



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF
PREVENTION, PESTICIDES AND TOXIC
SUBSTANCES

December 17, 2008

MEMORANDUM

SUBJECT: Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held September 16-18, 2008 on the Agency's Evaluation of the Toxicity Profile of Chlorpyrifos

TO: Debbie Edwards, Ph.D.
Director
Office of Pesticide Programs

FROM: Sharlene R. Matten, Ph.D.
Designated Federal Official
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

A handwritten signature in black ink, appearing to read "Sharlene R. Matten", written over a horizontal line.

THRU: Steven Knott, Executive Secretary
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

A handwritten signature in black ink, appearing to read "Steven M. Knott", written in a cursive style.

Frank Sanders
Director
Office of Science Coordination and Policy

A handwritten signature in black ink, appearing to read "Frank Sanders", written in a cursive style.

Attached, please find the meeting minutes of the FIFRA Scientific Advisory Panel open meeting held in Arlington, VA on September 16-18, 2008. This report addresses a set of scientific issues regarding the Agency's Evaluation of the Toxicity Profile of Chlorpyrifos.

Attachments

cc:

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Janice E. Chambers, Ph.D., D.A.B.T.,
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Kirby C. Donnelly, Ph.D
Steven G. Heeringa, Ph.D.
Carey N. Pope, Ph.D
Kenneth M. Portier, Ph.D. (FIFRA SAP
Session Chair)
Daniel Schlenk, Ph.D.

FQPA Science Review Board Members

Sophie J. Balk, M.D.
Laura Beane Freeman, Ph.D.
John F. Bowyer, Ph.D.
Russell L. Carr, Ph.D.
Michael DiBartolomeis, Ph.D., DABT
John Doull, M.D., Ph.D., ATS
Paul B. English, Ph.D., M.P.H.
Gaylia Jean Harry, Ph.D
Wendy J. Heiger-Bernays, Ph.D.

SAP Minutes No. 2008-04

**A Set of Scientific Issues Being Considered by the
Environmental Protection Agency Regarding:**

**The Agency's Evaluation of the Toxicity Profile of
Chlorpyrifos**

**September 16-18, 2008
FIFRA Scientific Advisory Panel Meeting
held at the
Holiday Inn - Rosslyn
Arlington, Virginia**

NOTICE

These meeting minutes have been written as part of the activities of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP). The meeting minutes represent the views and recommendations of the FIFRA SAP, not the United States Environmental Protection Agency (Agency). The content of the meeting minutes does not represent information approved or disseminated by the Agency. The meeting minutes have not been reviewed for approval by the Agency and, hence, the contents of these meeting minutes do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

The FIFRA SAP is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act and established under the provisions of FIFRA as amended by the Food Quality Protection Act (FQPA) of 1996. The FIFRA SAP provides advice, information, and recommendations to the Agency Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The Panel serves as the primary scientific peer review mechanism of the Environmental Protection Agency, Office of Pesticide Programs (OPP), and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. FQPA Science Review Board members serve the FIFRA SAP on an ad hoc basis to assist in reviews conducted by the FIFRA SAP. Further information about FIFRA SAP reports and activities can be obtained from its website at <http://www.epa.gov/scipoly/sap/> or the OPP Docket at (703) 305-5805. Interested persons are invited to contact Sharlene R. Matten, Ph.D., SAP Designated Federal Official, via e-mail at matten.sharlene@epa.gov.

In preparing these meeting minutes, the Panel carefully considered all information provided and presented by EPA, as well as information presented in public comment. This document addresses the information provided and presented by EPA within the structure of the charge.

TABLE OF CONTENTS

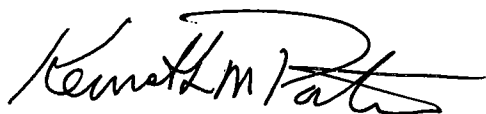
NOTICE	1
TABLE OF CONTENTS	3
PUBLIC COMMENTERS	9
SUMMARY OF PANEL DISCUSSION AND RECOMMENDATIONS	10
DETAILED RESPONSES TO CHARGE QUESTIONS	17
1. METABOLISM & TOXICOKINETICS	17
2. CHOLINESTERASE INHIBITION.	21
3. LABORATORY STUDIES ON THE DEVELOPING BRAIN.....	24
4. EPIDEMIOLOGY STUDIES IN CHILDREN AND MOTHERS.....	31
5. HUMAN INFORMATION AVAILABLE FOR RISK ASSESSMENT.....	44
6. POINTS OF DEPARTURE (POD) FOR RISK ASSESSMENT.....	50
7. EXTRAPOLATION/UNCERTAINTY FACTORS.....	55
REFERENCES	64

