farmers than conventional farmers.  8 It was used on 84 percent of conservation tillage corn  9 compared to 61 percent of conventional tillage corn.  10 And there's a number of reasons for that. I won't go  11 into detail but it's just ideally suited to  12 conservation tillage.  13 Because more farmers have converted to  14 conservation tillage there have been a number of  15 environmental benefits. Soil erosion reduction, the  16 USAD's national resources inventory whoops, if we can  17 go back one showed that between 1982 and 2001 there  18 was a 33 percent decline in soil erosion across the  19 U.S.  20 Conservation tillage also reduces the  21 runoff of sediment into streams of nutrients and  22 pesticides, all these things that can affect aquatic  23 habitats. For example, no till on the average in  24 controlled studies has reduced pesticide runoff by 70  25 percent.</p>	<p style="text-align: right;">Page 144</p> <p>1 streams. They farmers have abided by those label  2 changes and they're having an impact.  3 They've also adopted a number of  4 voluntary BMP's or what we call best management  5 practices, the conservation tillage I just talked  6 about. Post emergency applications, there have been  7 controlled studies that show when Atrazine is applied  8 after the corn and weeds emerge, that runoff of  9 Atrazine is 70 percent less than when applied to a bare  10 soil surface like we've traditionally done.  11 We can also use lower rates when you  12 apply post emergence so it further reduces runoff. And  13 that's been a great trend, a change in how Atrazine is  14 used.  15 Conservation buffers, by planting  16 vegetation adjacent to streams, that buffer acts in  17 entrapping anything that may be in the runoff from  18 sediment and nutrients by the pesticides like Atrazine.  19 On my own farm we seeded out several  20 miles of conservation buffers along streams. Other  21 farmers have as well and they're having an impact.  22 Next slide.  23 Monitoring studies have confirmed these  24 declines in Atrazine concentration in surface water.  25 The U.S. Geological Survey found about a 50 percent</p>
<p style="text-align: right;">Page 143</p> <p>1 Because farmers are making fewer trips,  2 especially those high intensity tillage trips, they're  3 using much less fuel today. Very few industries can  4 say that they use less fuel today than they used 10 or  5 15 years ago, but agriculture can, largely because of  6 conservation tillage. Just in corn alone, conservation  7 tillage corn alone is making a savings of 89 million  8 gallons of fuel annually in the United States. If  9 farmers were to revert back to conventional tillage  10 they would be using 89 million gallons of fuel more a  11 year. Next slide.  12 So Atrazine remains the most widely used  13 corn herbicide and yet what is interesting is that  14 Atrazine concentrations in surface water have declined  15 over the last decade and they continue to decline.  16 Next slide.  17 Why has this happened? Well, the  18 actions that growers have taken have succeeded. And I  19 think probably farmers feel sometimes they don't get  20 enough credit for it. But there have been a lot of  21 management changes. There were label changes in 1990  22 and in '92 there were changes in the Atrazine label  23 designed to try to protect water quality. Rates were  24 reduced, maximum allowed rates reduced, and setbacks or  25 untreated areas required more surface runoff in the</p>	<p style="text-align: right;">Page 145</p> <p>1 decline in median Atrazine concentrations in the early  2 growing season when you expect the highest  3 concentrations. This was over the period of 1989 to  4 1995.  5 And more recently the National Water  6 Quality Assessment or NAWQA, also has shown  7 significant  8 reductions in Atrazine concentrations in streams over  9 the period of '92 to 2001.  10 States have conducted thorough  11 evaluations of their databases. In Iowa the Department  12 of Natural Resources did a statistical analysis of a  13 very large database of pesticide in the water and  14 concluded that there had been a significant decline in  15 Atrazine, both in surface water and in ground water.  16 More recently it's useful to look at  17 some of the intensive monitoring that's been done on  18 drinking water reservoirs. Some of these are small  19 watersheds. I've worked personally on a number of  20 these across the midwest and with some educational  21 efforts we've seen the Atrazine concentrations decline  22 in these reservoirs, a lot of times by 50 percent or  23 more and really are stable and declining. We've had  24 the reductions over many years in different kinds of  25 weather conditions. Next, please.  26 So in conclusion, Atrazine remains a</p>

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1 valuable tool for farmers. It's used on more acreage  
2 than any other corn herbicide. And it facilitates the  
3 adoption of conservation tillage. Farmers have abided  
4 by the water protective label changes. They have  
5 adopted voluntary surface water best management  
6 practices which have resulted in reductions in the  
7 concentrations we find in surface water and those  
8 levels continue to decline.

9 Atrazine does provide many benefits  
10 including increased yield and the adoption of  
11 conservation, reduction of fuel use, reduction of  
12 pesticide and nutrient runoff in the surface water.

13 And farmers realize that they have to  
14 have good stewardship of products like Atrazine to keep  
15 it available in the future so they have a vested  
16 interest in using these practices to try to reduce  
17 runoff as much as possible.

18 I appreciate the chance here to speak to  
19 you and I'd be glad to answer any questions.

20 DR. HEERINGA: Thank you, Doctor Fossett.  
21 Any questions for Doctor Fossett? Thank you very much  
22 for your comments. Can you see that your PowerPoint is  
23 forwarded to Joe Bailey for inclusion, thank you.

24 Our next public commenter is going to be  
25 Jerry White who is also here representing the Triazine

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1 Network and also the Kansas Corn Growers Association  
2 and the Kansas Grain Sorghum Producers Association.  
3 Jerry White.

4 MR. WHITE: Thank you Mr. Chairman and  
5 members of the committee. My name is Jerry White. I'm  
6 the Executive Director of the Kansas Corn Growers  
7 Association and also the Kansas Grain Sorghum  
8 Producers  
9 and serve as Chairman, such as that is, of a coalition  
10 under the Triazine Network. And my expenses here today  
11 are covered by the Kansas farmers.

12 The Triazine Network was formed in 1995  
13 as a response by thousands of growers of over 30  
14 commodities and from over 40 states to provide input to  
15 the EPA special review of the Triazine herbicides.

16 Our objective is to ensure that the EPA  
17 has and uses the best science available. And it's  
18 probably no surprise, I'm not a scientist and we don't  
19 have a Holiday Express in Garnett, Kansas so I'm just  
20 here representing the farmers.

21 I have participated in every SAP  
22 concerning Atrazine since the beginning of the special  
23 review in 1994 and so I do recognize some of the faces  
24 here today.

25 Network membership encompasses farm  
groups from border to border and sea to sea. Our

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1 executive committee is composed of farm organizations  
2 from Kansas, Missouri, Florida, California and Hawaii.  
3 So you can see we are a very diverse group, focused on  
4 a single outcome and that's the science based review of  
5 the Triazines and in this case, Atrazine.

6 As Doctor Fossett commented earlier,  
7 Atrazine has been the foundation of midwest wheat  
8 control programs since the 1950's. It's been around  
9 for a long time and we know this product well. Even  
10 today it is associated with the best yields and many of  
11 the best practices, like conservation tillage as Doctor  
12 Fossett commented.

13 We know how to store Atrazine in a way  
14 that provides safety for ourselves and the environment  
15 in which we live and farm. And I think that's  
16 important to know. We're not talking about a  
17 philosophical situation, this is the land where we live  
18 and we farm and where our kids grow up.

19 We have seen the product's continued use  
20 challenge based on a number of different allegations  
21 over the years, and certainly since 1994. Yet we have  
22 seen science successfully sort out those allegations  
23 through the EPA process, including those like this  
24 week's SAP.

25 And I must say, diverting from my

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1 comments I'm a little taken aback at the challenge that  
2 was I think put forth to this panel and to EPA for  
3 maybe not doing the right thing in what they're  
4 attempting to do today when according to my  
5 recollection of the process, the reason that you're  
6 here today is because the same people raised that issue  
7 in court and got a consent decree to have you do what  
8 you're doing today. It just seems a little bit ironic.

9 We do not take the allegations of harm  
10 from the use of Atrazine lightly. But when the value  
11 of agriculture is so high, the science must be sound.  
12 When the activist community has made Atrazine their  
13 post child and they stall out on one front, they simply  
14 go after another one. Or, as in the case of this  
15 morning, several new ones.

16 We welcome the scrutiny but insist that  
17 science prevail.

18 And with Atrazine it always seems to be  
19 something. First it was cancer if you go back to the  
20 origination of the special review. And now it's frogs.

21 Certainly we care about both. Regulatory bodies around  
22 the world from the U.S. and the E.U. have concluded  
23 that Atrazine is not likely to cause cancer.

24 On a personal note, two months ago I  
25 buried my father, a farmer who lost his fight with

<p style="text-align: right;">Page 150</p> <p>1 cancer and I understand full well the implications of 2 the disease. 3 But it's important for me to know that 4 the tools my family and friends use on our farms are 5 safe. And the fact is they do need tools. Farming is 6 pretty simple when your field is a desk and your plow 7 is a pen. But where I come from it's a business that 8 requires real solutions to real problems. 9 We believe the scientific weight of the 10 evidence shows Atrazine to be both safe and effective 11 and that is the best kind of tool that farmers can 12 have. 13 As for frogs, contrary to the 14 sensational reports on their demise, they seem to be 15 doing quite well in Kansas. Apparently they haven't 16 read the reports. 17 I take personal pleasure in doing local 18 biological assessments from time to time which my wife 19 calls fishing. And I can tell you in the farm ponds 20 and reservoirs that I frequent when given the chance, 21 fish, turtles, minnows, algae and yes, frogs are having 22 a banner year. These are locations surrounded by corn 23 production as you can imagine. And based on what some 24 were stating as fact during the public comments in the 25 '03 SAP, this would seem illogical, this simply could</p>	<p style="text-align: right;">Page 152</p> <p>1 transparency of process and data. 2 EPA has now completed yet another 3 extensive review. My growers appreciate this thorough 4 review and look forward to a science based conclusion 5 concerning the use of Atrazine on their farms, it's 6 important to them. Not because of their uncertainty 7 with the product, but because the product has been the 8 target of those who would have us farm 40 acres with a 9 mule. And that might sound romantic until you figure 10 out it takes 15 acres to feed the mule and the 11 resultant greenhouse gases and soil erosion would 12 probably require at least two more SAP's to sort out. 13 We appreciate the work of this panel and 14 I don't mean to be facetious, the EPA has done a 15 fantastic job over the years, there have been a lot of 16 challenges, but science has risen to the challenge. 17 And certainly we appreciate from a grower's standpoint, 18 not only the work of the Agency, but those of you that 19 contribute your time to help sort out some of the 20 bigger and the tougher issues. 21 And I must say, the growers appreciate 22 the work of the registrant in stepping forward and 23 supplying the science that lets everyone else do their 24 work. 25 Thank you.</p>
<p style="text-align: right;">Page 151</p> <p>1 not exist. But they are there, not the sad frogs from 2 the other three PowerPoint presentations, but frogs 3 that seem to be living the good life in the environment 4 that I observe them. 5 Mark Twain philosophized in his writings 6 on life on the Mississippi, that there is something 7 fascinating about science, one gets such wholesale 8 returns of conjecture out of such a trifling investment 9 in fact. 10 Now I would not suggest that conjecture 11 concerning gonadal development in frogs in '03 was 12 absent some scientific merit for further review. But 13 the overall weight of the evidence suggests more 14 conjecture than fact. 15 Subsequent studies performed under the 16 direction of EPA have been sufficiently robust and have 17 resolved the questions set out by the previous SAP and 18 by the Agency. 19 The fact that they are industry funded 20 is irrelevant because that is a function of the system 21 that requires a registrant to pay for them, it's just 22 that simple. 23 Certainly the activist funded studies 24 paraded in front of the '03 SAP were done with minimum 25 guidance and quality control and with little</p>	<p style="text-align: right;">Page 153</p> <p>1 DR. HEERINGA: Thank you, Mr. White. 2 Comments from the panel on Mr. White's comments 3 representing the Corn Growers and Sorghum Growers 4 Associations of Kansas and the Triazine Network? Thank 5 you very much for your comments. 6 We have one additional public commenter 7 who has registered with our Designated Federal 8 Official, and that's Rick Robinson representing the 9 Iowa Farm Bureau. Rick, please step forward. 10 MR. ROBINSON: Good afternoon. First of 11 all let me say thank you as well to the panel for their 12 due diligence in the review of these issues. It's very 13 important, the work that you're doing and we don't take 14 it lightly at the Iowa Farm Bureau. 15 The Iowa Farm Bureau is Iowa's largest 16 general farm organization and my written comments today 17 reflect a lot of the benefits of the use of Atrazine by 18 Iowa corn farmers. 19 But I'm compelled to visit with you a 20 little bit more today about some other aspects and some 21 general reactions and kind of a 30,000 foot view to 22 this process and also an on the ground reaction to what 23 some of the water quality issues are in Iowa that we're 24 working on. 25 Let me also say that I was born on an</p>



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1 Iowa farm, grew up on an Iowa farm, I've been involved  
2 in agriculture all my life, some 47 years now. And  
3 over those years I've seen significant changes in  
4 agriculture, significant improvements in water quality  
5 and conservation efforts which sometimes aren't fully  
6 accounted for and they're hard to account for.

7 But my perspective is, with that in the  
8 background, looking at this process, at that 30,000  
9 foot view, Iowa farmers need an effective tool to deal  
10 with soil erosion. Believe it or not, sediment in  
11 water is our biggest issue in Iowa. It's not  
12 pesticides, it's not Atrazine. And Atrazine is an  
13 important tool, an effective tool in the no till  
14 systems, the conservation tillage systems that Doctor  
15 Fossett talked about. If Iowa farmers don't have this  
16 as a tool it will negatively impact water quality in  
17 the state of Iowa in ways that are hard to imagine.

18 So I want you to keep that in mind.  
19 That's why it's so important to Iowa farmers. It's  
20 been around for some 50 years and it's been around  
21 because it's effective, it's cost effective and it's  
22 safe for farmers and for the environment.

23 And I think this process just further  
24 reinforces how safe of a product this really is. I  
25 can't imagine other products having this degree of

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1 DR. HEERINGA: Thank you very much. And  
2 again the set of written comments submitted by Rick  
3 Robinson is available to the panel and will be included  
4 in the docket for this meeting.

5 So thank you very much to the public  
6 commenters.

7 Now, I'd like to put out one last call.  
8 This is the period of public comment. It is really the  
9 only official period of public comment during these  
10 meetings. If there is anyone who has not had a chance  
11 to speak but feels they would like a chance to speak in  
12 this period, just indicate so.

