AGENDA

FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
OPEN MEETING

October 9 - 12, 2007

FIFRA SAP WEB SITE http://www.epa.gov/scipoly/sap/
OPP Docket Telephone: (703) 305-5805
Docket Number: EPA-HQ-OPP-2007-0498

U.S. Environmental Protection Agency
Conference Center - Lobby Level
One Potomac Yard (South Bldg.)
2777 S. Crystal Drive, Arlington,VA 22202

The Potential for Atrazine to Affect Amphibian Gonadal Development

Tuesday, October 9, 2007

8:30 A.M.	**Opening of Meeting and Administrative Procedures** -- Joseph E. Bailey, Designated Federal Official, Office of Science Coordination and Policy, EPA
8:40 A.M.	**Introduction and Identification of Panel Members** -- Steven G. Heeringa, Ph.D., FIFRA Scientific Advisory Panel Chair
8:50 A.M.	**Welcome and Opening Remarks** -- William Jordan, Senior Policy Advisor, Office of Pesticide Programs, EPA
8:55 A.M.	**Introduction - Goals and Objectives** -- Arthur-Jean Williams, Acting Division Director, Environmental Fate and Effects Division, Office of Pesticide Programs, EPA
9:15 A.M	**Introduction - Historical Perspective** --Thomas Steeger, Ph.D., Environmental Fate and Effects Division, Office of Pesticide Programs, EPA
9:45 A.M.	**Break**
10:00 A.M	**Public Comment**
12:00 P.M.	**Lunch**
1:15 P.M.	**Public Comment**
2:45 P.M.	**Break**
3:00 P.M.	**Public Comment**
5:00 P.M.	**Adjournment**

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Wednesday, October 10, 2007

8:30 A.M. **Opening of Meeting and Administrative Procedures** -- Joseph E. Bailey, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:40 A.M. **Introduction and Identification of Panel Members** -- Steven G. Heeringa, Ph.D., FIFRA Scientific Advisory Panel Chair

8:50 A.M. **Overview of Open Literature** -- Thomas Steeger, Ph.D., Office of Pesticide Programs, EPA

9:30 A.M. **Scientific Approach to the Design of the Data Call-In (DCI) Studies** -- Joseph Tietge, M.S., Office of Research and Development, National Health and Environmental Effects Research Laboratory, EPA

10:15 A.M **Break**

10:30 A.M. **Overview of the Atrazine DCI Studies** -- Thomas Steeger, Ph.D., Office of Pesticide Programs, EPA

11:15 A.M. **Overview of Statistical Analysis and Highlights of the Results of the DCI Studies** -- Mary Frankenberry, Office of Pesticide Programs, EPA

11:45 P.M. **Agency Conclusions** --Thomas Steeger, Ph.D., Office of Pesticide Programs, EPA

12:00 P.M. **Lunch**

1:15 P.M. **Charge to Panel - Question 1**

In reviewing the available laboratory and field studies, the Agency used a number of criteria to evaluate individual investigations. Criteria such as experimental design, test protocols, and quality assurance information were used to evaluate the reliability of a study's ability to adequately assess a hypothesis that atrazine

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elicits developmental effects in amphibians, and if so, the nature and strength of associated dose-response relationships.

(a) Please provide comments and recommendations regarding the EPA's approach and criteria used to evaluate the studies.

(b) Given the evaluation criteria employed by the Agency, please comment on EPA's overall application of these criteria to the currently available studies.

2:15 P.M. Charge to Panel - Question 2

The Agency has concluded that the information contained in the open literature published since the 2003 SAP does not provide any additional information that could be used to refute or confirm the hypothesis that exposure to atrazine alone causes adverse developmental effects in amphibian gonads.

(a) Please comment on the comprehensiveness of the Agency's literature reviews relative to the potential effects of atrazine alone on amphibian gonadal development.

(b) Please comment on the Agency's evaluation of the open literature studies and the Agency's conclusion that the data derived from laboratory studies, both individually and collectively, are not sufficient to refute or confirm the hypothesis that atrazine exposure causes developmental effects in amphibian gonads.

(c) The Agency concluded that the field studies are not adequate for assessing the hypothesis at hand. Please comment on the Agency's conclusion. If the SAP concludes one or more of the field studies do provide the means to assess the hypothesis that atrazine exposure results in effects on amphibian gonadal development, please suggest interpretive and statistical methods that should be employed to evaluate the data.

