AGENDA
US ENVIRONMENTAL PROTECTION AGENCY (EPA)
FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
OPEN MEETING
April 10 – 13, 2012
FIFRA SAP WEB SITE http://www.epa.gov/scipoly/sap/
OPP Docket Telephone: (703) 305-5805
Docket Number: EPA-HQ-OPP-2012-0040
US Environmental Protection Agency
Conference Center Lobby Level
One Potomac Yard (South Bldg.)
2777 S. Crystal Drive, Arlington, VA 22202

Scientific Issues Associated with Chlorpyrifos Health Effects

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

Day 1
Tuesday, April 10, 2012

9:00 A.M. **Opening of Meeting and Administrative Procedures**
Fred Jenkins, Ph.D., Designated Federal Official, Office of Science Coordination and Policy, EPA

9:05 A.M. **Introduction and Identification of Panel Members**
Kenneth Portier, Ph.D., FIFRA SAP Chair

9:10 A.M. **Welcome and Opening Remarks**
Steven Bradbury, Ph.D., Director, Office of Pesticide Programs (OPP), EPA
Karen Whitby, Ph.D., Acting Director, Health Effects Division, OPP, EPA

9:35 A.M. **Introduction: Scientific Issues Concerning Health Effects of Chlorpyrifos**
Anna Lowit, Ph.D., OPP, EPA

10:00 A.M. **Adverse Outcome Pathways: Data for Chlorpyrifos at Varying Levels of Biological Organization**
William R. Mundy, Ph.D., Office of Research and Development (ORD), EPA

10:30 A.M. **Break**

10:45 A.M. **Chlorpyrifos Effects on the Developing Brain Animal Studies: Animal Studies**
Ginger Moser, Ph.D., DABT, Fellow ATS, (ORD), EPA

11:30 A.M. **Lunch**

12:30 P.M. **Review of Children's Health Epidemiology Cohort Studies**
Carol H. Christensen, Ph.D., MPH, OPP, EPA

2:00 P.M. **Review of Chlorpyrifos Biomonitoring Research and Interpretive Approaches**
Lieutenant Aaron Niman, US Public Health Service, OPP EPA

2:30 P.M. **Summary of Chlorpyrifos Health Effects**
Anna Lowit, Ph.D., OPP, EPA

3:00 P.M. **Break**

3:10 P.M. **Public Comments**

5:45 P.M. **Adjourn**

Day 2
Wednesday, April 11, 2012

9:00 A.M. **Opening of Meeting and Administrative Procedures**
Fred Jenkins, Ph.D. Designated Federal Official, Office of Science Coordination and Policy, EPA

9:05 A.M. **Introduction and Identification of Panel Members**
Kenneth Portier, Ph.D., FIFRA SAP Chair

9:10 A.M. **Public Comments (Cont'd)**

10:30 A.M. **Break**

10:45 A.M. **Public Comments (Cont'd)**

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

1:00 P.M. **Charge to the Panel**

Question 1.0 Mode of action/adverse outcome pathway: Acetylcholinesterase (AChE) inhibition

Question 1.0

It is well established that AChE inhibition is the primary mode of action/adverse outcome pathway for OPs, like chlorpyrifos. Because AChE inhibition is the initiating event for this mode of action/adverse outcome pathway, using AChE inhibition as a regulatory endpoint is protective of downstream cholinergic effects. Moreover, historically, given the sensitivity of AChE inhibition data for OPs, these data have been considered to be protective of other potential toxicities and/or modes of action for OPs. In 2008, the Agency performed a comprehensive review of the available AChE data from multiple lifestages. This review has been supplemented with the newest studies. Consistent with the recommendations from the 2008 SAP, the Agency believes that AChE data remain the most robust dose response data for deriving points of departure in *in vivo* experimental toxicology studies with laboratory animals. *Please comment on the Agency's preliminary conclusion that AChE data remain the most robust source of data for deriving points of departure for chlorpyrifos. Please include a discussion of the strengths and uncertainties of this preliminary conclusion.*

2:00 P.M. Charge to Panel (Cont'd)

Question 2.0 Mode(s) of action/adverse outcome pathway(s): Plausible pathways leading to potential neurodevelopmental outcomes

Question 2.1.