13 Okay, not seeing any additional  
14 interest, there are some written comments that have  
15 been submitted to the panel. Those will be included on  
16 the docket in response to the proceedings today and the  
17 next three days, will be available to everybody on the  
18 docket as well.

19 I want to, there is some interest on the  
20 part of the panel to return to a couple of questions  
21 related to the public comment and presentation by the  
22 Syngenta Crop Protection team and I wonder if they  
23 would be willing to come forward again to entertain a  
24 few more questions from the panel.

25 Thank you very much. Again to the panel

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1 scrutiny over the years.

2 I've been working on these issues for  
3 the Iowa Farm Bureau for 13 years now and this special  
4 review process has been going on for that period of  
5 time. The month that I started, 13 years ago this  
6 month, this special review process started and here we  
7 are today, 13 years later.

8 So, Iowa farmers are interested in  
9 resolving and answering these questions just as you  
10 are. And they're also interested in, once it is  
11 resolved, in the EPA communicating to the public what  
12 are the facts and what are the science. Because when I  
13 go out and, you know, do a Google search on Atrazine in  
14 frogs and pull up these websites that are out there  
15 that have bad science, inaccuracies, it's imperative,  
16 it's important to Iowa farmers that EPA also  
17 communicates to the public and to these folks what the  
18 facts are and what the science is so the public  
19 understands it and they also understand then what the  
20 water quality issues are and how Atrazine fits in to  
21 protecting water quality and aquatic life.

22 Thank you.

23 DR. HEERINGA: Thank you very much, Mr.  
24 Robinson. Questions for Mr. Robinson on his comments?

25 MR. ROBINSON: Thank you.

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1 members, I think we have an opportunity at this point  
2 to continue this morning's discussion.

3 There were two additional points I  
4 wanted to follow up on. Doctor Bailey had a question  
5 with regard to the error bars, including on the figure  
6 on page 30. I think that was just a question related  
7 to the width of those bars and his concern that they  
8 should have a similar size or a range, given the  
9 underlying structure.

10 And I think that was something that, Mr.  
11 Osmer, you were going to come back with a response at  
12 some point. It doesn't need to be now by any means but  
13 just to remind everybody.

14 And there was also a conversation which  
15 Doctor Schlenk was going to have with the  
16 representative from the team on the percentage basis on  
17 actual versus nominal levels of concentrations of  
18 Atrazine.

19 Have you addressed that?

20 DR. SCHLENK: Yeah, we met with, actually  
21 Peter and I have met with Tim to discuss that.

22 DR. HEERINGA: And you've reached a  
23 finding?

24 DR. SCHLENK: Yeah, well basically the  
25 idea was that concentrations in the, on page 15 of the

<p style="text-align: right;">Page 158</p> <p>1 presentation, it wasn't clear to Peter or myself  2 whether or not those values were actually between the  3 level of detection and the level of quantification.  4 And apparently they are between those values provided  5 on that particular slide.  6 DR. HEERINGA: Additional questions from  7 the panel for the Syngenta Crop Protection team?  8 Yes, Doctor Miller.  9 DR. MILLER: I have one for Doctor Wolfe.  10 Could you explain, did you score the histologic changes  11 or did you do a presence/absence?  12 DR. WOLFE: Yeah, this is Doctor Wolfe  13 from EPL. Yes, they were scored on a grading scale  14 from 1 to 4 for almost all the findings. There were  15 certain findings that were scored as present or absent  16 I believe, but that was a very few things like mixed  17 sex was scored as present rather than as given a  18 severity grade. But they were all severity grade  19 scored.  20 DR. HEERINGA: Additional questions?  21 Doctor Portier.  22 DR. PORTIER: I'm not quite sure how to  23 ask this question but I'll attempt it.  24 I guess I'm bothered by the loss of that  25 control that had the low levels of Atrazine. And in</p>	<p style="text-align: right;">Page 160</p> <p>1 I know they were tested for the nominal level of  2 chemical that you added. Were they also tested for the  3 estradiol, potential cross contamination with  4 estradiol? For example in whatever it is, next to  5 control one you have an estradiol treatment. Do we  6 know whether any of that went the other way? Were  7 those things tested for that kind of thing?  8 MR. OSMER: We tested all of the controls  9 for both the presence of Atrazine and estradiol and it  10 never had an occurrence in the controls.  11 I mean I think it's not coincidental,  12 the proximity of the control tanks to those high  13 levels, and it was not a singular event. There wasn't  14 a human error involved because we saw it chronically  15 over the long term through the study.  16 So there was some transfer in some  17 fashion systematically at low levels. I think it's  18 significant that we were able to detect it. The fact  19 that it was just barely above detection gives me more  20 confidence that the others were clear.  21 And as I said the, both the negative  22 controls, the other negative controls were sampled for  23 estradiol and Atrazine and never found to be present.  24 DR. HEERINGA: Doctor Isom.  25 DR. ISOM: Gary Isom. Just to follow up</p>
<p style="text-align: right;">Page 159</p> <p>1 the paper it was mentioned and you gave us a little bit  2 more insight as to what you observed.  3 But my question is, how did that happen  4 with the high level of quality control that you  5 indicated you have, and to still lose it this way, I  6 just wondered, you know, can you give me a little bit  7 more insight into what you think happened to produce  8 that level of contamination of the control?  9 MR. OSMER: This is Alan Osmer, Syngenta.  10 We, the short answer is we don't have a complete  11 explanation of how that happened.  12 What we do know is that because it was  13 randomized in the fashion, that you ended up with a ten  14 thousandfold difference between the LOQ for that dose  15 level and those tanks that were adjacent to it.  16 We did consider some possibilities, some  17 explanations, and were never able to resolve it  18 totally.  19 Fortunately the study was designed in a  20 robust fashion that allowed us to anticipate such  21 problems and continue with the study.  22 DR. PORTIER: You know, the thing for me  23 is that it raises additional questions that I worry  24 about.  25 For example, were all of the clusters</p>	<p style="text-align: right;">Page 161</p> <p>1 on that then. Your control group 2 at the top, the  2 blue one, was Atrazine detected in that also at any  3 levels? And that would be the second to highest level  4 of concentration.  5 MR. OSMER: No, there was never any  6 Atrazine detected in that cluster of you're referring  7 to the blue control 2?  8 DR. ISOM: Right.  9 MR. OSMER: Those were lost because of a  10 microbial bloom that was described earlier.  11 DR. HEERINGA: Yes, Peter Delorme.  12 DR. DELORME: Peter Delorme. Just  13 another question, Alan. Were those tanks covered?  14 MR. OSMER: Yes.  15 DR. DELORME: They were all covered?  16 MR. OSMER: Yes.  17 DR. DELORME: So you thought about  18 possible airborne contamination as a source?  19 MR. OSMER: We did, but what you're  20 reviewing there is a diagram of an environmental  21 chamber.  22 DR. DELORME: Right.  23 MR. OSMER: A large environmental  24 chamber. I think if it were airborne contamination you  25 would have expected to see it in more than just that</p>

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1 one cluster. And yes, they were covered.  
 2 DR. DELORME: Thank you.  
 3 DR. HEERINGA: Any additional questions?  
 4 Yes, Doctor Bucher.  
 5 DR. BUCHER: John Bucher. This is a  
 6 follow up to a question that I think Doctor Wolfe was  
 7 answering this morning and I've been thinking about it  
 8 over lunch.  
 9 I'm still a little confused about the  
 10 relationship between the diagnosis of mixed sex, inter-  
 11 sex, the testicular ovarian follicle and how these  
 12 various things are affected by the actual time it takes  
 13 these different populations of frogs to get through to  
 14 metamorphosis.  
 15 Could you expand on that just a little  
 16 bit so that I could get a little clearer on it?  
 17 DR. WOLFE: Okay, sure, this is Doctor  
 18 Wolfe again. The point I was trying to make is that I  
 19 think sometimes people look at testicular oocytes and  
 20 mixed sex as being somewhat apples and oranges and  
 21 wonder why didn't we see mixed sex why didn't we see  
 22 testicular oocytes in such and such a study and why did  
 23 we see mixed sex in another study.  
 24 And I think a lot of it has to do with  
 25 in my observations, in my opinion, is the reproductive

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1 age of the animals in that specific test. And a lot of  
 2 times that doesn't come out when you read the  
 3 literature on a specific study. They say they used  
 4 Stage 66 animals, but I think in some cases somebody's  
 5 Stage 66 animals are not the same reproductive age as  
 6 somebody else's Stage 66 animals.  
 7 So if you have animals that are more  
 8 reproductively mature my hypothesis is that they're  
 9 more likely to develop testicular oocytes because the  
 10 females at that particular reproductive age would also  
 11 be more likely to have perinuclear oocytes rather than  
 12 gonial cells, okay?  
 13 And that whereas at a younger age you're  
 14 more likely to get a mixed sex consisting of less  
 15 developed immature tissue.  
 16 Does that help?  
 17 DR. BUCHER: Yeah, that helps a lot,  
 18 thank you.  
 19 DR. HEERINGA: Okay, I think that we'll  
 20 be hearing more about the actual studies with the EPA  
 21 presentations and I think if any additional questions  
 22 come up which could be answered by the Syngenta Crop  
 23 Protection group that's conducted those studies, I'll  
 24 leave it to the EPA to call on them appropriately if  
 25 that makes sense.

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1 So I want to thank you all for your  
 2 contribution here. And at this point in time yes,  
 3 Mr. Osmer.  
 4 MR. OSMER: Thank you, Mr. Chairman.  
 5 Just for the record, we will correct that figure,  
 6 figure 15 and indicate the actual values that were  
 7 plotted and resubmit that with that figure.  
 8 DR. HEERINGA: Okay, we appreciate it,  
 9 thank you.  
 10 MR. OSMER: And we appreciate your time.  
 11 DR. HEERINGA: Thank you very much. At  
 12 this point in time I'd like to call the period of  
 13 public comment to a close and we are at 2:00 p.m. where  
 14 we were anticipating to be at, at 5:00 p.m.  
 15 And I think the EPA scientific staff I  
 16 understand through Joe Bailey is willing and able to  
 17 proceed at this point with the presentations that were  
 18 on the agenda for tomorrow morning.  
 19 Is that in fact the case? Okay. Let's  
 20 have Doctor Steeger and your team come forward.  
 21 While we're waiting to get set up here I  
 22 want to thank all of the participants in the public  
 23 comment period for not only the presentation of data  
 24 and experimental study results, but also comments and  
 25 views on this particular scientific question.

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1 Doctor Steeger, anytime you're ready,  
 2 please feel free to proceed.  
 3 DR. STEEGER: Thank you again for this  
 4 opportunity to present to the FIFRA SAP.  
 5 In this presentation I would like to  
 6 provide a brief overview of the open literature  
 7 published since the 2003 SAP.  
 8 In addition to the two studies submitted  
 9 by Syngenta in response to the data call in, a total of  
 10 18 laboratory and field studies combined were reviewed  
 11 by the Agency.  
 12 Although several of those studies were  
 13 published subsequent to the 2003 SAP which discussed  
 14 the affect of Atrazine on amphibian gonadal  
 15 development, they were not reviewed because they did  
 16 not contain primary data or they reported on affects  
 17 other than amphibian gonadal development.  
 18 As mentioned in the Agency's  
 19 introductory remarks the current focus concerns the  
 20 potential for Atrazine alone to act on gonadal  
 21 developmental affects.  
 22 Of the nine laboratory studies published  
 23 in the open literature, two, both by Cody, et al had  
 24 been previously reviewed as interim reports in the 2003  
 25 white paper.

<p style="text-align: right;">Page 166</p> <p>1 As was the case in 2003, laboratory  2 studies reported on a variety of measurement end points  3 such as survival, time and size at metamorphosis,  4 shifts in sex ratio, laryngeal muscle area, gonadal  5 abnormalities, plasma steroid levels and aromatase  6 activity.  7 All of the laboratory studies relied on  8 static renewal exposures. Atrazine exposures ranged  9 from a single concentration tested up to five  10 concentrations tested. Few of the laboratory studies  11 verified Atrazine and/or degradative concentrations.  12 The open literature studies generally  13 failed to account for potential sources of variability  14 that confound the interpretation of the data. For  15 example, loading rates, that is the number of animals  16 per volume of treated solution exceeded the ASTM  17 recommended rate of one tadpole per liter per day.  18 Using static renewal conditions the  19 majority of the laboratory studies had both incomplete  20 and infrequent exposures to solution changes which in  21 previous studies markedly decreased the water quality  22 conditions.  23 In some cases exposure chambers were  24 constructed of materials such as plastic that could  25 have influenced measurement end points. In general,</p>	<p style="text-align: right;">Page 168</p> <p>1 characterization of larval exposure conditions and  2 unusual weather events that may have compromised the  3 study.  4 The study designs did not address  5 potential sources of variability. In general the field  6 studies provided a very limited opportunity to  7 correlate Atrazine exposure to measurement end points.  8 In general, since 2003 a total of 35  9 documents have been reviewed and none of these study  10 reports have experimental designs or data sets  11 sufficiently robust to assess whether or not Atrazine  12 alone can affect gonadal development.  13 In the next three slides I depict all of  14 the studies reviewed for the 2007 white paper and it  15 represents Table 24 from the white paper itself. The  16 table provides the lead author and the test species and  17 the developmental stage used, the Atrazine  18 concentrations tested and the major results of the  19 study and the studies' limitations.  20 Only two of the ten laboratory studies  21 reported affects on gonadal development. Three of the  22 ten laboratory studies reported affects on time to  23 metamorphosis. None of the laboratory studies report a  24 consistent dose response and where affects were noted,  25 there were conflicting results for the same species,</p>
<p style="text-align: right;">Page 167</p> <p>1 environmental factors such as dissolved oxygen and  2 ammonia were not well controlled.  3 Similar to the laboratory studies  4 reviewed in 2003, the most recent laboratory studies  5 lacked consistent dose response. In some cases adult  6 rather than larval frogs were evaluated and survival  7 gonadal development was not measured.  8 In some of the studies there was a poor  9 response to positive controls, typically estradiol,  10 indicating that the test or assay was not sensitive at  11 means of measurement. High mortality was problematic  12 in some of the studies as well.  13 Although the Agency and the FIFRA SAP  14 had made recommendations for study designs to address  15 potential sources of variability and uncertainty, none  16 of the laboratory studies incorporated these design  17 elements.  18 With respect to the field studies, all  19 of the most recently reviewed field studies had  20 previously been reviewed in some capacity as interim  21 reports in the 2003 SAP. The field studies contained  22 that limitations that were identified in 2003.  23 These include the Atrazine or Atrazine  24 and Triazine and their degradatives in reference sites,  25 poor characterization of environmental conditions, poor</p>	<p style="text-align: right;">Page 169</p> <p>1 for example Northern Leopard frogs across labs.  2 Where Hayes, et al in 2006 reports no  3 gonadal abnormalities nor affects on time or size at  4 metamorphosis at Atrazine concentrations from 0 to .1  5 to 10 micrograms per liter, Orden, et al 2006 reports  6 testicular oocytes at 10 micrograms per liter.  7 Of the nine field studies, only one of  8 the studies showed an increased incidence of affects,  9 and that's Bidder's organ development in male Cane  10 toads collected from various sugarcane production sites  11 where measured concentrations of Atrazine were highest.  12 Also, in one of the two years in which Murphy, et al  13 2006 collected green frogs, the incidence of testicular  14 oocytes was correlated with Atrazine concentrations.  15 However, the affect was not reproducible across the  16 entire study period.  17 The open literature, taken as a whole  18 again suggests that Atrazine does not consistently  19 affect amphibian gonadal development.  20 In the presentations that follow, Doctor  21 Diggitts will provide an overview of the scientific  22 approach to the design of the DCI studies, the data  23 call in studies. Doctor Diggitts is a research aquatic  24 biologist with the Ecology Division of the EPA Office  25 of Research and Development in Duluth. And Doctor</p>



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1 Diggitts is kind enough to pinch hit for Mr. Joe Tugi  
2 who has been called away on a family emergency. Doctor  
3 Diggitts however has participated in the 2003 SAP and  
4 is familiar with the DCI study protocols and he has  
5 extensive experience conducting laboratory studies with  
6 samples.

