AGENDA
FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
OPEN MEETING
July 26 - 29, 2011

FIFRA SAP WEB SITE http://www.epa.gov/scipoly/sap/
OPP Docket Telephone: (703) 305-5805
Docket Number: EPA-HQ-OPP-2011-0399

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

Re-Evaluation of the Human Health Effects of Atrazine: Review of Non-Cancer Effects, Drinking Water Monitoring Frequency and Cancer Epidemiology

Please note that all times are approximate (see note at end of Agenda).

Day 1
Tuesday, July 26, 2011

8:30 a.m. **Opening of Meeting and Administrative Procedures** – Joseph Bailey, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:35 a.m. **Welcome and Introduction of Panel Members** – Daniel Schlenk, Ph.D., FIFRA Scientific Advisory Panel Session Chair

8:45 a.m. **Opening Remarks** – Steven Bradbury, Ph.D., Director, Office of Pesticide Programs (OPP), EPA

9:00 a.m. **Opening Remarks** – John R. Fowle III, Ph.D., Deputy Director, Health Effects Division (HED), OPP, EPA

9:05 a.m. **Atrazine Re-evaluation: Introduction and Status** – Elizabeth Mendez, Ph.D., HED, OPP, EPA

9:20 a.m. **Atrazine: Adverse Outcomes and Mode of Action -** Ralph C. Cooper, Ph.D., National Health and Environmental Effects Research Laboratory, Office of Research and Development, EPA

10:15 a.m. **Break**

10:30 a.m. **Review of Atrazine Cancer Epidemiology** - Carol H. Christensen, Ph.D., HED, OPP, EPA

11:00 a.m. **Integration of Epidemiology and Toxicity Data into Health Risk Assessment -** Elizabeth Mendez, Ph.D., HED, OPP, EPA

11:30 a.m. **Atrazine: Updates to the Dose-Response Assessment with Implications for Water Monitoring Frequency** - Chester Rodriguez, Ph.D., HED, OPP, EPA

12:30 p.m. **Lunch**

1:30 p.m. **Evaluating Atrazine Drinking Water Monitoring Data for Use in Human Health Assessments -** Nelson Thurman, M.S., Environmental Fate and Effects Division, OPP, EPA

2:30 p.m. **Atrazine Re-evaluation: Scientific Considerations in Potential Sensitivity of Infants and Children -** Elizabeth Mendez, Ph.D., HED, OPP, EPA

3:00 p.m. **Break**

3:15 p.m. **Case Studies: Application of Pharmacokinetic Modeling to Inform Water Monitoring -** Chester Rodriguez, Ph.D. and Nelson Thurman, M.S., OPP, EPA

4:00 p.m. **Public Comments**

6:00 p.m. **Meeting Adjourns**

Day 2
Wednesday, July 27, 2011

8:30 a.m. **Opening of Meeting and Administrative Procedures** – Joseph Bailey, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:35 a.m. **Introduction of Panel Members** – Daniel Schlenk, Ph.D., FIFRA Scientific Advisory Panel Session Chair

8:45 a.m. **Public Comment**

10:15 a.m. **Break**

10:30 a.m. **Charge to Panel - Charge Question 1 -** One approach for evaluating the performance of monitoring sampling designs is to simulate different sampling frequency strategies using robust (daily or near-daily sampling during the high use/runoff period) monitoring data. As noted in previous SAPs (April 2010 and September 2010), Heidelberg University's National Center for Water Quality Research (NCWQR) monitoring of selected watersheds in Ohio and the Atrazine Ecological Exposure Monitoring Program (AEEMP) monitoring of headwater streams in the corn belt provide the most robust datasets for atrazine. Using examples from these datasets, the USEPA presented a matrix approach for deriving a bias factor for different sampling frequencies (e.g., 4, 7, 14, 28 day intervals) for use in estimating concentrations for different exposure durations of concern (e.g., 4, 14, 28, 90 day durations).

a) Given that the factors are likely to vary based on watershed size and water body type, comment on the level of detail we would need to develop (e.g., flowing water *vs.* reservoir; small *vs.* medium *vs*. large watershed area). How many datasets would we need to analyze to provide a reasonable representation of a bias factor for each category?

b) Please comment on the advantages and disadvantages of deriving bias factors based on analyses of individual sites and years compared to taking percentiles of averages across sites/years.