As discussed in Section 3.2.1, although there are numerous mechanistic studies in the scientific literature, the research on different hypotheses does not provide sufficient data to establish causal linkages among different levels of biological organization to show how effects lead to adversity. As such, a mode of action or adverse outcome pathway leading to effects on the developing brain cannot be established at this time. Moreover, although multiple biologically plausible hypotheses are being pursued by researchers, based on the current state of the science, no one pathway has sufficient data to be considered more credible than the others. *Please comment on the Agency's preliminary conclusion that although there are multiple biologically plausible hypotheses being evaluated by research scientists, the mechanistic experimental toxicology data do not yet support a coherent set of key events in a mode of action/adverse outcome pathway.*

2:45 P.M. Break

3:00 P.M. Charge to the Panel (Cont'd)

Question 2.2.

Although a mode of action/adverse outcome pathway has not been established, qualitatively, the growing body of mechanistic studies does demonstrate that chlorpyrifos and/or its oxon are biologically active on a number of processes that affect the developing brain. Some mechanistic studies provide evidence of possible effects which are similarly sensitive or more sensitive than AChE inhibition (e.g., neurite outgrowth, binding to muscarinic receptors, axonal transport; serotonergic nervous system development). Some of these comparisons must be considered with caution since the amount of change in the *in vitro* systems required to elicit an adverse effect *in vivo* is unknown. Moreover, extrapolation from *in vitro* perturbations to *in vivo* effects has not been established, which introduces additional uncertainties. *Given the doses/concentrations evaluated in the in vitro and in vivo mechanism studies, Please comment on the degree to which these studies suggest that endpoints relevant to evaluating potential neurodevelopmental outcomes may or may not be more sensitive than AChE inhibition. Please include in your comments a discussion of the strengths and uncertainties. Please also include in your comments a discussion of the scientific understanding of dose response relationships for biological perturbations and the magnitude, frequency and/or duration of such perturbations that are can lead to adverse effects at higher levels of biological organization to support characterization of the likelihood of adverse outcomes in a human health risk assessment (as articulated in NRC 2007).*

4:00 P.M. Charge to the Panel (Cont'd)

Question 3.0 Neurodevelopmental data from laboratory animals

Question 3.1

As discussed in Section 3.2.2, the experimental toxicology data in laboratory rodents show neurobehavioral effects following developmental exposure with changes in a number of neurological domains. In 2008, the SAP agreed to this preliminary conclusion, and the nine additional studies available since 2008 add further support. *Please comment on the degree to which these studies show changes in a number of neurological domains and support the qualitative conclusion that chlorpyrifos exposure during gestation and/or early post-natal period may result in long-term adverse effects on the developing nervous system. What evidence does and does not support this conclusion? Please also include in your comments a discussion of the strengths and uncertainties. Please also include in your comments a discussion of the scientific understanding of dose response relationships for biological perturbations and the magnitude, frequency and/or duration of such perturbations that are can lead to adverse effects at higher levels of biological organization to support characterization of the likelihood of adverse outcomes in a human health risk assessment (as articulated in NRC 2007).*

4:45 P.M. Charge to the Panel (Cont'd)

Question 3.2

The dose response data in the *in vivo* experimental neurodevelopmental toxicity studies are not amenable to empirical dose response modeling as many studies use only one or two doses, and in some cases the lower dose, but not higher dose level, produced significant effects. Many studies report effects at a dose of 1 mg/kg/d-- a dose that produces some amount of brain ChE inhibition when given directly to the pups post-natally, but may or may not alter fetal brain ChE activity when given to the dams gestationally. One study (Braquenier et al., 2010) using lower doses, administered to the dam on GD15-LD14, reported a NOEL of 0.2 mg/kg/d. Comparing the NOEL of 0.2 mg/kg/d to a repeated dosing AChE inhibition $BMDL_{10}$ of 0.03 mg/kg/d suggests that AChE inhibition is a sensitive and protective endpoint.

a. Please comment on the scientific quality and robustness of the animal neurodevelopmental toxicity studies.

5:30 P.M. Adjourn

Day 3
Thursday, April 12, 2012

9:00 A.M. Opening of Meeting and Administrative Procedures
Fred Jenkins, Ph.D. Designated Federal Official, Office of Science Coordination and Policy, EPA

9:05 A.M. Introduction and Identification of Panel Members
Kenneth Portier, Ph.D., FIFRA Scientific Advisory Panel Session Chair

9:10 A.M. Charge to Panel (Cont'd)

Question 3.2

b. Please comment on the degree to which studies that measured AChE inhibition and those that measured neurodevelopmental outcomes can be integrated to evaluate whether points of departure based on 10% AChE inhibition provide more sensitive endpoints than endpoints measured in the experimental neurodevelopmental studies (as reviewed in Section 3.2.2). Please include in your comments a consideration of the strengths and uncertainties associated with this assessment.