7 DR. HEERINGA: Thank you very much,  
8 Doctor Steeger. Before we move on to Doctor Diggitts'  
9 presentation, are there any comments on the summary  
10 here of the open literature review?

11 Yes, Doctor Bucher.

12 DR. BUCHER: John Bucher. Given the fact  
13 that the aromatase theory has sort of fallen by the  
14 wayside according to some of the data we've seen, the  
15 utilization of the estradiol positive control and the  
16 failure to produce affects in some studies, was that  
17 taken into consideration in the selection of the  
18 positive control in the evaluation of the value of some  
19 of those studies where the positive control may not  
20 have worked?

21 DR. STEEGER: Estradiol was chosen as a  
22 positive control, not because it was intended to mimic  
23 the action, or the presumed action of Atrazine on  
24 amphibians, it was selected because it's known to  
25 produce gonadal developmental affects.

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1 alone. I think that whenever we look at field studies  
2 for ecological risk assessment we're trying to identify  
3 whether the study had proper reference sites that you  
4 could determine whether in any way the Atrazine could  
5 be related or the chemical in question could be related  
6 to any of the affects being measured.

7 In this case most of the field studies  
8 had such profound compromising affects in the way that  
9 the data were being collected, that it was difficult to  
10 even get to the point where we could ask that question.

11 In a lot of cases the animals were  
12 collected over protracted periods of time, were being  
13 held together in collection buckets for up to eight  
14 hours, and then they go out and they measure steroidal  
15 concentrations in the plasma. Well, you know, if you  
16 hold animals together for that long it's a little  
17 difficult to believe that males and females are not  
18 going to react to one another and that could  
19 potentially influence the parameter that's being  
20 measured.

21 In many of the studies concentrations,  
22 not only of Atrazine, but of chemicals, other triazine  
23 herbicides, the degradates, a large variety of  
24 pesticides were found in the reference sites as well as  
25 the, what were supposed to be the treatment sites.

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1 And it was necessary to demonstrate that  
2 the protocols that were being followed were capable of  
3 detecting a change in gonadal development. That was  
4 the only reason that estradiol was chosen as a positive  
5 control. Because we do know that it can result in  
6 affects on the sex ratio and on the incidence of mixed  
7 sex ovarian tissue in the testes of males.

8 The studies that had been conducted and  
9 reported in the open literature, where we were privy to  
10 some of the details concerning those studies it became  
11 clear that in many cases the animals, because of  
12 husbandry conditions were so poorly developed that they  
13 weren't even responding to a strong estrogenic  
14 chemical.

15 DR. HEERINGA: Doctor Skelley.

16 DR. SKELLEY: Doctor Steeger, I just want  
17 to make sure I understand clearly in particular how  
18 field studies were evaluated.

19 Is it the case that a couple of your  
20 slides, the way that you were reviewing these studies,  
21 they needed to be able to show a clear unambiguous  
22 association with Atrazine alone in order for you to  
23 conclude that there was evidence?

24 DR. STEEGER: No, I don't think we were  
25 looking for just a clear indication from Atrazine

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1 So there was no really, there was no way  
2 to distinguish what was the treatment and what was the  
3 control.

4 DR. SKELLEY: This is David Skelley  
5 again. So I'd like to ask you specifically about the  
6 Cane toad sugarcane study. Could you summarize just  
7 very briefly what you see as the major compromising  
8 issues there?

9 DR. STEEGER: To be candid, the Florida  
10 study of the Cane toad was one of the most compromised  
11 studies I've ever read in my career here at EPA.

12 The reference to the Atrazine levels  
13 that were reported in the plasma of the animals, those  
14 concentrations were on an order of magnitude below the  
15 level of detection of the assay that was being used to  
16 measure them. The animals were held for protracted  
17 periods of time in the collection vessels. That was  
18 the eight hours in the collection, in the field  
19 collection. They were sampled by cardiac puncture and  
20 then weighed and so the weights of the animal depended  
21 on the volume of blood that was sampled. It would have  
22 been difficult to believe that it did not influence  
23 that measurement end point.

24 The animals were collected over several  
25 seasons and they were combined. So looking at the

<p style="text-align: right;">Page 174</p> <p>1 differences in the you have a mixed, potentially  2 mixed developmental stages for all of the animals that  3 were collected.  4 Even though the study stated that adults  5 would be sampled and that only animals beyond a certain  6 range in size would be included in that sample, in  7 actuality when you go to the data, at least 40 percent  8 of the animals were lower than that and many of them  9 appeared to be juvenile animals.  10 The study author failed to measure other  11 pesticides at the treatment sites and I think that  12 and those are only the major difficulties with the  13 study. In general there was not much utility that  14 could be gleaned from the study.  15 Also the authors state that the Bidder's  16 organ can develop in males depending on the state of  17 sexual development. So given that the animals could  18 have been at various stages of development it would  19 have been difficult to know whether that was a natural  20 process or whether that was somehow chemically induced.  21 DR. HEERINGA: Yes, okay, Doctor Furlow.  22 DR. FURLOW: David Furlow, UC Davis, so  23 as a bench scientist I'm just kind of curious and maybe  24 some of the other folks who work in wildlife and doing  25 field studies so in your opinion none of the wildlife</p>	<p style="text-align: right;">Page 176</p> <p>1 What would you really need to do in  2 order to answer the question as to whether Atrazine is  3 affecting amphibian development?  4 And we had proposed that first of all  5 you'd want before you moved into the field, let's  6 first establish in the lab whether you can get  7 cause/effect relationship. Because if you can't do  8 that in the lab there's no point in going out in the  9 field to determine whether that relationship exists  10 when there are many more confounding factors that would  11 limit your ability to draw that cause/effect  12 relationship.  13 DR. HEERINGA: Doctor Denver.  14 DR. DENVER: Bob Denver. I have a  15 related question to the one that Dave Furlow just  16 asked. And that is, in reading the white paper it  17 wasn't clear to me that EPA considered any of the  18 published literature to be sufficiently robust that it  19 would tell us anything for or against the effects of  20 Atrazine.  21 Is that fair to say?  22 DR. STEEGER: I think it's fair to say  23 that the open literature as it was in 2003 is as it is  24 2007.  25 There are excuse me, there are</p>
<p style="text-align: right;">Page 175</p> <p>1 or the field studies represent anything that indicates  2 or that you can't make any conclusions from it.  3 It's not one way or the other, you can't  4 draw any conclusions? That's the first question.  5 The second question is, based on what  6 you're saying though, and maybe some of the other  7 experts can weigh in, can an adequate field study be  8 proactively designed to say, look, you know, this is  9 what we need, these are the criteria that we need to  10 meet, let's do the experiment and decide one way or the  11 other?  12 DR. STEEGER: I think that a field study  13 can be properly designed. The intent of our review  14 wasn't to preclude the use of field studies.  15 The fact is that none of the field  16 studies that we were presented with had the proper  17 design elements to address a question as to whether  18 chemical exposure could be correlated with any affects  19 that are being measured.  20 When we went to the 2003 SAP the  21 question was put forth that there are a lot of  22 uncertainties surrounding the data that we had and most  23 of them had to do with sources of variability and how  24 we could better control them. And the Agency proposed  25 a process for trying to do that very thing.</p>	<p style="text-align: right;">Page 177</p> <p>1 uncertainties regarding how the data were collected  2 which limited the Agency's understanding of how to  3 interpret them.  4 I think that we could continue to draw  5 on lines of evidence and state that there are  6 indications that Atrazine may be affecting amphibian  7 gonadal development such as in the case of the  8 development of Bidder's organ, as in the case of  9 delayed metamorphosis in the Freeman study.  10 But in terms of looking across, has  11 anyone replicated those results? When you try and do  12 the study similar to what the authors did, do they come  13 up with the same results? Is there any consistency in  14 the information that's being presented?  15 There's a smattering, you get a result,  16 there you don't. The Agency identified a way of  17 getting around that and we still see that back and  18 forth and that's why the DCI studies were critical to  19 our analysis.  20 DR. DENVER: Can I just have a follow up?  21 Right, so you get variable results depending on the  22 study, but I'm curious, are any of the published  23 papers, do you consider any of those to be sufficiently  24 well done that you would put them in the same category  25 as the two DCI studies?</p>

<p style="text-align: right;">Page 178</p> <p>1 DR. STEEGER: No.</p> <p>2 DR. HEERINGA: Any additional questions</p> <p>3 for Doctor Steeger?</p> <p>4 DR. STEEGER: I'd like to make a follow</p> <p>5 up statement to</p> <p>6 DR. HEERINGA: You may, absolutely.</p> <p>7 DR. STEEGER: The tool that the Agency</p> <p>8 uses to assure that a study is conducted in accordance</p> <p>9 with the guidelines or the process that we've</p> <p>10 identified need to be followed, is good laboratory</p> <p>11 practice.</p> <p>12 It isn't possible for most researchers</p> <p>13 to maintain the rigor that's required under a GLP study</p> <p>14 in terms of tracking, keeping track of data, having</p> <p>15 standard operating procedures, having protocols that</p> <p>16 are being followed where the Agency then has the luxury</p> <p>17 of going through and analyzing the data ourselves as</p> <p>18 though we had done the experiment ourselves.</p> <p>19 The open literature can't hope to</p> <p>20 compete against that standard.</p> <p>21 DR. HEERINGA: We'll have an opportunity</p> <p>22 if additional questions come up but at this point I'd</p> <p>23 like to move to Doctor Diggitts and his presentation</p> <p>24 and again he is stepping in for Joseph Tugi who is</p> <p>25 away. The panel should have copies of this</p>	<p style="text-align: right;">Page 180</p> <p>1 The major uncertainties about Atrazine's</p> <p>2 potential affects on amphibian gonadal development</p> <p>3 based on the data available in 2003 were characterized</p> <p>4 as a small number of affirmative studies. In 2003,</p> <p>5 three studies conducted under laboratory conditions</p> <p>6 demonstrated gonadal abnormalities in males indicative</p> <p>7 of mixed sex gonads, that is, ovarian tissues present</p> <p>8 in predominantly testicular tissues.</p> <p>9 There was limited evidence of</p> <p>10 repeatability. When comparable laboratory studies were</p> <p>11 evaluated some demonstrated an affect while others did</p> <p>12 not. The dose response relationship was undefined.</p> <p>13 The studies which demonstrated an affect</p> <p>14 on Atrazine on gonad development did not provide</p> <p>15 convincing reproducible evidence of a dose response or</p> <p>16 exposure response relationship, whether it be linear or</p> <p>17 nonlinear.</p> <p>18 Understanding the dose response</p> <p>19 relationship is a necessary component of the risk</p> <p>20 assessment process because it forms the basis for</p> <p>21 determining the risk associated with environmental</p> <p>22 concentration of the chemicals in question.</p> <p>23 The mechanistic plausibility was</p> <p>24 unsupported. The hypothesis presented at the time</p> <p>25 regarding excuse me the affect was not supported by</p>
<p style="text-align: right;">Page 179</p> <p>1 presentation. It's labeled with Joe Tugi's name.</p> <p>2 Please proceed, Doctor Tugi Diggitts.</p> <p>3 DR. DIGGITTs: In this presentation I</p> <p>4 would like to accomplish the following three</p> <p>5 objectives.</p> <p>6 First I will recap the conclusions of</p> <p>7 the 2003 white paper, particularly as they apply to the</p> <p>8 scientific approach developed to assess the risk of</p> <p>9 Atrazine using a tiered analysis plan.</p> <p>10 Second, I will summarize the comments of</p> <p>11 the 2003 SAP which are pertinent to the analysis plan</p> <p>12 that was proposed in 2003.</p> <p>13 And third, I will review the rationale</p> <p>14 and details of the study plan, including a time line</p> <p>15 activities from 2003 to 2007.</p> <p>16 The EPA's analysis of data available in</p> <p>17 2003 suggests that aneurine reproductive fitness may be</p> <p>18 adversely affected by exposure to Atrazine. However</p> <p>19 the data were insufficient to conclude that Atrazine</p> <p>20 adversely affect aneurine reproduction through affects</p> <p>21 on gonadal development.</p> <p>22 Therefore, further studies were proposed</p> <p>23 following the guidelines of ecological risk assessment</p> <p>24 to reduce the uncertainties and permit eventual risk</p> <p>25 characterization if warranted.</p>	<p style="text-align: right;">Page 181</p> <p>1 appropriate experimentation and data, specifically the</p> <p>2 working hypothesis or risk hypothesis was that</p> <p>3 aromatase led to increased estradiol levels which were</p> <p>4 of sufficient magnitude and duration to feminize male</p> <p>5 gonads resulting in individuals of mixed sex, sometimes</p> <p>6 referred to as hermaphrodites.</p> <p>7 To date this mechanism has not been</p> <p>8 demonstrated in the species tested.</p> <p>9 The ecological relevance was</p> <p>10 undetermined. The assessment end points used in</p> <p>11 evaluating ecological risk is at the population level,</p> <p>12 that is adverse affects are considered important in the</p> <p>13 ecological risk assessment process if there is evidence</p> <p>14 that the affects result in population reductions or</p> <p>15 loss.</p> <p>16 Obviously successful reproduction is</p> <p>17 necessary for the maintenance of population, however</p> <p>18 none of the reports demonstrated impaired reproduction</p> <p>19 in either laboratory experiments or in field studies.</p> <p>20 So the EPA proposed to the SAP in 2003</p> <p>21 that a tiered approach be used to examine the</p> <p>22 cause/effect, dose response, mechanistic plausibility</p> <p>23 and ecological relevance of Atrazine exposure to</p> <p>24 amphibians.</p> <p>25 Such a systematic approach would reduce</p>