11:30 a.m. **Charge to Panel - Charge Question 2 -** The September 2010 FIFRA SAP on atrazine recommended combining a regression model such as WARP with either a deterministic model such as PRZM or a geostatistical approach in order to estimate a time series of atrazine concentrations from less frequent monitoring. In developing methods based on the SAP's recommendations, the USEPA was able to derive reasonable estimations of the time series for sampling intervals of 7-days or shorter using conditional simulations of variogram models without incorporating additional models. Although the simulations

underestimated the 1-day maximums, they appeared to provide reasonable bounds for rolling average concentrations as short as 4 days.

a) Please comment on the Agency's method of estimating time series using conditional simulations of variograms for monitoring data sets such as the AMP CWS monitoring that have 7-day sampling frequencies.

b) Based on the USEPA's analysis using WARP with longer duration sampling intervals (Appendix D.1), what advantages does the SAP see of including WARP modeling in this approach (i.e., better estimation of the daily maximum value)?

12:30 p.m. Lunch

1:30 p.m. Charge to Panel - Charge Question 3 - Given that most monitoring data for pesticides are based on less frequent sampling intervals (e.g., bi-weekly, monthly), the USEPA also explored additional approaches that combined variogram models with covariate approaches – in particular, correlation with flow within a narrow window – or with WARP. We also considered methods of filling in time series concentrations using a deterministic model such as PRZM or a mass balance model, although such approaches would be more resource/data intensive.

a) Please comment on these additional modeling approaches for interpreting sparse (less frequently sampled) monitoring datasets.

2:30 p.m. Charge to Panel - Charge Question 4 - In characterizing overall uncertainty in exposure estimates from monitoring data, the USEPA must also consider how many years of monitoring are necessary to provide a reasonable bound on the year-to-year variability or, alternatively, develop methods of placing the existing monitoring data in context of likely exposures that may occur over a time period of interest (for instance, 15 year cycles for registration review).

a) Please comment on the sufficiency of existing atrazine/triazine monitoring data available to the Agency – in particular the Atrazine Monitoring Program (AMP) coupled with the earlier Voluntary Monitoring Program (VMP), which conceivably span from 1993 to the present for some CWS – for use in characterizing the likely range in year-to-year variability in atrazine/TCT concentrations.

b) Please comment on the Agency's suggestion for using a PRZM hybrid model, calibrated on the current years of monitoring, to provide estimates for a wider time frame by modeling additional years using weather data that span a 30- to 50-year period.

c) What other possible approaches can the SAP recommend for capturing year-to-year variability?

3:30 p.m. Break

3:45 p.m. Charge to Panel - Charge Question 5 - In 2000, the SAP agreed with the Agency's proposal for atrazine's neuroendocrine MOA, and they further concluded that it is unlikely that the mode of action by which atrazine induces mammary tumors in adult female Sprague Dawley rats could be operational in humans. The SAP further concluded that it is not unreasonable to expect, however, that atrazine might cause adverse effects on hypothalamic-pituitary-gonadal (HPG) function in humans if exposures were sufficiently high and that perturbation of the HPG axis was relevant for developmental and reproductive effects (FIFRA SAP, 2000). In the 2003 IRED, the Agency identified perturbations of the neuroendocrine system (particularly LH regulation) leading to reproductive toxicity as the most biologically plausible and sensitive effects attributable to atrazine exposure. The adverse outcomes occurring as a consequence of disruptions to the HPG axis in rats include

disruption of estrous cyclicity and delays in puberty onset (males and females). An additional effect – not directly linked to LH disruption – is the decreased suckling-induced prolactin release in milk early in life (perinatally), which leads to increased incidence of prostatitis in young adult rats. All of these effects can be linked to and/or occur at higher doses than the atrazine-induced changes in LH secretion. Research conducted since the 2003 IRED continues to point to LH surge attenuation as the most sensitive effect in the atrazine database. Consequently, the Agency will continue to use changes in LH secretion as a sentinel endpoint for HPG perturbations and the basis of the atrazine risk assessment. The September 2010 SAP " agreed with the Agency's conclusion that, based on the available data, a benchmark dose (BMD) modeled from data on suppression of the LH surge appears to be protective for other endpoints, since this phenomenon occurs at doses lower than for the wide range of effects identified in a rather extensive toxicological database."

a) Currently available data show that in the rat a brief exposure (as brief as 4 days) to low levels of atrazine can elicit decreases in LH. Please comment on the biological plausibility of these brief changes leading to an adverse outcome taking into account typical variability and how long and how much a LH surge reduction is needed to cause the observed adverse effects (i.e., disruptions in cyclicity, delayed puberty, and prostatitis).