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**Kenneth M. Portier, Ph.D.
FIFRA SAP Session Chair
FIFRA Scientific Advisory Panel**

Date: 12/17/08



**Sharlene R. Matten, Ph.D.
Designated Federal Official
FIFRA Scientific Advisory
Panel Staff**

Date: 12/17/08

**Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
September 16-18, 2008**

The Agency's Evaluation of the Toxicity Profile of Chlorpyrifos

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FIFRA SAP Session Chair

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INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of **The Agency's Evaluation of the Toxicity Profile of Chlorpyrifos**. Advance notice of the SAP meeting was published in the *Federal Register* on **July 9, 2008 and August 28, 2008**. The review was conducted in an open panel meeting September 16-18, 2008 held at the Holiday Inn-Rosslyn, Arlington, Virginia. Dr. Kenneth M. Portier chaired the meeting. Dr. Sharlene R. Matten served as the Designated Federal Official. Dr. Tina Levine, Director, Health Effects Division, Office of Pesticide Programs (OPP), provided opening remarks at the meeting. Presentations of technical background materials were provided by Dr. Anna Lowit and Ms. Deborah Smegal, MPH, Health Effects Division, OPP and by Dr. Ginger Moser, EPA-ORD-National Health and Environmental Effects Research Laboratory (NHEERL). Additional technical assistance was provided by Dr. John Liccione and Dr. John Doherty of the Health Effects Division, OPP.

Chlorpyrifos (O,O-diethyl-O-3,5,6-trichloro -2-pyridinyl phosphorothioate) is a broad-spectrum, chlorinated organophosphorus (OP) insecticide. Chlorpyrifos is one of the most widely used OPs in the U.S. In 2000, nearly all residential uses were voluntarily cancelled by Dow AgroSciences, LLC. However, chlorpyrifos continues to be used extensively in commercial agriculture. Since 2000, there has been extensive research on various aspects of chlorpyrifos toxicity, particularly on effects in animals and humans from gestational and postnatal exposure. Many new studies in rats investigating different endpoints including acetylcholinesterase (AChE) inhibition and adverse effects on the developing brain are now available. In addition, manuscripts have recently been published from three cohorts of pregnant women and children exposed *in utero* to organophosphates (OPs). At this time, the Agency is re-evaluating the extent to which toxicity endpoints and extrapolation/uncertainty factors for chlorpyrifos require updating based on this new information. The Agency's issue paper and associated appendices contain the proposed updates and the scientific foundation for the proposed revisions. The contents and conclusions drawn in the issue paper and appendices are preliminary. The ultimate goal of the Agency's ongoing work is to improve the scientific support for the Agency's risk assessment. This will be accomplished by 1) evaluating new data on potentially susceptible subpopulations and 2) incorporating improved approaches, e.g., benchmark dose modeling instead of relying on no-observed-adverse-effect levels (NOAELs) for points of departure; and using extrapolation factors based on data instead of relying on default factors to account for differences in animals and humans and among humans. The Agency has progressed to a point in the review that feedback from the FIFRA SAP would be helpful.

PUBLIC COMMENTERS

Oral statements were presented by:

- 1) Daland Juberg, Ph.D., Dow AgroSciences, LLC
- 2) Charles Timchalk, Ph.D., DABT, Battelle Center for Biological Monitoring and Modeling
- 3) Carol Burns, Ph.D., Dow Chemical Company
- 4) Pamela Mink, Ph.D., MPH, Department of Epidemiology, Emory University
- 5) Michael Bartels, Ph.D., Dow Chemical Company
- 6) Douglas Weed, M.D., MPH, Ph.D., DLW Consulting Services
- 7) Robert Sielken, Ph.D., Sielken & Associates Consulting, Inc.
- 8) Michael Dourson, Ph.D., DABT, ATS, Toxicology Excellence for Risk Assessment (TERA)
- 9) Mr. Ray McAllister, Crop Life America
- 10) Elliot Gordon, Ph.D., Elliot Gordon Consulting, LLC
- 11) Jennifer Sass, Ph.D., Natural Resources Defense Council (NRDC) and on behalf of Pesticide Action Network North America (PANNA)
- 12) Michael Fry, Ph.D., American Bird Conservancy
- 13) Robin M. Whyatt, Ph.D., and Virginia A. Rauh, Ph.D., Columbia Center for Children's Environmental Health, Mailman School of Public Health, Columbia University