<p style="text-align: right;">Page 182</p> <p>1 these major uncertainties and permit a more thorough 2 analysis of risk.</p> <p>3 In this very simplified diagram of the 4 ecological risk assessment paradigm one can see the 5 three major phases, namely problem formulation, 6 analysis and risk characterization.</p> <p>7 As Doctor Steeger has pointed out in his 8 earlier presentation in more detail, the conceptual 9 model or risk hypothesis is defined in the problem 10 formulation phase. The conceptual model is based on 11 the currently available information and sets the stage 12 for developing an analysis plan.</p> <p>13 The analysis plan is a set of studies 14 that determines the affects of the chemical on specific 15 end points and the extent and likelihood of exposure. 16 Risk characterization follows, and is the phase in 17 which the effects and exposure data are integrated.</p> <p>18 The next two slides will present the 19 conceptual model which originates in the problem 20 formulation phase and the tiered analysis plan which 21 originates in the analysis phase as they were proposed 22 in 2003.</p> <p>23 The proposed tiered analysis plan was 24 designed to run a conceptual model of risk hypothesis 25 on Atrazine action. The hypothesized affects are</p>	<p style="text-align: right;">Page 184</p> <p>1 hypothesis and inform the mechanistic plausibility, 2 they do not necessarily provide meaningful information 3 on the ecological relevance of a potential gonadal 4 affect.</p> <p>5 Therefore if gonad affects are observed 6 at the organismal level, the studies which evaluate 7 fertility and reproduction end points that are relevant 8 to maintenance of population which is indicated in this 9 slide as an ecological relevance should be pursued.</p> <p>10 If the working hypothesis is ordered by 11 the organism and sub-organismal studies, then it may be 12 possible to confirm the mode of action by conducting 13 confirmatory studies which utilize known aromatase 14 inhibitors. Rescue of the normal male phenotype by an 15 aromatase inhibitor co-administered with Atrazine could 16 provide substantial support for the working hypothesis.</p> <p>17 If no affects are observed at the 18 organismal level then there may be no need to continue 19 with any further testing above or below the organismal 20 level. If the organismal level tests are affirmative 21 and any of the sub-organismal studies are negative, 22 then an alternative hypothesis could be considered.</p> <p>23 So if the tier one test for gonad 24 affects is pivotal to the implementation of the tiered 25 analysis plan, I would like to provide some more detail</p>
<p style="text-align: right;">Page 183</p> <p>1 initiated by an undefined molecular interaction. This 2 interaction results in a hypothetical increase in 3 aromatase which results in a hypothetical elevation of 4 indogenous estradiol which affects changes in male 5 gonads.</p> <p>6 If this affect impairs the fertility of 7 the male, then reduced reproductive fitness could 8 result, leading to impaired population maintenance and 9 recruitment which is the assessment end point.</p> <p>10 This slide depicts the proposed tiered 11 analysis plan essentially as presented to the SAP in 12 2003. The steps outlined in the conceptual model shown 13 in the previous slides can be systematically tested 14 using a tiered approach. Beginning at the organismal 15 level the affects of Atrazine on gonad development, 16 particularly in males should be the entry point of this 17 analysis.</p> <p>18 If these tests are affirmative, then 19 affects on Atrazine exposure on sex steroids could be 20 evaluated if feasible. If estrogen levels are elevated 21 in the Atrazine treated organisms, then evaluating the 22 affects of Atrazine exposure on aromatase could be 23 indicated.</p> <p>24 Although sex steroids and aromatase 25 measurements are necessary to test of working</p>	<p style="text-align: right;">Page 185</p> <p>1 about the objectives, the recommended experimental 2 approach and the use of study quality indicators as 3 performance criteria by which the quality of the study 4 can be judged.</p> <p>5 The objective of the tier one studies 6 were to determine Atrazine exposure results on gonadal 7 affects in males under controlled laboratory conditions 8 and determine the shape of the dose response 9 relationship, if any.</p> <p>10 So as many of the studies reviewed in 11 2003 had a variety of experimental problems, we 12 proposed an approach that would follow current 13 standards in aquatic toxicology and we specified 14 several parameters.</p> <p>15 The species recommended was <i>Xenopus</i> 16 <i>laevis</i>. The recommendation was based on the fact that 17 some previously conducted studies had suggested that 18 this species was sensitive to the affect of Atrazine. 19 Furthermore, from a practical standpoint this is the 20 most widely available and most robust experimental 21 model species among aneurines.</p> <p>22 The tests should be conducted such that 23 the stage known to be sensitive to the affects of 24 estradiol on gonad development are included. The study 25 should terminate at Stage 66 which is completion of</p>



<p style="text-align: right;">Page 186</p> <p>1 metamorphosis. The tests should be conducted using a  2 flow through conditions and should conform to the ASTM  3 standards for organismal loading. Atrazine  4 concentrations should bracket those used in other  5 studies, particularly those which demonstrate an affect  6 on gonad development, and Atrazine concentrations must  7 be verified analytically.</p> <p>8 A positive control, 17 beta estradiol  9 for E2 should be included to demonstrate the  10 sensitivity of the species under the test conditions  11 used.</p> <p>12 Sample size should be sufficient to test  13 the hypothesis to determine a priority by power  14 analysis. Minimal replication was set at two tanks per  15 treatment. All organisms on tests were to be sampled.</p> <p>16 The principal end points were to include  17 growth, survival, development, gross gonadal morphology  18 and gonadal histopathology.</p> <p>19 Again, based on experimental problems  20 observed in the studies available for review in 2003  21 several quality indicators were proposed to ensure that  22 a quality tier one study was conducted.</p> <p>23 Proposed test conditions required that  24 the organism loading did not exceed eight STM standards  25 and a minimum pH ammonia and dissolved oxygen were</p>	<p style="text-align: right;">Page 188</p> <p>1 SAP's major responses to the Agency's analysis were  2 that EPA's reviews and conclusions were thorough,  3 appropriate and valid, that significant data existed to  4 formulate a hypothesis that Atrazine exposure causes  5 gonadal abnormalities, but existing data were  6 insufficient to test the hypothesis, and that  7 additional studies were warranted.</p> <p>8 The SAP endorsed the tiered analysis  9 plan as logical and recommended that tier one studies  10 should proceed immediately. The SAP also suggested the  11 ecological relevance of the studies should be initiated  12 as early as possible within the framework of an  13 analysis plan.</p> <p>14 Finally the SAP agreed with the Agency  15 that standard methods needed to be used which conform  16 to ASTM standards, including the use of flow through  17 exposure conditions.</p> <p>18 Given the Agency's recommendations for a  19 tiered analysis plan and an endorsement of that plan by  20 the SAP, how was the tier one study approached?</p> <p>21 As I mentioned earlier, we recommended  22 that estradiol be used as a positive control in the  23 tier one study as an indicator of species sensitivity  24 towards estradiol affects under the test conditions  25 used. However there was insufficient information to</p>
<p style="text-align: right;">Page 187</p> <p>1 monitored regularly and did not exceed acceptable  2 levels. The required survival of test organisms should  3 meet or exceed 90 percent.</p> <p>4 Growth as determined by body weight  5 should approach a maximum of approximately 1.5  6 grams at  7 Stage 60 and the terminal body weight at Stage 66 at  8 the end of the test should be approximately 50 percent  9 maximal.</p> <p>10 This recommendation was based on the  11 fact that the maximal body weights are typically  12 achieved between Stage 58 and 60, followed by a period  13 of weight loss through metamorphic climax.</p> <p>14 And finally metamorphosis should be  15 completed in less than 10 weeks.</p> <p>16 To summarize our recommendations for the  17 2003 analysis, in order to reduce the major  18 uncertainties associated with the potential risk of  19 Atrazine to amphibians, the Agency recommended that  20 additional studies be conducted that followed a tiered  21 sequence of laboratory investigations that focus on the  22 critical components of the risk hypothesis. The  23 currently available, high quality methods which are  24 standard for aquatic toxicology establish and adhere to  25 study quality indicators.</p> <p>In response to the 2003 white paper the</p>	<p style="text-align: right;">Page 189</p> <p>1 establish an estradiol test concentration. So the  2 registrant decided to develop estradiol dose response  3 data in a preliminary study to ensure the appropriate  4 test concentrations would be used in the tier one  5 study.</p> <p>6 Once that was accomplished the tier one  7 Atrazine study could be conducted which was the subject  8 of the Agency data call in.</p> <p>9 So what was the rationale for the  10 estradiol study?</p> <p>11 By way of review the risk hypothesis  12 that I presented earlier assumed that elevated  13 endogenous E2 estradiol levels were responsible for  14 gonadal affects in males although it should be pointed  15 out that other mechanisms could be operative as well.</p> <p>16 Therefore, to reinforce the validity of  17 the tier one Atrazine study an E2 positive control was  18 included by the registrants, primarily to test the  19 sensitivity of the species using a specified  20 experimental protocol.</p> <p>21 The preliminary work was also used to  22 establish histological sampling technique and develop  23 diagnostic histopathology terminology. The  24 recommendation was that estradiol concentrations could  25 be set at the EC50 concentration based on complete sex</p>

<p style="text-align: right;">Page 190</p> <p>1 reversal, basically altered male/female sex ratios.  2 The preliminary estradiol study results  3 demonstrate the EC50 to be .2 micrograms per liter.  4 In November of 2004 a data call in was  5 issued to the registrant to conduct the tier one study  6 as recommended by EPA and endorsed by the SAP.  Earlier  7 I showed the recommended approach. Here I would like  8 to show how the actual study was conducted compared to  9 the original recommendation.  10 Xenopus laevis was used as the test  11 species and the developmental stage utilized in the  12 study included most of the estrogen sensitive period.  13 The test was terminated when organisms attained Stage  14 66. Flow through conditions were used and loading  15 rates were below the 1 gram per liter per day ASTM  16 recommendation.  17 The Atrazine concentrations were .01,  18 .1, 1, 25 and 100 micrograms per liter which bracketed  19 the range of concentrations used in the previous  20 studies. These concentrations were analytically  21 verified by LCMSMS periodically throughout the study.  22 As discussed earlier an estradiol  23 positive control at 2 micrograms per liter was  24 incorporated into the experimental design. The number  25 of organisms on test in each tank was 25. Tank</p>	<p style="text-align: right;">Page 192</p> <p>1 followed the recommended approach, there were  2 experimental deviations. Atrazine contamination was  3 discovered in a block of four control tanks in one of  4 the laboratories and in the other laboratory Atrazine  5 contamination was found in the estradiol positive  6 control. This contamination events were discovered  7 through the routine chemical analyses conducted  8 periodically throughout the studies. The magnitude and  9 time and duration of the contamination will be  10 discussed in more detail in the analysis presentation  11 which follows.  12 And in addition, two replicate tanks for  13 the 1 microgram per liter Atrazine treatment group in  14 one laboratory were lost due to mortalities, explained  15 by the registrant as the result of an algae bloom.  16 Again, the implications of these lost replicates will  17 be addressed in the analysis presentation.  18 To provide you with a sense of how this  19 work unfolded over time, the critical events are mapped  20 onto a time line which spans an interval from the  21 previous SAP meeting in 2003 to the current meeting of  22 the SAP.  23 Starting on the left I will walk you  24 through the time line. In February 2003 all of the  25 data from the relevant studies were collected and the</p>
<p style="text-align: right;">Page 191</p> <p>1 replication was 8 for each of the Atrazine and  2 estradiol treatments and 16 for the clean water  3 controls. All organisms on test were sampled.  4 Gross survival, development, gross  5 gonadal morphology and gonadal histopathology were  6 evaluated as recommended.  7 In terms of the quality indicators the  8 study met the ASTM standards for loading. As I  9 previously mentioned, the water quality parameters of  10 pH, ammonia, dissolved oxygen were within acceptable  11 ranges. Several exceeded 90 percent with the minimum  12 survival survival exceeded 90 percent with a minimal  13 survival of 93.5 percent for one of the replicate  14 tanks.  15 Although originally recommended maximal  16 body weights were not measured due to the excessive  17 handling that would be required in the middle of the  18 test, terminal body weights at Stage 66 were  19 approximately 500 milligrams which suggested the  20 protocol was sufficient to promote acceptable growth.  21 And finally metamorphosis was complete  22 within seven weeks, well below the ten weeks maximum,  23 indicating that the test conditions were adequate to  24 promote normal metamorphic development.  25 Although the conduct of the DCI study</p>	<p style="text-align: right;">Page 193</p> <p>1 original Agency white paper was developed and submitted  2 to the SAP which met in June 2003.  3 Following the SAP meeting the registrant  4 submitted a preliminary study design based on the  5 outcome of the SAP meeting and began additional  6 preparative work, such as coordinating the power  7 analysis and establishing facilities that could  8 accommodate these relatively large studies, which the  9 registrant at two independent laboratories, one in the  10 U.S. and the other in Germany.  11 In May of 2004 the E2 positive control  12 study was submitted to the Agency for comment and those  13 studies were initiated in 2004.  14 The Agency data call in was issued in  15 November of 2004 and the E2 positive control study  16 exposures were completed in December of 2004.  17 The tier one study design was submitted  18 to the Agency for comment in April of 2005. The tier  19 study exposures were initiated in September of 2005 and  20 were completed in December of 2005.  21 The pathology was submitted in April of  22 was completed in April of 2007 and the final report in  23 response to the data call in was submitted to the  24 Agency in June of 2007 which brings us to the current  25 SAP meeting.</p>