10:15 A.M. Break

10:30 A.M. Charge to Panel (Cont'd)

Question 4.0 Epidemiology Regarding Children's Health

Question 4.1. Section 4.0 and Appendices 5 and 6 provide the Agency's review of the available epidemiology studies from the Columbia Mothers and Newborn study, the Mt. Sinai Child Development study, and the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) study. Consistent with the 2008 SAP recommendations, the Agency has considered information offered from each of the three cohort investigations; however EPA acknowledges the primacy of the Columbia cohort data for the purposes of informing risk assessment because researchers measured chlorpyrifos parent compound directly in this study. *Please comment on the sufficiency, clarity, and quality of the Agency's epidemiology review as contained in Section 4.0 and Appendices 5 and 6 of the draft issue paper with respect to identifying the major strengths and limitations of each study.*

11:20 A.M. Charge to Panel (Cont'd)

Question 4.2. Similar to the initial conclusions from 2008, the Agency has preliminarily concluded that, qualitatively, chlorpyrifos likely played a role in the neurodevelopmental outcomes reported in the epidemiologic studies, and that information available since 2008, including both new etiologic investigations as well as epidemiologic methods papers, strengthens this conclusion. *Please comment on the Agency's preliminary, qualitative conclusion that chlorpyrifos likely played a role in the neurodevelopmental outcomes observed in the epidemiologic studies. Please include in your comments a discussion of the strengths and uncertainties associated with this preliminary conclusion.*

12:15 P.M. Lunch

1:15 P.M. Charge to Panel (Cont'd)

Question 4.3. As discussed in Question 2.0, a mode of action/adverse outcome pathway has not yet been fully elucidated for the potential neurodevelopmental outcomes as a result of prenatal chlorpyrifos exposure. Although this does not undermine the qualitative interpretation of these studies, and the preliminarily conclusion stated above (Question 4.2), the identification of the dose response for neurodevelopmental effects based on mode of action is not possible. Further, given the urine and cord blood sampling frequency in the study there is a large degree of uncertainty in estimating absolute exposure-response relationships, as opposed to establishing relative exposure groups for evaluating associations. With respect to dose-response, critical durations of exposure, and windows of susceptibility are unknown. In 2008, the SAP cautioned against using the Columbia cohort data for deriving a point of departure due, in part, to only measuring biomarkers (3rd trimester maternal, cord blood, meconium) at one point in time, and because they cannot exclude possibility that the effects seen were due to chlorpyrifos in combination with other pesticides. In 2008, the SAP advised against using data from the epidemiology studies (including the Columbia Mothers and Newborn study which measured chlorpyrifos directly) for deriving a point of departure due to limitations of the exposure assessment in these epidemiology studies for the purpose of risk assessment, *e.g.*, lack of repeated exposure estimates to ascertain more specifically the variability and periodicity of exposure over time (*i.e.*, predominant use of one-time exposure estimate).

a. Due to the limitations of exposure assessment performed in the epidemiologic investigations for the purposes of quantitative risk assessment, the Agency has concluded that the epidemiologic data are not sufficient for deriving points of departure for quantitative risk assessment. The Agency proposes that AChE inhibition data from laboratory animals remain the most appropriate data to use for dose-response modeling and the derivation of points of departure. *Please comment on the scientific evidence that does and does not support this conclusion, as well as the strengths and limitations of the evidence.*

2:15 P.M. Break

2:30 P.M. Charge to Panel (Cont'd)

Question 4.3.

b. The Agency does, however, believe that the epidemiologic data are useful to informing other key aspects of the chlorpyrifos risk assessment including hazard characterization, exposure characterization, and quantitative uncertainty characterization and analysis. *Please suggest approaches/analyses for potentially using the epidemiology data in different parts of the chlorpyrifos risk assessment including those noted above.* (Note: Some of these may also be covered in Question 5.4 below.)