Written statements were provided by:

- 1) Torka S. Poet, Ph.D. and Charles Timchalk, Ph.D., DABT, Battelle Center for Biological Monitoring and Modeling, Battelle
- 2) Charles Timchalk, Ph.D., Battelle Center for Biological Monitoring and Modeling
- 3) David Eaton, Ph.D., DABT, FATS, Center for Ecogenetics and Environmental Health and Associate Vice Provost for Research, University of Washington on behalf of the authors of Eaton et al. 2008
- 4) Theodore Slotkin, Ph.D., Professor of Pharmacology and Cancer Biology and Psychiatry and Behavioral Sciences and Neurobiology and Director of Graduate Studies, Integrated Toxicology and Environmental Health Program, Duke University Medical Center
- 5) Scott Phillips, M.D., Department of Medicine, University of Colorado Health Sciences Center
- 6) Pamela Mink, Ph.D., MPH, Department of Epidemiology, Emory University
- 7) Douglas Weed, M.D., MPH, Ph.D., Founder and Managing Member, DLW Consulting Services, LLC
- 8) Kenneth D. Racke, Ph.D., Dow AgroSciences, LLC
- 9) Gary J. Mihlan, Ph.D., CIH and Walter Schmitt, Ph.D., Bayer CropScience
- 10) Michael Dourson, Ph.D., DABT, ATS, Bernard Gadagbui, Ph.D., DABT, and Lynne Haber, Ph.D., DABT, Toxicology Excellence for Risk Assessment (TERA)

SUMMARY OF PANEL DISCUSSION AND RECOMMENDATIONS

The Panel acknowledged the extent of the chlorpyrifos database and commended the Agency for preparing a comprehensive document considering the scientific evidence as a whole. Some of the more significant new data available to the Agency since the preparation of the 2000 chlorpyrifos risk assessment comes from three large prospective cohort studies of pregnant women and their children. Throughout the two-day discussion, Panel members referred to the results of these studies in an attempt to integrate their findings with the toxicology data from laboratory animal experiments. Despite the large volume of data available to address the risks of chlorpyrifos exposure from agricultural uses, several Panel members were concerned that a high degree of uncertainty is evident in the available data, particularly under low dose, chronic conditions. Uncertainty was expressed in attributing observed adverse effects to chlorpyrifos in the epidemiological studies where exposure was to metabolites of chlorpyrifos or to a mixture of chlorpyrifos and two additional anticholinesterase insecticides. The Panel agreed that the epidemiological studies have utility for risk assessment, but not as the principal basis for characterization of the point of departure (PoD). There was extensive discussion on experimental and epidemiological studies, e.g., of low-dose exposure in animals, of exposures in agricultural and pesticide handlers, and of the mode of action including the need to develop chlorpyrifos-specific PBPK models, that could provide the information needed to address critical data gaps and reduce uncertainty.

1. Metabolism & Toxicokinetics

The Panel concluded that a weight of evidence evaluation of available information supports the Agency's conclusions that 1) sensitivity to the adverse effects of chlorpyrifos is influenced by age, with young animals having lesser total ability to detoxify chlorpyrifos and many other organophosphorus compounds, and 2) that the age-dependent sensitivity observed in experimental animals is due mostly to toxicokinetic (TK) differences between juveniles and adults instead of only being the result of toxicodynamic (TD) differences.

The Panel agreed that current scientific data on chlorpyrifos uptake, transport, sequestration and excretion suggest that individual differences in metabolism and transformation will explain much of the variability seen in these factors, but that other potential TK differences between juveniles and adults should not be dismissed. For instance, the high respiratory rate of children may enhance the absorption of chlorpyrifos present in the air. Children have a greater cardiac output compared to adults, together with their less developed blood-brain barrier; facilitate some of the chlorpyrifos-oxon reaching the brains of exposed infants.

Some panel members questioned whether detoxication of the oxon plays a significant role in explaining the differential susceptibility between adults and juveniles at lower levels of chlorpyrifos exposure. Toxicokinetic differences are less likely to be relevant under low dose conditions compared to high dose conditions where enzyme systems may become saturated. Human tissue data specific to enzyme-mediated detoxication are minimal, however. While blood levels of detoxifying enzymes (e.g., PON1, carboxylesterases) have been studied, data on chlorpyrifos detoxication in specific organs (e.g., the liver) from humans are limited, making it