<p style="text-align: right;">Page 194</p> <p>1 Through this presentation I have  2 detailed the approach taken to develop and implement  3 the scientifically sound analysis plan which would  4 provide additional data to aid in the assessment of  5 Atrazine risk as it pertains to the affects of Atrazine  6 on gonad development in <i>Xenopus laevis</i>.  7 First I summarized the conclusions and  8 recommendations of the original Agency white paper  9 presented to the SAP in 2003 which indicated that there  10 were significant weaknesses in the existing data at the  11 time that prevented one from clear assessing the  12 hypothesis that Atrazine exposure resulted in gonad  13 affects in aneurines.  14 The Agency proposed a tiered analysis  15 plan which addressed the uncertainties at various  16 levels in the risk hypothesis. The SAP agreed with the  17 Agency's analysis and endorsed the tiered experimental  18 strategy embodied in the analysis plan.  19 The registrant submitted a tier one  20 study plan in response to the Agency's data call in and  21 finally a time line was presented that details the  22 implementation of the tier one study into 2007.  23 Including the conduct of the preliminary  24 E2 studies and the tier one Atrazine studies, in  25 general the registrant met the intent of the data call</p>	<p style="text-align: right;">Page 196</p> <p>1 cluster.  2 DR. FRANKENBERRY: This is Mary  3 Frankenberry, I'm giving some of the stat analysis but  4 that was probably detailed in it. The company did do a  5 test the cluster differences on every end point and  6 with every two tanks and I think as Doctor Silken said  7 they found 1 out of 160 or so.  8 We noted that the test was not very  9 powerful but we didn't go beyond that and we did  10 collapse and use the tanks as replicates, not clusters  11 and I think the company did as well.  12 DR. BAILEY: Okay, Ted Bailey again. I  13 wasn't talking about the analysis, I was talking about  14 the application of the treatments. And when you  15 applied the flow to those four containers, that  16 essentially is one replication, not eight, because you  17 didn't do the complete containers independently. It  18 was not randomized across those four, let alone those  19 eight containers.  20 So the experimental unit was a group of  21 four tanks and those four tanks all received the same  22 treatment. So that would not be eight replications or  23 four replications even.  24 DR. DIGGITS: Well it would still be  25 because they used tank splitters so that the flow to</p>
<p style="text-align: right;">Page 195</p> <p>1 in for these studies and though these studies generally  2 met the study quality requirements, there were  3 deviations in the actual conduct of the study. These  4 deviations will be addressed in the analysis of the  5 study results which will be covered in the next two  6 presentatons.  7 Thank you.  8 DR. HEERINGA: Thank you very much,  9 Doctor Diggitts. At this point I'd like to open it to  10 the panel for any questions of clarification by Doctor  11 Diggitts, the speaker on this particular presentation.  12 Yes, Doctor Bailey.  13 DR. BAILEY: Ted Bailey. On page 6, your  14 side number 18 you indicate 8 replications for Atrazine  15 treatments. And I think in lieu of our discussion this  16 morning that that's not going to be accepted because  17 the four tanks that received the flow were treated as  18 one unit. They were not randomized. I mean they  19 weren't filled independently, the tanks.  20 So each time the four tanks were filled  21 that would correspond to one application, the way the  22 flow of the treatment came.  23 DR. DIGGITS: The flow goes into  24 clusters of four tanks and there's two cluster per  25 treatment, yes. We did not analyze the data by</p>	<p style="text-align: right;">Page 197</p> <p>1 the group of tanks was split four equal ways.  2 DR. BAILEY: But there was one mixing cup  3 that provided that flow.  4 DR. DIGGITS: So you're suggesting that  5 the mixing cup is the source of replication and  6 conventionally it's the tank.  7 DR. BAILEY: You would have had, on one  8 of those clusters it would have been necessary to have  9 four mixing cups, not one. Four, one for each of them,  10 mix it up four times for the four tanks for that to be  11 an experimental unit.  12 DR. HEERINGA: I think at this point  13 we'll return to this in the presentation, the  14 discussion of the statistical analysis and then in our  15 comments. I take the point but is everybody clear on  16 the actual mechanics of the delivery of the flow, one  17 mixing vial with a mixing gauge essentially through  18 four separate routes to the four separate tanks?  19 Yes, Doctor Delorme.  20 DR. DELORME: Peter Delorme. I was just  21 wondering if you could go to slide 20 and comment on a  22 disparity.  23 You say that there was contamination in  24 the eight replicate tanks, yet the presentation this  25 morning said four.</p>

<p style="text-align: right;">Page 198</p> <p>1 DR. STEEGER: It's four, it's a typo on 2 the slide. 3 DR. DELORME: Okay. And the same for the 4 loss of two replicate tanks and the .1 would be the 5 bloom effect? 6 DR. STEEGER: Yes. 7 DR. DELORME: Okay, thank you. 8 DR. HEERINGA: Yes. 9 MR. PAULI: This is Bruce Pauli, 10 Environment Canada. Can we go to 17 please? 11 I was just wondering, something that 12 I've been thinking about and this comes back to a 13 question Doctor Patino asked this morning. The 14 protocol that was settled on was to go from 42 to 54, 15 right? And that didn't happen in the end, it's just 16 the developmental stage when the exposures happened. 17 I'm interested in guidelines as I think 18 you know and I wondered if this is a deviation that we 19 might be addressing shortly or is this, did that happen 20 basically because of logistics that the animals had to 21 get to Berlin? 22 DR. STEEGER: It happened because of 23 logistics and because our experience in the pilot 24 studies indicated that starting at an earlier stage 25 there was a higher rate of mortality in the treatments.</p>	<p style="text-align: right;">Page 200</p> <p>1 points that you kind of brushed up on was a decision 2 not to pursue studies of North American species and I 3 wondered if you can flesh that out? 4 If you're going to do it later that's 5 fine as well. 6 DR. STEEGER: The decision not to pursue 7 testing with indigenous species came about for two 8 reasons. One, because we were unable to demonstrate an 9 affect with Xenopus in the previous SAP. It indicated 10 that there was no difference between Xenopus in terms 11 of biochemical pathways, physiological responses 12 compared to indigenous species. 13 The second reason is that it took 14 roughly two years to develop the protocols for 15 conducting the definitive Atrazine study using a 16 regularly tested amphibian species that could be 17 induced to spawn, that would have a reasonable amount 18 of time to complete metamorphosis within the study 19 period. 20 Using indigenous species the husbandry, 21 coming up with the proper husbandry and standards for 22 the conduct of that study seems to be a daunting task 23 at this point. 24 DR. SKELLEY: Well as someone who works 25 with this is Dave Skelley again as someone who</p>
<p style="text-align: right;">Page 199</p> <p>1 But just to get the animals to Berlin 2 required that both studies start at developmental Stage 3 46 as opposed to 42. 4 MR. PAULI: It's Bruce Pauli, so the 5 pre-studies with E2 were full window, 42 to 54? 6 DR. STEEGER: I don't recall, I'd have to 7 ask Mr. Osmer. 8 DR. HEERINGA: Mr. Osmer, if you want to 9 come on up please. 10 MR. OSMER: Alan Osmer, Syngenta. I 11 don't recall if they were at 42 or 43, what that stage 12 was. We did attempt earlier staging. The commercial 13 supplier, Xenopus Express, had, or Xenopus One had 14 advised against it. You know, these people ship 15 Xenopus around the world. They advised us against it. 16 We tried several times, and as Doctor 17 Steeger mentioned, just the physical handling, whether 18 they were going to Maryland or Berlin, just that 19 handling led to high mortalities and we essentially 20 reverted back to what most researchers were using, the 21 Stage 46, 48 as the starting point. 22 DR. HEERINGA: Doctor Skelley. 23 DR. SKELLEY: Doctor Steeger, I'm not 24 sure if this question's for you but, and if you're 25 going to address it later that's fine, one of the</p>	<p style="text-align: right;">Page 201</p> <p>1 works with North American species I'll take that as a 2 compliment. 3 So as you know the 2003 SAP report 4 actually strongly encouraged that on the basis that, I 5 guess the short way to put this is Xenopus is strange, 6 it's kind of an outlier among amphibians, you name it, 7 everything is different. 8 So what is the basis of your confidence 9 that this wouldn't have turned out differently with a 10 different, say a North American species? 11 DR. STEEGER: We do not have any 12 information to substantiate that claim. Our confidence 13 is only based on the fact that the SAP in 2003 could 14 not identify a reason that Xenopus would not serve as a 15 reasonable model for representing amphibian species, 16 nor could they identify any process in Xenopus that 17 would be different than an indigenous species. 18 You are correct, they are very strange 19 animals, they're purely aquatic and have a lot of 20 baggage to support the fact that they are strange. 21 DR. HEERINGA: Doctor Schlenk. 22 DR. SCHLENK: Just a question of 23 curiosity and life history, I'm curious, does Xenopus 24 actually live under flow through conditions or is I 25 mean I realize you have to do the flow through</p>



<p style="text-align: right;">Page 202</p> <p>1 conditions for the water quality issues, but in the  2 wild are they actually under flow through conditions or  3 are they more of a, you know, stagnant water type of  4 life history stage for where they survive?  5 DR. STEEGER: My understanding, and this  6 is based on personal opinion, is that the Xenopus  7 appear to be able to live just about anywhere. They  8 live in static conditions as well as flowing, but it  9 appears as though much of their habitat is static.  10 We do have in the audience Louis Dupree  11 who is very well versed on Xenopus. If Louis Dupree  12 wants to comment on that.  13 DR. HEERINGA: Doctor Dupree, if you'd  14 come forward please.  15 DR. DUPREE: This is Louis Dupree,  16 Northwest University of South Africa.  17 The way you described it is very  18 accurate. Xenopus is a very opportunistic frog. You  19 will find it from roadside pools to bigger dams and you  20 do find them in rivers and streams. But primarily in  21 static water. But they do very well in any water body.  22 And the best place to find them is in sewage ponds.  23 DR. HEERINGA: Thank you, Doctor Dupree.  24 Doctor Delorme and then Doctor Portier.  25 DR. DELORME: Just an additional comment</p>	<p style="text-align: right;">Page 204</p> <p>1 being a statistician is that I don't have to go in  2 sewage ponds looking for frogs.  3 Twice today there has been mentioned to  4 a power study or a power analysis that was done. And I  5 wondered if somebody could give a little bit more  6 information on what outcomes were used as the basis of  7 the power and whether there was really discussion on  8 what affect sizes were we looking for when you settled  9 on sample sizes? And that may be covered in the  10 analysis phase, but we're talking design right now and  11 for me design is power.  12 DR. FRANKENBERRY: Yes, actually EPA did  13 not do an after the fact power analysis. In the  14 protocol there was one done and I think the protocol  15 then subsequently changed. I just learned this morning  16 that Syngenta has done an extensive one I guess in the  17 past few weeks. And there is maybe much more  18 definitive than anything done before.  19 At some point maybe they could discuss  20 it. I'll be able to tell you what we've done after the  21 fact but it's not as extensive.  22 DR. PORTIER: And it just, something I  23 haven't seen to indicate that power might have been  24 based on the male/female ratio which would have been a  25 simple outcome. And I just wondered if that was kind</p>
<p style="text-align: right;">Page 203</p> <p>1 to what David was saying earlier. I was looking at our  2 response in 2003, I was part of that panel so I  3 actually have my copy here with me, I believe it's e of  4 question let me get the number here anyways, it's  5 one of the later questions that we were asked and I can  6 read out the question for the record.  7 In this regard are there important  8 differences between species to conclude that any  9 affected developmental processes observed in Xenopus  10 would not occur in Rana?  11 Several panel members stated there are  12 little or no evidence to demonstrate that there are  13 significant differences in development processes that  14 would preclude the Agency from using Xenopus as a  15 model  16 in future studies. However some panel members noted  17 that there are significant differences between the two  18 groups of species in timing of life cycle events such  19 that concerns about differences in developmental  20 pathways cannot be eliminated.  21 So I think our conclusion as a panel was  22 they're not one for one and you cannot totally  23 eliminate the differences between them. Just for  24 clarification.  25 DR. HEERINGA: Doctor Portier.  DR. PORTIER: One of the benefits of</p>	<p style="text-align: right;">Page 205</p> <p>1 of what they were originally thinking.  2 DR. HEERINGA: I think Doctor Silken's  3 motioning. Are you willing to have him come forward  4 and discuss the Syngenta power  5 DR. PORTIER: Yes.  6 DR. HEERINGA: Doctor Silken, please.  7 DR. SILKEN: This is Doctor Silken and I  8 really don't want to interrupt EPA's flow, so I'd like  9 to come back to this a little bit later when we can do  10 this a little more extensively.  11 But we did for Syngenta as the  12 statistical people on the study, we did do both an  13 early pre-study evaluation of the power looking at what  14 affect sizes we could detect, depending upon the  15 numbers of tanks and the number of animals within the  16 tank and assuming a different correlation structure  17 within the tank.  18 So there was a pre-power analysis.  19 There was also a post or after the fact power analysis  20 which was done by simulation to take into account the  21 whole statistical analysis regime. And that was done  22 for both measurement end points such as age, body  23 weight, time to metamorphosis, those continuous  24 measures.  25 There was also a power analysis done for</p>