3:30 P.M. Charge to Panel (Cont'd)

Question 5.0 Exposure Profile & Biomonitoring Research

Question 5.1:

a. Section 5 of the draft issue paper presents an overview of the principal chlorpyrifos biomarkers and a comparison of biomonitoring studies that measured urinary TCPy levels in a range of study populations involving both the general population and potentially vulnerable populations, including children, workers, and farm families. *Please comment on the degree to which the Agency identified the primary chlorpyrifos biomarkers of exposure, appropriately discussed the strengths and limitations of such biomarkers, and how the strengths and limitations affect the interpretation of the chlorpyrifos biomonitoring data.*

4:30 P.M. Charge to Panel (Cont'd)

b. Section 5 of the draft issue paper compares biomonitoring findings from the three children's health cohorts with other major observational exposure studies in the United States. Based on comparison with NHANES 2001-2002, median TCPy levels in the CHAMACOS and Mount Sinai cohorts were slightly higher than in the general population. It should be noted that the exposures experienced by the CHAMACOS and Mount Sinai cohorts overlapped the start of the residential chlorpyrifos phase-out. By contrast, median TCPy levels in the Columbia cohort, for which sampling occurred when chlorpyrifos use should have rapidly declined due to the voluntary cancelation, were

slightly lower than the levels measured by NHANES in the general population. *Please comment on the adequacy of the Agency's comparison for the purposes of evaluating chlorpyrifos exposure levels in the three children's health cohorts. Are there any additional biomonitoring studies that should included in the Agency's comparison?*

5:30 P.M. Adjourn

Day 4
Friday, April 13, 2012

9:00 A.M. Opening of Meeting and Administrative Procedures
Fred Jenkins, Ph.D. Designated Federal Official, Office of Science Coordination and Policy, EPA

9:05 A.M. Introduction and Identification of Panel Members
Kenneth Portier, Ph.D., FIFRA Scientific Advisory Panel Session Chair

9:10 A.M. Charge to Panel (Cont'd)

Question 5.2:
In Section 5.0 of the draft issue paper, the Agency summarized the 2008 preliminary findings on the association between urinary TCPy levels and AChE/BuChE inhibition and discussed two recent studies involving manufacturing workers in the US and Egypt. *Please comment on the scientific quality of these studies and their findings. Please include a discussion of their strengths and limitations. Please comment on the strengths and limitations of the evidence from this research to show an association between TCPy and AChE/BuChE inhibition at exposure levels experienced by occupational populations.*

10:00 A.M. Charge to Panel (Cont'd)

Question 5.3:
Several approaches ranging from qualitative to the most sophisticated PBPK/PD modeling approach were introduced as potential options for analyzing the chlorpyrifos biomonitoring data. *Please comment on the strengths and limitations of these approaches. In addition, please suggest, if appropriate, alternative approaches or analyses not identified by the Agency.*

10:45 A.M. Break

11:00 A.M. Charge to Panel (Cont'd)

Question 5.4:
Characterization of chlorpyrifos exposure experienced by women in the Columbia cohort, particularly during the pre-cancellation period, remains an important uncertainty in using these data in quantitative risk assessment. Exposure levels in the range measured in the cord blood data from the epidemiology studies (pg/g plasma) are probably low enough that is unlikely that the cohort mothers were experiencing AChE inhibition at the time of delivery; however, the biomonitoring data were taken after birth and not necessarily associated in time with an application of chlorpyrifos. As such, the actual level of such exposure particularly during any critical window(s) of susceptibility is not known, and a better understanding of the range of possible exposures and the degree to which they may or may not have elicited inhibition of AChE, remains a key scientific question. *In light of Panel discussions of Questions 4.3 and 5.3, please suggest approaches and/or analyses which would inform the understanding of the degree to which exposure levels experienced by the Columbia cohort participants may or may not have been below doses which result in 10% inhibition of AChE in the most sensitive lifestage. Please discuss the strengths and uncertainties associated with such analyses. Please include in your discussions approaches involving chlorpyrifos and its metabolites and also chlorpyrifos plus other AChE-inhibiting pesticides (propoxur, diazinon) which the cohort participants were exposed too.*

11:45: A.M. Charge to Panel (Cont'd)

Question 6: Characterizing the range of potential risks.

The 2009 NRC report, *Science and Decisions*, focused on improving the *technical analysis* through the development and use of scientific knowledge and information to promote more accurate characterizations of risk, and thus improving the *utility* of risk assessment for risk-management decisions. The NRC report also pointed out that regulatory risk assessment does not routinely approach public health and environmental problems by arraying a wide range of options for dealing with them. *In the case of chlorpyrifos, in light of the discussions of Questions 1-5, please provide guidance for assessing and presenting the range of plausible responses at given doses, and the effect of the overall uncertainty and variability around that range.*

12:30 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, Dr. Fred Jenkins, via telephone: (202) 564-3327; fax: (202) 564-8382; or email: jenkins.fred@epa.gov.