3:00 P.M. Break

3:15 P.M. Charge to Panel - Question 3

Please comment on the Agency's evaluation of the final study design. For example, the Agency concluded that the minor changes in the experimental design [*i.e.*, omitting atrazine degradate (DACT, DEA and DIA) analysis and not conducting differential cell counts for ovarian and testicular histology] did not compromise the means to assess the hypothesis that atrazine exposure can affect amphibian gonadal development. If the SAP concludes that the alterations in the study design preclude or significantly compromise the ability to assess the hypothesis, please discuss to the extent possible, how the specific design modifications could impact the means to assess the hypothesis. Please provide

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comments on other aspects of the Agency's evaluation as well.

4:15 P.M. Charge to Panel - Question 4

The Agency has described the exposure profiles for studies conducted in response to the DCI and has stated that mean-measured concentrations in the studies were lower than target nominal concentrations. However, the Agency concluded that the frequent analytical measurements provide a sufficiently comprehensive understanding of the exposure profile over the course of the studies. Please comment on the Agency's conclusion that the atrazine exposure concentration profile is reasonably characterized and sufficient for documenting the potential effects of atrazine over a broad range of exposure concentrations. In addition, provide comments on whether the actual concentrations were consistent and sufficiently stable to establish the means to analyze exposure concentration-response relationships.

5:00 P.M. Adjournment

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The Potential for Atrazine to Affect Amphibian Gonadal Development

Thursday, October 11, 2007

8:30 A.M. **Opening of Meeting and Administrative Procedures** -- Joseph E. Bailey, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:40 A.M. **Introduction and Identification of Panel Members** -- Steven G. Heeringa, Ph.D., FIFRA Scientific Advisory Panel Chair

8:50 A.M. **Charge to Panel - Question 5**

The Agency described atrazine contamination of negative controls in one out of the two studies and concluded that since the experimental design had twice the number of controls relative to other treatments, the data from these atrazine-contaminated controls could be removed from the analyses without invalidating the statistical interpretation of the results.

(a) Please comment on the Agency's decision to omit half of the controls from the WLI study in the statistical analyses and on the conclusion that the study is still scientific valid. If the SAP has an alternative approach to treating these control data in the statistical analyses, please provide specific recommendations.

10:00 A.M. **Break**

10:15 A.M. **Charge to Panel - Question 6**

The original White Paper (USEPA 2003) identified measurement endpoints that included the possible enumeration of specific histological structures such as the

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number of oogonia in ovaries and the number of spermatids in testes. Such a detailed analysis was not conducted in the studies that are in response to the DCI. Rather, a qualitative assessment of the incidence of ovarian and testicular gonadocytes was conducted. The Agency has concluded that the lack of these data does not limit the means to assess the hypothesis that atrazine exposure affects amphibian gonadal development.

(a) Please comment on whether the lack of these histological data limits the utility of the available information to fail to support the hypothesis that atrazine exposure affects amphibian gonadal development.

(**b)** If the SAP concludes these data are necessary to adequately assess the hypothesis, please provide options to processing and analyzing these data in an efficient and robust manner.

11:15 A.M. Charge to Panel - Question 7

The Agency has described a number of measurement endpoints (*e.g*., translucent gonads, unpigmented ovaries, pigmented testes) based on histology results that were reported in the studies. The Agency, however, based on its understanding of relevant scientific literature, could not conclude that these measurement endpoints are biologically relevant indicators of effects on growth or reproductive success (*i.e.,* the Agency did not interpret these responses as adverse effects *per se*) nor was the Agency aware of any information that established these responses as precursors to the apical endpoints of primary interest (*i..e*., time to and size at metamorphosis, sex ratio, and the presence of mixed and/or intersex animals).

(a) Please comment on the biological relevancy of these endpoints and the extent to which they may reflect reliable measures of developmental abnormalities.

12:00 P.M. Lunch
1:15 P.M. Charge to Panel - Question 8

The Agency's analysis of potential developmental effects in studies responsive to the DCI has focused on histological data as opposed to gross morphological data. The histological data from these studies are based on the analyses of a single certified pathologist. While this approach eliminates the potential variability associated with having multiple pathologists analyze the histological slides, it may introduce an avidity bias.

(**a)** Please comment on whether a single pathologist is sufficient for interpreting the histology data. If the SAP believes that a single pathologist is not sufficient, please comment on the potential value of

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convening a pathology review board to evaluate the findings of the DCI study.

(b) Please also comment on the potential value of having a pathology review board evaluate materials (*e.g.*, digital images of gross morphology and microscope slides containing histological sections) from studies published in the open literature. These data could be submitted voluntarily by the authors and could include slides to evaluate similarities or differences in identifying or describing histological features and/or describing and quantifying histological responses.