<p style="text-align: right;">Page 206</p> <p>1 incidence based, the percentage, the counts data. And  2 we did, we do have slides that we can show about the  3 different affect sizes and how those affect sizes were  4 affected by 8 versus 16 controls. And we can show that  5 the power for E2 versus Atrazine were comparable.  6 So at an appropriate time we can give a  7 quantitative as well a qualitative discussion of power  8 at your convenience.  9 DR. HEERINGA: Doctor Silken, if you  10 wouldn't mind what I would prefer to do is coordinate  11 with the EPA scientific staff and we'll try to find a  12 way. I appreciate that way you've handled that and I  13 want to make sure that anything that's presented at  14 this point comes with their approval and at their  15 request. So we'll do that.  16 What I'd like to do, any other immediate  17 questions, and I think the power analysis issue too as  18 long as we consider it in conjunction with the  19 statistical analysis discussion, I think would be  20 appropriate, even though it is a design stage issue, it  21 bears on the question of interpretation of the data  22 too. So we'll consider it there.  23 Are there any other questions at this  24 point? In that case I would like to take a fifteen  25 minute break and return at 3:20.</p>	<p style="text-align: right;">Page 208</p> <p>1 DR. LEBLANC: Gerry LeBlanc, just sort of  2 a general question. It seems that one of the  3 criticisms EPA has received in this whole process is  4 basically not putting a lot of weight in the open  5 literature. And I understand why. It's perfectly  6 logical to me.  7 But I'm just wondering if in the intent  8 for openness and inclusiveness, did you ever look at  9 the contract study results which were done under GLP's  10 and we had good control over, look at the results and  11 then go back to the open literature and say, now does  12 it support it, does it contradict it? Is there any  13 benefit, anything added if we look at the open  14 literature now in comparison to that data?  15 DR. STEEGER: I think we tried this is  16 Tom Steeger I think that the Agency always tries to  17 go back and look at how studies that have been  18 conducted according to Agency guidance compares to  19 what's showing up in open literature in terms of  20 affects and at what concentrations.  21 There were as I pointed out in the  22 slide, looking at the 19 studies that have been  23 conducted since the 2003 SAP, some concordance with  24 what the DCI, the data call in studies have indicated,  25 that although a majority of studies that were</p>
<p style="text-align: right;">Page 207</p> <p>1 Panel members, if we could just meet  2 briefly in the breakout room just for a short  3 administrative note, and I'd like to speak I guess with  4 Doctor Frankenberry and Doctor Steeger as to how they  5 might want to handle this supplemental discussion.  6 (WHEREUPON, there was a recess.)  7 DR. PORTIER: Okay, we're moving quite  8 fast on our program here and talking with Doctor  9 Heeringa, we're going to attempt to go through the  10 overview of the DCI studies and then the overview of  11 the statistical analysis. And that'll probably be the  12 end of day today and we'll come back tomorrow morning  13 with a discussion of the power analysis which gives the  14 EPA staff time to look at Doctor Silken's material.  15 And then at that point we'll have the  16 Agency conclusions and that'll start our panel  17 deliberations at that point.  18 So I'm figuring we have about another  19 hour or a little less or a little more.  20 And before we move into the next  21 presentation I'm going to continue to see if the panel  22 has any additional questions for the overview of the  23 open literature or the scientific approach to the  24 design of the data call in studies. Do we have any  25 additional questions or comments? Yes, Doctor Leblanc.</p>	<p style="text-align: right;">Page 209</p> <p>1 available, there is no affect that has been produced by  2 Atrazine on amphibian gonadal development.  3 I did not want to give the impression  4 that we have discarded open literature as a source of  5 information. Clearly in 2003 we raised they hypothesis  6 that Atrazine could potentially affect amphibian  7 gonadal development and we're here today because of the  8 open literature that was available to us at that time.  9 So there were a lot of lessons learned  10 and much of the information in terms of putting this  11 very detailed study together and actually being able to  12 accomplish it was a result of the open literature and  13 what we learned from it.  14 DR. LEBLANC: Just as a follow up I  15 agree. I think the value of the open literature is  16 enabling the Agency to establish the hypothesis in the  17 first place.  18 But it just, I guess when, in reading  19 the white paper it just wasn't clear to me as to  20 whether or not the Agency ever then looked at that data  21 and the additional open literature data a second time  22 to see if there's any value there now to contribute to  23 the more definitive questions that are being asked, or  24 whether it simply was used simply to establish the  25 hypothesis and nothing further?</p>

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1 DR. STEEGER: No, we did use the open  
2 literature subsequent to 2003 as lines of evidence to  
3 confirm that in addition to the DCI studies, that it  
4 does not appear that Atrazine exposure results in  
5 consistent affects on amphibian gonadal development.  
6 There does not appear to be a dose  
7 response, there doesn't even appear to be a  
8 cause/effect relationship across most of the studies  
9 that are available in the open literature.  
10 DR. LEBLANC: And that's important.  
11 Again I don't want to belabor the point but I think  
12 that the, it's important to make it clear that you  
13 embrace the open literature in the decision making,  
14 rather than just simply excluding the open literature  
15 because of a variety of problems.  
16 DR. STEEGER: Yes. We do make use of the  
17 open literature.  
18 DR. PORTIER: Any additional questions?  
19 Well, seeing none I guess we'll move on with the next  
20 presentation by Doctor Steeger on overview of the  
21 Atrazine DCI studies.  
22 DR. STEEGER: In this presentation I'm  
23 going to continue to build on what Doctor Diggitts just  
24 discussed regarding the DCI study design. I will  
25 provide an overview of the study conducted by the

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1 registrant in response to the data call in that was  
2 issued in November of 2004.  
3 In response to both the EPA and the  
4 FIFRA SAP in 2003 which recommended a tiered study  
5 approach that initially focused on laboratory studies,  
6 Syngenta developed a tier one study protocol.  
7 In November of 2004 the Agency notified  
8 the technical registrants that they were required to  
9 conduct a study to address the uncertainties identified  
10 during the 2003 SAP.  
11 Consistent with the recommendations made  
12 by both EPA and the SAP, the tier one studies were  
13 laboratory based and used *Xenopus laevis* larva.  
14 The Agency reviewed the registrant's  
15 proposed study protocol and its associated standard  
16 operating procedures throughout the development of  
17 these documents.  
18 The registrant conducted pilot studies  
19 using 17 beta estradiol to ensure that the protocols  
20 were adequate for measuring the potential affects of  
21 chemicals on amphibian gonadal development. During  
22 the  
23 pilot studies EPA inspected both in live phase  
24 laboratories to ensure that the protocols were being  
25 followed.  
Based on the pilot studies and EPA's

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1 inspections, the Agency made additional  
2 recommendations  
3 on the proposed study protocols and the registrant  
4 incorporated the necessary changes.  
5 Feeding regimes and algae blooms that  
6 resulted from too much food being provided was the  
7 predominant component of the modified protocols.  
8 The registrant conducted two independent  
9 laboratory studies with Atrazine. One of the studies  
10 was conducted with Wildlife International in Easton,  
11 Maryland and the other study was conducted by the  
12 Leibniz Institute for Freshwater Biology and Ecology in  
13 Berlin, Germany.  
14 All aspects of the definitive Atrazine  
15 studies were conducted to follow good laboratory  
16 practice, procedures for quality assurance and quality  
17 control.  
18 EPA staff from the Office of Pesticides  
19 Programs and the Office of Enforcement, Compliance and  
20 Assurance conducted inspections of each of the  
21 laboratories involved in the DCI studies and as part of  
22 the inspections reviewed data and the quality assurance  
23 processes in place.  
24 The German GLP Federal Bureau of the  
25 Federal Institute for Risk Assessment also conducted  
inspections of the IGB facility during the conduct of

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1 the study.  
2 For the in life phase of the tier one  
3 Atrazine studies, each study consisted of five Atrazine  
4 treatment groups with nominal concentrations of .01,  
5 .1, 1, 25 and 100 micrograms per liter that were  
6 intended to bracket the concentrations reported in  
7 previous studies to cause gonadal affects in  
8 amphibians. Nominal concentrations were verified  
9 through HPLC and tandem mass spectroscopy. Exposure  
10 solutions were delivered through a continuous flow  
11 through system at a rate sufficient to maintain a  
12 loading rate of less than 1 gram per liter per day.  
13 The positive estradiol control relied on  
14 a concentration of 0.2 micrograms per liter of  
15 estradio, representing the median effect concentration  
16 of estradiol for the feminization of males. And that  
17 is the increased frequency of males resulting in a  
18 shift in the sex ratio of males to females.  
19 Negative controls were also run. All  
20 treatment tanks were color coded to ensure that the  
21 study was suitably blinded to prevent bias in the data  
22 measurements.  
23 The study was initiated using *Xenopus*  
24 *laevis* larva, eight days post fertilization or six days  
25 post hatch, developmental Stages 46 to 48. And

<p>Page 214</p> <p>1 exposure continued through metamorphosis which is at 2 the complete tail resorption or Stage 66, or after 75 3 days, whichever came first.</p> <p>4 Flow rates through each of the study 5 units was adjusted to yield a loading rate of less than 6 1 gram per liter per day and flow rates resulted in 7 seven complete volume changes in each tank per day.</p> <p>8 Each study unit consisted of a nine 9 liter glass aquarium consisting of 25 larvae and a 10 seven liter treatment solution. Each treatment was 11 replicated each time. Negative controls consisted of 12 16 replicates. With 25 animals per tank, 8 tanks per 13 treatment, 16 for negative controls, each study 14 utilized a total of 64 tanks and 1,600 animals. Each 15 tank was treated as a replicate.</p> <p>16 Again, all the tanks were color coded by 17 treatment to limit potential biases.</p> <p>18 Based on recommendations from EPA test 19 animals were fed Sera Micron two times per day 20 beginning on day 21 of exposure. Supplemental 21 variation was provided to each of the treatment tanks 22 to prevent dissolved oxygen from dropping since one of 23 the performance criteria was that dissolved oxygen 24 levels would remain greater than 60 percent of 25 saturation.</p>	<p>Page 216</p> <p>1 the histology portion were analyzed by Silken &amp; 2 Associates Consulting, Incorporated in Texas. 3 Protocols for these analysis in terms of hypotheses 4 tested and the statistical approaches used were 5 reviewed by the Agency prior to the analysis.</p> <p>6 Most of the statistical analyses were 7 conducted using statistical analysis systems software 8 or SASS software and standard statistical tests.</p> <p>9 The next presentation will provide 10 greater detail on the statistical analysis.</p> <p>11 Although relatively vigorous study 12 conditions were maintained throughout the course of the 13 study, some of the protocol considerations were 14 identified. Issues included the contamination of 4 out 15 of 16 negative controls with Atrazine at 0.1 micrograms 16 per liter at Wildlife International. However because 17 of the frequent weekly analytical measurements it was 18 determined that the contamination was limited to a 19 specific cluster of control tanks and those tanks were 20 discarded from further analysis.</p> <p>21 Also at Wildlife an algae bloom occurred 22 in four additional tanks and these tanks were also 23 discarded.</p> <p>24 Due to a combination of algae blooms and 25 Atrazine contamination a total of 8 out of 16 tanks or</p>
<p>Page 215</p> <p>1 At completion of metamorphosis or after 2 75 days of exposure, whichever came first, the test 3 animals were sacrifice by immersion in tricaine methyl 4 sulphonate. Animals were then weighed and measured, 5 dissected and gross morphology recorded. Digital 6 images were taken of each of the frogs and gonadal 7 surface area was measured with a digital image.</p> <p>8 Afterwards the animals were fixed in 9 solution for histology. Fixed tissues from both 10 Wildlife International and the Leibniz Institute were 11 forwarded to and processed by Experimental Pathology 12 Lab, Incorporated in Sterling, Virginia. Once 13 specimens were embedded in paraffin, longitudinal 14 sections were made of the gonads and kidneys.</p> <p>15 Sectioning continued until the vertebral column was 16 reached. Step sections of 4 to 5 microns in thickness 17 were cut at 12 micron intervals and sections were 18 affixed to glass slides.</p> <p>19 Only slides with gonadal tissues were 20 read. Generally 20 to 30 sections per animal were read 21 by the pathologist.</p> <p>22 For both study laboratories a minimum of 23 57,340 sections were reviewed.</p> <p>24 All of the statistical analysis for data 25 collected during the in life portion of the study and</p>	<p>Page 217</p> <p>1 replicates were dropped from the study. Thus at 2 Wildlife the number of control tanks used in later 3 analysis was the same as in the Atrazine treatments, 4 that's 8 replicates.</p> <p>5 Early in the study algae blooms were 6 observed in 1 out of the 8 tanks in one of the Atrazine 7 treatment groups at IGB, resulting in high mortality. 8 This tank was also dropped from the analysis.</p> <p>9 Additionally, Atrazine was inadvertently 10 added to the positive estradiol controls in one week of 11 the entire exposure at IGB.</p> <p>12 Atrazine degradates were not measured in 13 any of the treatment tanks. Given the measured 14 concentrations deviated from nominal concentrations it 15 would have been helpful to know the extent to which 16 Atrazine was being degraded.</p> <p>17 However, the flow through delivery 18 system was intended to reduce the accumulation of 19 metabolites in the water column and plus the study was 20 not specifically designed to assess the toxicity of 21 Atrazine degradants. Water samples from the study are 22 archived and could be analyzed if necessary.</p> <p>23 Subsequent to the completion of the 24 white paper, Syngenta has provided preliminary analysis 25 of the archived exposure solutions. These preliminary</p>



<p>Page 218</p> <p>1 data indicate that out of the three primary Atrazine 2 degradates diammino chloroatrazine or DACT, 3 deisopropylatrazine, DIA and deethylatrazine, DEA, only 4 DIA and DEA were measured above the level of detection.</p> <p>5 The maximum measured concentrations in 6 the two degradates, DIA and DEA were around .1 part per 7 billion in the highest, that is the 100 microgram per 8 liter Atrazine treatment solution.</p> <p>9 Measured concentrations in the stock 10 solutions were consistent with great than 90 percent, 11 although measured concentrations in treatment units 12 deviated from nominal actual concentrations verified on 13 a weekly basis throughout the course of the study. 14 Reductions in Atrazine concentrations may have been due 15 to uptake by the test organisms or other biological 16 processes. However the actual concentrations did span 17 the intended four orders of magnitude and did not 18 overlap.</p> <p>19 This table reports the mean measured 20 concentrations and their associated standard errors for 21 each of the Atrazine treatment groups by laboratory. 22 The range and percent of nominal is also presented.</p> <p>23 Across the entire study period, measured 24 concentrations averaged between 87 to 112 percent of 25 nominal at Wildlife International, and between 55 to 88</p>	<p>Page 220</p> <p>1 animal with testicular oocytes in the 0.1 microgram per 2 liter treatment. No other occurrence of mixed gonadal 3 tissue was observed in the Atrazine treated animals.</p> <p>4 This study did provide a broad range of 5 histological end points, some of which were 6 statistically significant. However, the biological and 7 mechanistic relevance of those end points in gonadal 8 development is unclear.</p> <p>9 As mentioned earlier, fused kidneys and 10 renal mineralization were statistically significant in 11 both laboratories. However, there is not an apparent 12 relationship with these measurement end points to 13 gonadal development.</p> <p>14 With respect to some of the end point 15 there is uncertainty regarding their interpretation. 16 The relevance of some of the histological end points of 17 the hypothesis is not clear. Observations such as 18 fused kidneys and renal mineralization are two such 19 observations.</p> <p>20 In defense of the researchers though, 21 the Agency requested that the report include any 22 abnormalities or lesions observed in the renal tissue 23 as well as gonads.</p> <p>24 With respect to the histological 25 analysis conducted by Experimental Pathology</p>
<p>Page 219</p> <p>1 percent at Leibniz Institute. The highest amount of 2 variability was associated with the lower treatment 3 concentrations.</p> <p>4 Study results, although there were 5 limitations in the DCI studies, the rigor with which 6 the studies were conducted rendered the studies of use 7 in addressing the hypothesis that Atrazine exposure 8 causes affects on amphibian gonadal development.</p> <p>9 The estradiol positive control 10 demonstrated that the study protocol was sufficient to 11 measure affects on amphibian gonadal development. Sex 12 ratio in the estradiol control was 75/25 female to male 13 and is consistent with the target EC50 for estradiol 14 under flow through conditions.</p> <p>15 The most relevant end points in the 16 study to assess the hypothesis were the extent of 17 inter-sex or mixed sex, sex ratio and time to, and size 18 at metamorphosis.</p> <p>19 The study demonstrated that Atrazine 20 concentrations ranging over four orders of magnitude 21 from .01 to 100 micrograms per liter did not result in 22 an affect on time or size at metamorphosis, sex ratio 23 or the incidence of inter-sex or mixed sex.</p> <p>24 The histological analysis of the gonadal 25 tissue in Atrazine treated frogs only revealed a single</p>	<p>Page 221</p> <p>1 Laboratories where the severity of the measurement end 2 point was rated, it is unclear what serves as a 3 reference. Since all the sections that were reviewed 4 by the pathologist color coded the reader would not 5 have known which animals represented controls and 6 which 7 represented treated.</p> <p>8 There is uncertainty regarding whether 9 some of the comparisons such as the number of gonad 10 oocytes were made relative to amphibian or fish 11 histomorphology.</p> <p>12 There is uncertainty regarding the 13 relevance of gross morphological end points. The terms 14 used as descriptors of some of those morphological 15 features implied an understanding of the underlying 16 cause that would not have been apparent based on the 17 gross morphology and could be determined only through 18 histology. Therefore the histomorphology is considered 19 more definitive than the gross morphology.</p> <p>20 In the next presentation Mary 21 Frankenberry, a Senior Statistician in the 22 Environmental Fate and Effects Division, and coauthor 23 of the 2003 white paper will provide an overview of the 24 statistical analysis of the DCI studies.</p> <p>25 DR. PORTIER: Okay, before we go on do we any questions on the DCI study? I think we've covered</p>