5:00 p.m. Meeting Adjourns

Day 3
Thursday, July 28, 2011

8:30 a.m. **Opening of Meeting and Administrative Procedures** – Joseph Bailey, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:35 a.m. **Introduction of Panel Members** – Daniel Schlenk, Ph.D., FIFRA Scientific Advisory Panel Session Chair

8:45 a.m. **Charge to Panel - Charge Question 6 -** During the September 2010 SAP, the Panel raised the issue of single *vs.* multiple atrazine exposure effects on the LH surge. In their report to the Agency the SAP commented:

"Data are clear in identifying that a greater-than-one pulse of exposure to atrazine is necessary for attenuation of the LH surge. For example, single high doses (over 100 mg/kg) administered on the morning of proestrus did not alter characteristics of the LH surge occurring later the same day. Additional data clearly demonstrate a once daily dose for 4 days and beginning on estrus can induce significant inhibition of the LH surge peak. In this instance, a dose response is observed. However, what is not clear is if less than 4, but greater than 1 days' exposure is sufficient to alter the LH surge. Further complicating the matter, it is not clear if a 4-day exposure, beginning on a different day of the cycle, will result in changes in the LH surge similar to those when dosing begins on the morning of proestrus. Understanding of the relationship between duration of exposure and phase of the cycle will be key in translating rodent data to humans for risk assessment purposes."

In response to the Panel's comments, EPA scientists in the Office of Research and Development have undertaken a series of experiments to try to elucidate the nexus between phase of the cycle and duration of exposure. This research is in the early stages. Initial results suggest that a single high dose of atrazine (100 mg/kg bw) can affect the LH surge. However, the effect seen was an increase in LH rather than the decrease observed after 4 days of exposure.

a) Please comment on the potential relevance of one day exposure to elicit an adverse outcome(s) and the significance of an increase *vs.* a decrease in LH.

9:30 a.m. Charge to Panel - Charge Question 7 - An increased incidence of prostatitis has been observed in the offspring of rats exposed to atrazine from PND 1 to 4. This effect was not linked to an LH alteration, but rather the atrazine related suppression of suckling-induced prolactin release in the lactating dams. Prolactin plays a crucial role in the neonatal brain for normal TIDA neuron development. In the adult offspring, the impaired TIDA regulation is reflected by elevated prolactin levels (hyperprolactinemia). It is this elevated level of circulating prolactin in the adult male rats that has been linked to an increased incidence of prostatitis. It is unknown when the TIDA neurons develop in the human fetus or whether this development is dependent on the maternal prolactin concentrations.

a) Given the biological processes involved in the atrazine-mediated prostatitis in rats, please comment on the human relevance of these findings in rats for the overall hazard characterization for atrazine.

10:15 a.m. Break

10:30 a.m. Charge to Panel - Charge Question 8 - When evaluating the data on mammary gland development, the September 2010 SAP report concluded that the "use of the existing data on rat mammary gland development to assess the potential human risk of atrazine is not warranted at the present time." Regarding the methodological differences between the Rayner *et al.,* and the Coder studies, the Panel commented that "it is surprising that they did not employ both qualitative and quantitative scoring measures of mammary gland development, which would have provided a definitive inter-study comparison." In response to this comment, the Agency has conducted a set of experiments investigating the potential impact of *in utero* atrazine exposure on mammary gland development (MGD) in Sprague Dawley rats using both the subjective scoring methodology described by Rayner *et al.* and a computer-based quantitative methodology (morphometric analysis). Using either quantitative or subjective measures to evaluate mammary gland development, no differences in MGD were found between control or atrazine-exposed rats indicating that gestational atrazine exposure had no demonstrable effect on normal mammary gland development.

a) Please comment on the Agency's findings in addressing the issues raised by the SAP during the September 2010 meeting. Please comment on whether this study (along with the negative studies by Coder) adds to the weight of evidence that it is unlikely that atrazine impacts mammary gland development.