2:00 P.M. Charge to Panel - Question 9

After an evaluation of the laboratory-based studies submitted in response to the DCI, the Agency has concluded that these studies do not provide sufficient evidence to support the hypothesis that atrazine causes adverse gonadal developmental effects in amphibians.

(a) In light of the responses to Questions 3 – 8, please comment on whether the results from the study in response to the DCI are sufficiently robust to address the hypothesis that atrazine exposure causes gonadal abnormalities in *X. laevis*. If the SAP concludes these results are not sufficiently robust, what recommendations can the SAP provide to efficiently and reasonably address remaining uncertainties? For example, if the SAP does not believe the DCI study is sufficiently robust to assess the hypothesis, does the SAP believe either the two experiments or a specific component of the two experiments should be reanalyzed or repeated? Please provide the rationale for recommending any additional analyses and/or experiments.

(b) Please comment and provide recommendations on alternate statistical analyses, if any, to evaluate the data derived from the study. If alternative approaches are suggested, please comment, to the extent possible, on the rationale for these approaches and how they represent improvements in the existing statistical interpretations.

2:45 P.M. Break
3:00 P.M. Charge to Panel - Question 10

Is the SAP aware of any other laboratory-based or field-based studies not included in this White Paper that contradict the Agency's conclusions that 1) the designs associated with current studies available in the open literature are not appropriate for evaluating the hypothesis that atrazine affects amphibian gonadal development and 2) the available data in the open literature combined with the

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results of DCI study indicate that atrazine does not cause adverse effects on gonadal development in *X. laevis* when investigated under conditions consistent with those recommended by the SAP in its previous report (SAP 2003). If so, please identify the studies and briefly outline how the results from these studies would contradict the conclusion that atrazine at concentrations up to 100 µg/L does not cause adverse effects on amphibian gonadal development.

4:00 P.M. Charge to Panel - Question 11

The Agency is not aware of data that establish a mechanistic basis for how atrazine could affect amphibian gonadal development. Please identify and comment on any studies that demonstrate the mechanistic steps by which amphibian gonadal development could be affected by atrazine, and thereby contradict the Agency's overall conclusions based on the studies evaluated for this SAP review. If the SAP is aware of any relevant study(ies), please comment on the data from this study(ies) and how the data indicate and quantify a mechanistic pathway from atrazine's molecular site of action to histological and apical endpoints associated with adverse effects on amphibian gonadal development. Please also comment on any dose-response relationships associated with the steps in the reported toxicity pathway.

5:00 P.M. Adjournment

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Friday, October 12, 2007

8:30 A.M. **Opening of Meeting and Administrative Procedures** -- Joseph E. Bailey, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:40 A.M. **Introduction and Identification of Panel Members** -- Steven G. Heeringa, Ph.D., FIFRA Scientific Advisory Panel Chair

8:50 A.M. **Charge to Panel - Question 12**

In its 2003 White Paper the Agency proposed a research approach using focused, empirical laboratory studies based on initial investigations with *X. laevis,* potentially followed by selective, confirmatory laboratory studies with frog species native to North America. However, the 2003 SAP did not identify any important differences between amphibian species to conclude that any affected developmental and/or mechanistic processes observed in *X. laevis* would not be applicable to indigenous ranid species.

(a) Please comment on the Agency's recommendation that data derived from *X. laevis* in the studies evaluated for this review are sufficient to conclude that additional testing with indigenous species is not warranted.

10:00 A.M. **Break**

10:15 A.M. **Charge to Panel - Question 13**

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Based on the available data provided by the DCI studies, the Agency has concluded that atrazine does not adversely affect amphibian gonadal development. The Agency has further concluded that no additional studies are required to address the hypothesis that atrazine adversely affects amphibian gonadal development.

Please comment on the Agency's recommendation that the current body of data is sufficient to refute the hypothesis that atrazine by itself can adversely affect amphibian gonadal development and that no additional data are required to address this hypothesis.

11:15 A.M. Continued Panel Discussion (as needed)
12:00 P.M. Lunch
1:15 P.M. Continued Panel Discussion (as needed)
2:45 P.M. Break
3:00 P.M. Continued Panel Discussion (as needed)
5:00 P.M. Adjournment

Please be advised that agenda times are approximate; when the discussion for one topic is completed, discussions for the next topic will begin. For further information, please contact the Designated Federal Official for this meeting, Joseph Bailey, via telephone: (202) 564-2045; fax: (202) 564-8382; or email: bailey.joseph@epa.gov