<p style="text-align: right;">Page 222</p> <p>1 a lot of those questions already. I think we'll go on.  2 Doctor Frankenberry.  3 DR. FRANKENBERRY: Thank you. What I  4 have is an overview of the analysis plan and the  5 analysis of the study and then some summary slides of  6 the results that I hope will organize what both the DCI  7 study and EPA's evaluation found in them. Next slide,  8 thank you.  9 The study design employed multiple  10 levels with replicated tanks and controls. As you've  11 heard, we did treat the tank level as the level of  12 replication in the study. There were five Atrazine  13 treatment levels, one positive control and at the  14 beginning of the study, two negative controls and  15 subsequently one at the end with 8 tanks in each group.  16 25 animals per tank developed into approximately 10 to  17 15 males and females, although that ratio was more  18 skewed in some of the tanks. So when the individual  19 sexes were analyzed there were some where the numbers  20 were fairly small per tank.  21 The data were analyzed using one-way  22 analysis of variance followed by comparisons and trend  23 tests. The Kruskal-Wallis and Wilcoxon and Mann-  24 Whitney were the nonparametric equivalent tests used.  25 Many of the major apical end points were represented by</p>	<p style="text-align: right;">Page 224</p> <p>1 One major difference between the DCI  2 study and EPA's evaluation is that EPA tested most of  3 the categorical variables for a one-sided increase in  4 affect across the Atrazine treatment while the DCI  5 study employed more two-sided testing, many not for  6 many more variables, but more than we did.  7 The overall outcome of the analyses were  8 really the same except that EPA found two additional  9 effects as statistically significant in pairwise  10 comparisons and those were fused kidneys and renal  11 mineralization. That was as a result of looking at the  12 one-sided testing rather than the two-sided.  13 Just summing up the differences again,  14 more two-sided testing in the DCI study and mostly one-  15 sided testing with EPA. Also the DCI study assumed  16 that there would be no differences for any pairwise  17 comparisons that followed a non-significant F test.  18 EPA ran those comparisons for the major end points  19 since in some percentage of tests we have found  20 differences. In this case however there were no  21 differences.  22 And then finally EPA required that the  23 contaminated controls not be used in the analyses.  24 Actually one further difference was, I  25 think we mentioned severity codes this morning, EPA did</p>
<p style="text-align: right;">Page 223</p> <p>1 continuous variables, but most of the secondary gross  2 of histology affects were categorical variables.  3 Now a protocol for the statistical  4 analysis was submitted by the registrant to the Agency  5 and reviewed before the pilot studies began. It was  6 subsequently changed, partly by the estradiol, results  7 of the estradiol study and partly in response to  8 comments that EPA made that, some recommendations  9 that  10 were consistent with Agency study evaluation protocols.  11 And then both the study authors and the  12 Agency and its evaluation followed the final analysis  13 plan for evaluating the data.  14 The scope of EPA's review of the  15 studies, over 330 SASS files were submitted to the  16 Agency as part of the studies analysis of the data.  17 They contained data sets and output files as well as  18 program files for running the tests.  19 EPA reviewed all of these, performed  20 quality checks, verified the data sets and outputs and  21 then ran the programs for all end points with a few  22 minor modifications that I'll mention in the upcoming  23 slides.  24 Also for the major, the primary end  25 points EPA ran our own independent Agency programs  and</p>	<p style="text-align: right;">Page 225</p> <p>1 not use the severity codes in our analysis but grouped  2 all of the levels into one measure for affect. The  3 higher level severity codes were so infrequent that we  4 though this made sense and was probably more reliable  5 to do.  6 Now for the major affects or the apical  7 affects, starting out showing no difference as you have  8 seen in many slides this morning. Mortality, failure  9 to complete metamorphosis, age at completion, percent  10 of males as a measurement for sex ratio and mixed sex,  11 and I think as was noted also this morning, there was  12 only one animal in all of the Atrazine treated groups  13 with a strictly defined, the definition of mixed sex.  14 For the apical affects where we did see  15 differences, and this was in pairwise comparisons as  16 well as others, length and weight differences were  17 significant at the same three levels in the IGB lab,  18 both at IGB, both in females and there was no dose  19 response apparent, relationship apparent to us. These  20 were not significant at the Wildlife lab.  21 And if we look at, these are our graphs,  22 they're similar to what you've seen this morning.  23 I did over lunch calculate the affect  24 size which we probably should have had in the white  25 paper that wasn't there.</p>

<p style="text-align: right;">Page 226</p> <p>1 At IGB the decrease for females was 7  2 percent and that was significant. At Wildlife the  3 largest decrease at all, and this was strictly in males  4 also, was six and a half and it was not significant.  5 For snout-vent length the significant  6 affect size at IGB was 2.2 to 3.3 depending on which  7 dose you looked at, somewhere in that range. At  8 Wildlife the largest difference was 1.6 and it was not  9 significant. This may be a case where the 8 extra  10 control tanks would have helped. We don't know but  11 maybe Doctor Silken can help tomorrow morning.  12 For the histology end points where we  13 found a difference, fused kidneys and renal  14 mineralization, they were both in males. This was in  15 pairwise comparisons again. They were at both labs,  16 one lab had one, one at the other, of course both at  17 the 1 part per billion treatment level. This I think  18 was the result of one-sided testing and we don't see a  19 dose response, just at that one treatment level.  20 The secondary gross morphological  21 affects, again in pairwise comparison, these are the  22 significant end points. They cross, include both sexes  23 and both labs, probably about equal numbers. I guess  24 there were a few more at Wildlife here in these, than  25 at IGB. No dose response again and for a gonadal image</p>	<p style="text-align: right;">Page 228</p> <p>1 Wildlife. It was significant in the trend test at IGB,  2 renal mineralization was significant in pairwise  3 comparisons at IGB and those are the two main effects.  4 The Atrazine treated, you'll see  5 consistency between the two labs in the positive  6 control for dilated testis tubules dividing gonad  7 oocytes and internal melanophores. Other effects for  8 the Atrazine treated animals vary between the labs.  9 For Atrazine treated several end points showed a  10 significant overall difference among all levels tested,  11 but no significant differences between any of the, a  12 pairwise comparison between any treatment and control,  13 and these are highlighted with pink but marked as non-  14 significant. Also for these end point, often a major  15 contributing factor to the significance of this test  16 was the difference between two treatment levels, but  17 was greater than the difference between any treatment  18 and control.  19 And finally for the secondary gross  20 effects, hypoplasia was detected in the Atrazine  21 treated animals at one lab and in the positive control  22 at both. Other effects were significant at one lab or  23 the other, including segmental translucence. I think  24 that was significant for both Atrazine treated males  25 and females at Wildlife along with the positive</p>
<p style="text-align: right;">Page 227</p> <p>1 area there was a significant increase in pairwise  2 comparisons at the Wildlife lab. But if you look at  3 the data from IGB that was significant for a decreasing  4 trend in the data. I point that out. Next slide.  5 This is just a summary of the trend  6 tests that were significant at two to four treatment  7 levels. For the first three affects of decreased  8 ovarian cavity size and pigmentation, also  9 mineralization. The trend includes three levels of  10 treatment, were significant at three levels. All at  11 the IGB lab. The gonadal segmental translucence is  12 down at the bottom. It covers four of the five levels.  13 And summary slides similar to what  14 you've seen in the registrant's report, but combined  15 with, put alongside the Atrazine data and the positive  16 controls. The major affects among the Atrazine treated  17 animals, again only the length and weight in the one  18 lab and in the females showed significant differences,  19 pairwise differences, these are shaded in red.  20 Estradiol animals consistently in both  21 labs showed significant affects for the time to  22 complete metamorphosis, the sex ratio and mixed sex.  23 For the histology end points, fused  24 kidneys end point showed significant tests at both  25 laboratories, but in pairwise comparisons, only at</p>	<p style="text-align: right;">Page 229</p> <p>1 controls at Wildlife.  2 The gonadal image area again was  3 significant at Wildlife but decreasing in a significant  4 trend at IGB. The positive controls at both labs  5 showed an increase similar to the increase at Wildlife.  6 Again we have a lighter shading for the  7 end points that showed the significance in the overall  8 tests but were not significant in any pairwise  9 comparison.  10 Finally in conclusion, for many of the  11 categorical end points, a moderate frequency  12 variability in the data was such that results were not  13 reproduced in both labs. For the apical end points in  14 general there appeared to be a sufficient power to  15 detect small to moderate differences, particularly for  16 those represented by continuous end points. But  17 finally the reproductive relevance of a number of these  18 other effects still remains in question.  19 DR. PORTIER: Okay. Doctor Handwerger.  20 DR. HANDWERGER: I'm sorry, I should  21 have asked this question this morning. What do you  22 mean by renal mineralization? Are you talking about  23 calcium deposits? And if you're talking about calcium  24 deposits, where are they, are they tubular, what are we  25 talking about by the term renal mineralization here?</p>



<p style="text-align: right;">Page 230</p> <p>1 DR. WOLFE: Yes, this is Doctor Wolfe.  2 We did not assay them to find out exactly what mineral  3 they were made of. The diagnosis is based purely on a  4 histomorphological conclusion based on my experience in  5 many species of animals.  6 Renal mineralization, I do a lot of work  7 with fish, very, very common in fish. Many species,  8 both, I see it in wild fish, I see it in cultured fish,  9 especially in cultured fish it may have something to do  10 with the way we raise them.  11 But I don't want to get off on a tangent  12 here. In this particular case you asked where in the  13 kidneys they were found. They were often found in  14 tubules. We also had gonadal mineralization for that  15 matter. We had mineralization occurring just at random  16 sites within the gonads.  17 So again this may be part of the fact  18 that our husbandry, while it's good it's not 100  19 percent, or it may be just something that just tends  20 too happen in certain species of animals.  21 DR. HANDWERGER: I don't know much about  22 fish but if it were a human with renal calcium deposits  23 I'd really be very concerned.  24 DR. WOLFE: No, it is extremely common in  25 many species of fish that you look at, from salmonids</p>	<p style="text-align: right;">Page 232</p> <p>1 other and there really was little overlap in terms of  2 numbers. We at first expected that there would be  3 fewer end points that showed up significant at Wildlife  4 and that wasn't the case, at least not in the secondary  5 gross effects.  6 That doesn't mean that some weren't  7 missed of course.  8 We looked at, for the primary end points  9 we did look at the affect sizes that were seen and  10 declared significant. And in general they ranged  11 between about 2 percent and 8 percent. For two of the,  12 for failure to complete metamorphosis and mixed sex  13 those effects were nearly nonexistent across both labs.  14 There was nothing to work with there.  15 The frequency of males between the two  16 labs, there were some tanks that were higher and some  17 were lower, there was variability there but they  18 averaged at most 10 percent in both labs.  19 We didn't go on beyond that.  20 DR. PORTIER: I was struck by the number  21 of zeros in the data set. Doctor Yeater?  22 DR. YEATER: I was wondering if you could  23 clarify by tank because when you were speaking it  24 sounded like you were talking about both labs but then  25 on the slide this is just data from the IGB lab?</p>
<p style="text-align: right;">Page 231</p> <p>1 to small aquarium species, we see it all the time.  2 DR. PORTIER: A lot of statistical  3 questions. I'll hold mine and start with Doctor Bailey  4 I guess.  5 DR. BAILEY: Yeah, Ted Bailey. You have  6 the same experiment conducted at two different  7 locations. Did you consider a joint or a combined  8 analysis of the data?  9 DR. FRANKENBERRY: I think in the  10 original protocol there was a discussion of that. We  11 were not in favor of it and I think the experimenters  12 weren't either toward the end.  13 My personal feeling is that seeing  14 effects in one lab that are not repeated in the other  15 does not negate the finding in the one lab. And I  16 don't think they were controlled well enough to do that  17 in my mind, although we could have tested for them.  18 DR. PORTIER: Kind of associated with  19 that Ken Portier did you see really differences in  20 underlying variability between the two lab studies? I  21 mean I know you did a lot of homogeneity tests within  22 the studies and I wondered if there was a comparison  23 between the study?  24 DR. FRANKENBERRY: We did look at the end  25 points that were significant across, in one lab or the</p>	<p style="text-align: right;">Page 233</p> <p>1 DR. FRANKENBERRY: It's only IGB, I'm  2 sorry  3 DR. YEATER: Okay.  4 DR. FRANKENBERRY: yes.  5 DR. YEATER: And then what are the  6 asterisks for?  7 DR. FRANKENBERRY: Those are the  8 significant  9 DR. YEATER: Thank you.  10 DR. FRANKENBERRY: levels.  11 DR. PORTIER: Doctor LeBlanc, did you  12 have a  13 DR. LEBLANC: No.  14 DR. PORTIER: Okay, Doctor Miller.  15 DR. MILLER: And just to clarify, for the  16 histopath, when they were scored did you say that you  17 did not include those scorings or you actually did on  18 the present/absents?  19 DR. FRANKENBERRY: We combined any  20 level  21 of affect as affect or no affect. I think the  22 company's analysis, even though there were four  23 severity levels put out at the outset, I think they  24 looked at only two, well three, they are no affect and  25 then I think affect at the high any affect greater  than severity level one. And the numbers in those</p>