11:30 a.m. Charge to Panel - Charge Question 9 - In 2003, an FQPA Safety Factor was retained in part to address the lack of data evaluating the potential for differences in sensitivity across life stages. Since then, multiple studies evaluating atrazine's potential impact following exposure during the prenatal, perinatal, prepubertal, and adult stages of life have been conducted to address these data gaps. None of the new studies has identified an enhanced sensitivity in the young and the LH surge attenuation observed in females of reproductive age continues to be the most sensitive endpoint.

a) Please comment on the weight of the evidence analysis conducted by the Agency and the extent to which the uncertainties related to the potential for differential sensitivity of the young are addressed with the additional data.

12:15 p.m. Lunch

1:15 p.m. Charge to Panel - Charge Question 10 - Section 3.0 and Appendices B-3 through B-5 of the draft Issue Paper provide the Agency's reviews and synthesis of the atrazine cancer epidemiology studies. These studies examine a variety of cancer endpoints, notably reproductive and endocrine system tumors including prostate, breast, ovarian and thyroid tumors, cancers of the lymphohematopoietic system including

non-Hodgkin lymphoma (NHL), and other cancer types including glioma, pediatric cancers and colon cancer. Section 3.3 integrates the findings of the epidemiology and experimental toxicology studies.

a) Please comment on the sufficiency of the Agency's cancer epidemiology reviews with respect to identifying the major strengths and limitations of each study, and overall synthesis of results by cancer types.

2:15 p.m. Charge to Panel - Charge Question 11 - There is no compelling evidence in the available experimental toxicology database that atrazine may be carcinogenic in humans. This database was reviewed by the SAP in April 2010. Briefly, the results of both guideline and non-guideline *in vivo* as well as *in vitro* studies do not suggest atrazine has mutagenic or carcinogenic properties. With regard to mammary tumors, several internal and external peer reviews have concluded that the mode of action through which atrazine influences mammary tumor development is not operational in humans. Further, EPA's current review of the atrazine cancer epidemiology database did not identify evidence across any of the cancer-specific databases evaluated as to the carcinogenic potential of atrazine that EPA finds sufficiently convincing to change its conclusions. Therefore, in view of the evidence in the experimental toxicology and epidemiologic databases, EPA concludes atrazine is not likely to be carcinogenic in the human population. The observational data lend further support for the human relevance of the laboratory rodent tumor findings, *i.e.*, the databases lack evidence of an association between atrazine and cancer in the human population.

a) Please comment on the extent to which the scientific information supports the integrative analysis contained in Section 3.3 with respect to the similarities, differences of the experimental toxicology and epidemiologic findings. Please comment on any significant uncertainties in the epidemiologic findings.

b) Please comment on whether the epidemiology literature published since the last SAP review including the AHS findings is sufficient to justify changing the Agency's conclusions that atrazine is not likely to be carcinogenic to humans.

3:15 p.m. Break

3:30 p.m. Charge to Panel - Charge Question 12 - The proposed refined dose response assessment for atrazine will be based on internal measures of exposure. At the September 2010 SAP meeting, the Agency presented estimates of area under the concentration-time curve (AUC) for plasma triazines based on a rat [^{14}C]-atrazine study (i.e., Thede 1987). The Panel concluded that "…on the basis of the currently available data, plasma appears to be a reasonable biological compartment that is reflective of tissue dose, and that use of area under the plasma concentration time curve (AUC) provides an appropriate measure of internal exposure." The Panel also noted that "the use of total chlorotriazine based on total ^{14}C-compounds is a reasonable first step (particularly in the absence of information on the pharmacodynamic activity of the parent compound and individual metabolites). However, the Panel believed that the Thede (1987) data, had limitations, and should be interpreted with caution." In response to the comments by the Panel, the Agency has evaluated additional pharmacokinetic studies involving different species including humans and two additional rat^{14}C-atrazine studies that support the plasma clearance estimates obtained from the Thede 1987 study. Based on the consistent linear pharmacokinetic behavior of plasma triazines resulting from orally administered doses of atrazine across the different studies, the Agency proposes to use an interim pharmacokinetic modeling approach based on a one-compartment linear model to inform internal dosimetry that seems to adequately describe the pharmacokinetics of plasma triazines in rats from orally administered atrazine.

a) Please comment on the strengths and limitations associated with this simplified pharmacokinetic modeling approach for human extrapolation.

b) Compare and contrast the strengths and weaknesses of using total radioactivity for a pharmacokinetic analysis (as presented in the Agency's issue paper) as opposed to using available pharmacokinetic data for the parent and the chloro-s-triazine metabolites that have similar toxicological properties to the parent?

c) As pointed out in the Agency issue paper, we are still reviewing a PBPK model submitted by Syngenta. As we complete our review of the Syngenta model, please comment on key aspects that EPA should be considering concerning a PBPK model including model credibility (e.g., structure, parameter values, documentation), model reliability (e.g., how well does the model simulate the dose metrics relevant to the mode of action), and model applicability (e.g., does the model have essential features for intended application).

d) Please comment on the extent to which the one-compartment linear model of total plasma radioactivity derived from ^{14}C labeled atrazine may account for interspecies differences in pharmacokinetics.

5:00 p.m. Meeting Adjourns

Day 4
Friday, July 29, 2011

8:30 a.m. **Opening of Meeting and Administrative Procedures** – Joseph Bailey, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:35 a.m. **Introduction of Panel Members** – Daniel Schlenk, Ph.D., FIFRA Scientific Advisory Panel Session Chair

8:45 a.m. **Charge to Panel - Charge Question 13 -** Any risk assessment of atrazine ideally should account for the temporal relationship between exposure and toxicological endpoint (i.e., LH attenuation). The Agency is relying on rat studies involving constant dosing frequency and dose level to elucidate this relationship. The time-to-effect in rats appears to be based on the build-up of plasma triazines to *pseudo* steady state (*i.e.,* plasma triazine levels stay within a constant range). The Agency is using this information to estimate the allometrically scaled equivalent human time-to-*pseudo* steady state plasma triazine levels. However, the Agency is cognizant that human exposure is different from controlled rat studies in that both the dose level and the frequency of exposure through drinking water are variable. Thus, the Agency has identified several possible durations of human exposure, which collectively bracket the exposure intervals of concern for LH attenuation in humans:

- 28 days: a duration predicted by allometrically scaling the rat plasma elimination kinetics. In both rats and humans, the time estimated to reach *pseudo* steady state plasma triazines coincides with the respective length of their ovarian cycles (i.e., 4 and 28 days, respectively).

- 14 days: Proposed to serve as a midpoint between the other two durations for better characterization of water monitoring frequencies.

- 4 days: the duration of exposure needed to reach pseudo steady state in rats and corresponding to the follicular phase in the human menstrual cycle.

a) Please comment on the rationale used by the Agency for selecting these exposure duration options. Please discuss the rationale for other alternative durations of concern, if any.

b) Please comment on which exposure duration in humans most closely corresponds to the exposure duration found to cause adverse effects in rats.

c) Please comment on the approach used by the Agency (*i.e.,* the one-compartment linear model) to relate atrazine levels from the water chemographs to predict corresponding human plasma triazine levels for the proposed durations of concern. In particular, please comment on the Agency's proposed approach to use water AUC estimates to calculate a time-weighted daily average of atrazine exposure for a given duration of concern. Please suggest alternative approaches as appropriate.

9: 45 a.m. Charge to Panel - Charge Question 14 - For the case study, the Agency used the 95th and 5th percentile of conditional simulations of daily concentrations from variogram models based on 7-day sampling intervals to predict human plasma AUC for triazines. The estimations of daily concentrations from weekly sampling were used to calculate the rolling average concentrations for the potential critical window of exposure from 4 to 28 days. The simulation models underestimated a single day peak concentration but appear to provide reasonable approximations of rolling average concentrations with durations as short as 4 days as well as the length of time of the potential exceedance.

a) Please comment on the use of a 95th percentile of the conditional simulations for providing an upper bound on rolling average concentrations in the case study.

10:30 a.m. Break
10:45 a.m. Charge to Panel
12:00 p.m. Lunch
1:00 p.m. Charge to Panel
3:00 p.m. Break
3:15 p.m. Charge to Panel
5:00 p.m. Adjourn

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