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1 categories at greater than one up through four were  
2 fairly small for most variables.  
3 And I think we had a little bit of  
4 question about how easy it was to reproduce that.  
5 DR. STEEGER: This is Tom Steeger. To  
6 add to Mary's response, as I indicated in my  
7 presentation, EPA conducted a number of inspections on  
8 the labs and during one of the inspections to EPL I  
9 requested that Doctor Wolfe reread several of his  
10 slides. I had his original diagnoses in front of me  
11 and my intent was to see how well he would replicate  
12 his readings.  
13 So I chose the slides at random plus I  
14 had a few in there that I knew had some marked  
15 pathologies. And while Doctor Wolfe was able to very  
16 well replicate the different lesions, his scorings of  
17 the severity tended to deviate from what is original  
18 reads were.  
19 And so based on what appeared to me to  
20 be somewhat a subjective interpretation by the  
21 pathologist, it moved us towards not sticking with the  
22 original severity ratings.  
23 DR. PORTIER: Doctor Patino.  
24 DR. PATINO: Reynaldo Patino. I think  
25 there was a discussion earlier about what the unit of

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1 You talked about pairwise comparisons  
2 and can you tell me kind of exactly what you did? I'm  
3 trying to decide whether what you did was conservative  
4 or liberal. And I couldn't quite get that by and  
5 that's for statisticians, you know, whether it's  
6 conservative or liberal, it has nothing to do with  
7 politics.  
8 DR. FRANKENBERRY: Yes, actually we can  
9 look at the slide. For the analysis of variance,  
10 anything with a continuous end point we followed up  
11 with pairwise contrast comparisons. For the Kruskal-  
12 Wallace we use the Wilcoxon and Mann-Whitney.  
13 DR. PORTIER: And so the contrasts were  
14 all done on the 5 percent level, .05 --  
15 DR. FRANKENBERRY: Yes.  
16 DR. PORTIER: for significance level.  
17 So there were no Bunn-Ferroni adjustments in here,  
18 nothing that would actually --  
19 DR. FRANKENBERRY: I'm sorry, I think we  
20 did use Dunnance.  
21 DR. PORTIER: Okay, you did a Dunnance  
22 procedure?  
23 DR. FRANKENBERRY: I can look to be sure  
24 though.  
25 DR. PORTIER: As a different meaning.

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1 replication is or should be, but assuming it is a tank,  
2 in slide 2 you show that there was 25 total animals and  
3 when you did the analysis by sex there were as little  
4 as 10 of one or the other sex per tank.  
5 And I was wondering, for the categorical  
6 variables, this indicates that the ability to find an  
7 affect is not the limit of detection, and I don't know  
8 if that's the right term. Was it like 10 percent, that  
9 anything lower than 10 percent, assuming that the tank  
10 is the unit of replication, you would not be able to  
11 detect it?  
12 Is that what you took?  
13 DR. FRANKENBERRY: Yeah, some, that could  
14 explain why we saw a lot of zeros and there may have,  
15 out of 8 tanks there may have 6 tanks with zero  
16 frequency and then perhaps 2 that did have 5 or 6  
17 animals that resulted in a higher frequency overall.  
18 And yes, we could miss the low frequency  
19 numbers. On the other hand we had 8 chances of seeing  
20 them.  
21 DR. PORTIER: I think the phrase you were  
22 looking for is the affect resolution.  
23 DR. PATINO: Yes.  
24 DR. PORTIER: Was like 10 percent or even  
25 less in some, or higher in some cases, 12 percent.

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1 Doctor Bailey.  
2 DR. BAILEY: I think I remember reading  
3 that you did this only after the F test was, will  
4 begin?  
5 DR. FRANKENBERRY: Yes.  
6 DR. BAILEY: Because this would help put  
7 it on the considered us test.  
8 DR. SCHLENK: Dan Schlenk. Just a quick  
9 question, it's more for Doctor Steeger I think. But  
10 again going back I just want to ask you the same  
11 question that I asked the Syngenta folks.  
12 On slide 16 there's the summary for all  
13 the secondary gross morphological affects I guess.  
14 That's what I was getting at this morning, was the  
15 hypoplasia in the male Atrazine dose, which I think was  
16 at the .1, and I hate to do this but if you had seen a  
17 significant affect in both labs, would that have raised  
18 any concerns at all?  
19 I realize that there was a discrepancy  
20 with another indicators that showed the opposite  
21 affect, but I'm just curious what your evaluation of  
22 that particular data set says?  
23 DR. STEEGER: This is Tom Steeger. If  
24 there was an affect noted in both labs, yes, we would  
25 have been concerned.

<p style="text-align: right;">Page 238</p> <p>1 But in general I did not know what to  2 make of the gross morphological affects because  3 hypoplasia, hyperplasia, those terms to me imply that  4 you have an understanding of the causality in terms of  5 there's too few cells or there's too many cells. You  6 can't tell that from a gross morphological basis. You  7 can only tell that the organ was smaller.  8 And so it's only the histological end  9 points that we grade, that I gave greater import to.  10 DR. SCHLENK: And basically what you're  11 saying is that didn't match the histological analysis?  12 DR. STEEGER: In many cases the histology  13 did not match the gross morphological, right.  14 DR. PORTIER: Doctor Handwerker?  15 DR. HANDWERGER: Stuart Handwerker, I'd  16 like to go back to the point that Doctor Miller made  17 about the pathology. I mean I'm not surprised that you  18 would go through the same pathologist and get two  19 different, differences in severity. I see that a lot  20 of time clinically and I'm not surprised by that.  21 But what I am surprised, is that you  22 abandon then with an attempt to quantitate things and  23 I'm wondering why you chose to negate the quantitation  24 by not getting perhaps the import from only one  25 pathologist to handle that.</p>	<p style="text-align: right;">Page 240</p> <p>1 One is that if you look, take any one of these gross  2 morphological features or many of them, when you look  3 at these features histologically, you actually could  4 come up with multiple different types of histologic  5 diagnoses for any one of these gross findings.  6 So for example you said take something  7 like translucence. Translucence on a gross basis, on a  8 microscopic basis that could be dilated tubules, it  9 could be decreased germ cells, one might not be able to  10 find anything histologically to correlate it.  11 So that's one issue about gross findings  12 that is kind of important, is why in gross findings  13 there's a hazard with that.  14 The second thing is I think hypoplasia  15 again was only one treatment group or one dose group,  16 so there wasn't any kind of dose response, it wasn't  17 common between the two different laboratories. And  18 everybody should also remember that another exercise  19 that was done in this study that really wasn't  20 emphasized very much was, we did actually do gonad  21 areas, we did morphometric measurements of gonad areas  22 among the various animals and these were not different  23 among those groups.  24 And to me that's a lot more sensitive  25 measurement than actually estimating and saying, well,</p>
<p style="text-align: right;">Page 239</p> <p>1 And I think in many studies that I read  2 and review where you really want to grade things like  3 that, you have more than one pathologist doing the  4 reading, recognizing the fact that there is this  5 inconsistency, going back and reading the same slide,  6 two people looking at the same slide may come up with  7 different interpretations.  8 So I think if the pathology is really  9 critical to this study and you see that there is this  10 variation, I'm wondering why you didn't have more than  11 one pathologist analyzing some of the critical data.  12 I'd like to just hear what you can say  13 about that.  14 DR. STEEGER: It's our understanding that  15 it is a common practice for a single pathologist to  16 review slides. And it is a charge to the panel whether  17 that is sufficient in this case.  18 DR. PORTIER: I think Doctor Wolfe had a  19 comment on the previous question.  20 DR. WOLFE: Yes. This is Doctor Wolfe.  21 One thing I wanted to follow up on the hypoplasia, I  22 believe again that the hypoplasia was, is supposed to  23 be an indication of the general size of the gonad based  24 upon the gross morphological features.  25 But there's several considerations here.</p>	<p style="text-align: right;">Page 241</p> <p>1 that gonad looks like it's a little smaller than I  2 expect it to be.  3 DR. PORTIER: Is this the same thing as a  4 GSI, would that be a comparable measurement, the  5 hypoplasia measurement, is that the same type of end  6 point?  7 DR. WOLFE: I think that probably is a  8 similar type of calculation. I think the actual gonad  9 are in this case is a lot better than a GSI would be.  10 When you talk about, you know, when we flash these  11 gonads up there on the screen, they look humongous.  12 Okay, we're talking about something that are, you know,  13 a millimeter or less actually when you're looking at  14 them, even under a dissecting microscope, these things  15 are tiny.  16 There would be no way to do a GSI in  17 this particular case. But yeah, you're getting I think  18 similar types of information.  19 DR. PORTIER: And what's a GSI?  20 DR. WOLFE: I'm sorry, this is Doctor  21 Wolfe again, gonadal somatic index, which is a fancy  22 term for, you weight the gonads, you weigh the animal  23 and you can get a ratio.  24 DR. STEEGER: Just as a follow up the GSI  25 was not measured in this study because the organs were</p>

<p style="text-align: right;">Page 242</p> <p>1 not weighed.</p> <p>2 DR. PORTIER: Any additional questions?</p> <p>3 MR. PAULI: Sorry, Bruce Pauli here, can</p> <p>4 we just go over gonadal image area. You were just</p> <p>5 talking about gonad size and I'm just looking at the</p> <p>6 table up there with the image area.</p> <p>7 Is that a can you just explain that</p> <p>8 measurement and whether or not this is a is this a</p> <p>9 one tail?</p> <p>10 DR. STEEGER: The measurement is recorded</p> <p>11 off the digital image and it's just digital analysis</p> <p>12 software that's being used. Mary, do you want to talk</p> <p>13 about this?</p> <p>14 DR. FRANKENBERRY: This was a two tail</p> <p>15 test I'm sure. We looked for an increase or decrease</p> <p>16 and we did see both.</p> <p>17 DR. PORTIER: It looks like the panel has</p> <p>18 run out of questions for the day. And it usually</p> <p>19 happens the first day anyway, we kind of run out of</p> <p>20 steam. It's a lot of material for us to process at one</p> <p>21 time even though we've all read.</p> <p>22 Oh, we've got one more on the end here.</p> <p>23 Doctor Bucher.</p> <p>24 DR. BUCHER: I can't let you get by</p> <p>25 John Bucher. So I've been sitting here looking at the</p>	<p style="text-align: right;">Page 244</p> <p>1 And our expectation is that probably</p> <p>2 after the morning break we'll start with the charge</p> <p>3 questions to the panel.</p> <p>4 I think at this point we're going to</p> <p>5 call today's meeting to an end. We will start again</p> <p>6 tomorrow morning at 8:20 sharp and hope to see you all</p> <p>7 here.</p> <p>8 I'd like to see the panel for a few</p> <p>9 minutes in the break room once you get your stuff</p> <p>10 together and I'll turn it over to Joe Bailey for some</p> <p>11 final comments.</p> <p>12 MR. BAILEY: Just very briefly I just</p> <p>13 wanted to thank the public for attending today and</p> <p>14 thank those who did present public comments during the</p> <p>15 comment opportunity.</p> <p>16 I want to thank EPA presenters for</p> <p>17 giving their presentations today and I want to</p> <p>18 especially thank the panel for their discussions and</p> <p>19 asking questions of the presenters.</p> <p>20 And thank Doctor Portier and Doctor</p> <p>21 Heeringa who will join us back tomorrow.</p> <p>22 So thank you all for being here.</p> <p>23 (WHEREUPON, the meeting was adjourned for the day.)</p> <p>24</p> <p>25</p>
<p style="text-align: right;">Page 243</p> <p>1 estradiol measurements and you've got a dose here I</p> <p>2 think that was used that created 50 percent, it was an</p> <p>3 EC50 dose, right?</p> <p>4 DR. FRANKENBERRY: That's right.</p> <p>5 DR. BUCHER: And looking back of some the</p> <p>6 Hayes work, he's used a dose of half of this and has</p> <p>7 gotten 100 percent sex reversals in his work.</p> <p>8 Have you, have you actually compared</p> <p>9 what he's recorded in some of his papers with what has</p> <p>10 been reported here to try to get a sense of the</p> <p>11 sensitivity of these different studies?</p> <p>12 DR. STEEGER: No, we did not go back and</p> <p>13 do a comparison between the histology of this study and</p> <p>14 that of his.</p> <p>15 DR. PORTIER: This is Ken Portier. Did</p> <p>16 his frogs come from the same source?</p> <p>17 DR. STEEGER: My understanding this is</p> <p>18 Tom Steeger Doctor Hayes' research animals are from</p> <p>19 an in-house culture.</p> <p>20 DR. PORTIER: Someone was just asking me</p> <p>21 whether we were going to do the conclusions, but the</p> <p>22 ground rule is we're going to start tomorrow morning</p> <p>23 with a discussion of the power and then have the</p> <p>24 conclusions and any additional comments that the EPA</p> <p>25 staff want to make to the panel.</p>	<p style="text-align: right;">Page 245</p> <p>1 CAPTION</p> <p>2</p> <p>3</p> <p>4 The foregoing matter was taken on the date,</p> <p>5 and at the time and place set out on the Title</p> <p>6 page hereof.</p> <p>7 It was requested that the matter be taken by</p> <p>8 the reporter and that the same be reduced to</p> <p>9 typewritten form.</p> <p>10 Further, as relates to depositions, it was</p> <p>11 agreed by and between counsel and the parties that</p> <p>12 the reading and signing of the transcript, be and</p> <p>13 the same is hereby waived.</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>

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 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  
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 15 I further certify that the inspection,  
 16 reading and signing of said deposition were waived  
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 18 witness.  
 19 I certify that I am not a relative or  
 20 employee of either counsel, and that I am in no  
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