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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

July 6, 2004

MEMORANDUM

Subject: Transmission of Background Materials and Charge to the Panel for the Session of the July 29-30, 2004 FIFRA Scientific Advisory Panel Entitled "Dimethoate: Issues Related to Hazard and Dose Response Assessment."

To: Myrta Christian, Designated Federal Official
FIFRA SAP
Office of Science Coordination and Policy (7101C)

From: Byong Han (Paul) Chin, Ph.D, Toxicologist
Diana Locke, Ph.D., Toxicologist
Anna Lowit, Ph.D., Toxicologist
Kathleen Raffaele, Ph.D., Toxicologist
Office of Pesticide Programs,
Health Effects Division (7509C)

Cheryl Chaffey, Head, Toxicology Re-evaluation Section
Mary Mitchell, Head, Exposure Re-evaluation Section
Health Evaluation Division
Pest Management Regulatory Agency (PMRA),
Canada

Through: Margaret Stasikowski, Director
Office of Pesticide Programs,
Health Effects Division (7509C)

Attached are the document entitled, "Dimethoate: Issues Related to Hazard and Dose Response Assessment", charge to the FIFRA Scientific Advisory Panel (SAP), and supporting appendices.

The Food Quality Protection Act of 1996 requires EPA to reassess all previously approved pesticide tolerances by August 2006. As part of the reassessment process, EPA's Office of Pesticide Programs (OPP) is developing risk assessments for each of the individual organophosphate pesticides (OPs), including dimethoate. At this time, the US EPA's Office of Pesticide Programs along with Canada's Pest Management Regulatory Agency are requesting the FIFRA SAP to provide comments on specific

issues related to the dimethoate hazard and dose-response assessment: interpretation of results from the dimethoate neurotoxicity study and evaluation of dermal penetration. Please note that no confidential business information in contained in the attached documents; position paper and supporting documents (Appendices listed below).

Appendices:

Appendix 1
E-file name: 035001ha.003.wpd
DIMETHOATE: 2nd Report of the Hazard Identification Assessment Review Committee. Paul Chin. March 26, 2002.

Appendix 2
E-file name: 45529703.der.wpd
DATA EVALUATION RECORD. DIMETHOATE/035001. STUDY TYPE: DEVELOPMENTAL NEUROTOXICITY STUDY - RAT; OPPTS 870.6300. MRID 45529703. EPA Reviewer: K. Raffaele. January 14, 2002.

Appendix 3
E-file name: 45529701.der.wpd
DATA EVALUATION RECORD. DIMETHOATE. Study Type: DOSE-FINDING DEVELOPMENTAL NEUROTOXICITY[NON-GUIDELINE] MRID 45529701. EPA Reviewer: K. Raffaele. January 14, 2002.

Appendix 4
E-file name: 45529702.der.wpd
DATA EVALUATION RECORD. DIMETHOATE. Study Type: SPECIAL STUDY, CHOLINESTERASE INHIBITION [NON-GUIDELINE]. MRID 45529702. EPA Reviewer: K. Raffaele. January 18, 2002.

Appendix 5
E-file name: D273221.me2.wpd
D273221: Dimethoate (035001). Review of Data on Developmental Neurotoxicity Based on: a 6(a) 2 Report; Preliminary Data Submissions from a Range Finding Study (CHV/068), a Developmental Neurotoxicity Study (CHV/069), and a Cholinesterase Study (CHV/070); and a Data Audit of these 3 Studies. Kathleen Raffaele and William F. Sette. March 22, 2001.

Appendix 6
E-file name: 46214501.der.wpd
Cross Fostering Study (Non Guideline) - Rat (MRID 46214501). Elissa Reaves and Susan Makris. June 24, 2004

Appendix 7
E-file name: 035001_0013000_030393_TX010065_R014928.tif

EPA ID# 035001: Dimethoate - Review of Reproductive Toxicity in Rats. Paul Chin. March 3, 1993.

Appendix 8
E-file name: 43964001.der.metabolism and dermal absorption.wpd
DATA EVALUATION RECORD. MRID 43964001. STUDY TYPE: Metabolism - Rat; OPPTS 870.7485 [§85-1] Dermal Absorption. Paul Chin. September 25, 1996.

Appendix 9
E-file name: 45530501.der.dermal absorption.wpd
DATA EVALUATION RECORD. MRID 45530501. STUDY TYPE: Dermal Penetration - Rat. Rebecca Daiss. October 23, 2003.

Appendix 10
E-file name: 45922602.der.in vitro DERMAL absorption.wpd
DATA EVALUATION RECORD. MRID 45922602. STUDY TYPE: *in vitro* Dermal Absorption - (human and rat). Robert P Zendzian. May 16, 2003.

Appendix 11
E-file name: mem.Response to Rebuttal to EPA's Dermal Penetration Factor.wpd
DIMETHOATE: Response to Rebuttal to EPA's Dermal Penetration Factor (MRID No. 45922601). Paul Chin. June 6, 2003.

Charge to the Panel:

Since the release of EPA's preliminary risk assessment for dimethoate in 1999, new data related to developmental neurotoxicity and dermal penetration have become available. These new data have resulted in significant revisions to the hazard characterization and dose-response assessment for dimethoate. EPA and PMRA have jointly prepared the paper entitled "Dimethoate: Issues Related to the Hazard and Dose-Response Assessment" and are requesting comment from the FIFRA SAP on these key scientific issues.

Issue 1. Interpretation of the results from the developmental neurotoxicity (DNT) and related comparative ChE inhibition and cross-fostering studies

Question 1.1

In 2001, EPA was notified of unanticipated adverse effects in the DNT study. The adverse effects observed were a potential increase in the number of deaths in young pups when dams were exposed orally to dimethoate during gestation and lactation. Following a detailed review of this study, both EPA and PMRA have determined that there is a dose-related increase in pup mortality. Typically in developmental and reproductive toxicity studies, the litter is considered the appropriate unit of analysis. As part of the review of the dimethoate DNT study, the individual pup has been treated both qualitatively and statistically as the appropriate unit of analysis. This evaluation has included pups which died and whole litters which were humanely sacrificed and includes, for example, mortality of 15 pups which was limited to a litter from a single dam at 0.5 mg/kg/day.

Please comment on the biological and statistical considerations important in evaluating the dose-response data such as the pup mortality incidence reported in the DNT.

Question 1.2

Section II.D of the issue paper describes the total weight of the evidence used by EPA and PMRA to reach their conclusions regarding the pup mortality observed in the main DNT study.

Please comment on the clarity and completeness of this discussion.

Question 1.3

The underlying cause of the pup mortality is unclear. The study design for the DNT study includes both pre- and post-natal exposures; the impact of *in utero* exposure on pup mortality can not be distinguished from post-natal exposures (either through lactation or direct dosing) in this study. In order to further characterize the cause of pup mortality, and specifically, the influence of maternal neglect, the pesticide registrant designed and performed a cross-fostering study where untreated dams reared pups exposed *in utero*; treated dams reared pups not exposed *in utero*; and treated dams reared their own litters. EPA and PMRA have reviewed the pup mortality reported in the cross-fostering study along with observations specifically targeted to evaluate maternal neglect (e.g., maternal restlessness, scattering of pups, absence of milk in the stomach). These data have been evaluated in context with observations from the main DNT study and related comparative ChE and range-finding studies.

Please comment on the information available for dimethoate which characterizes the underlying cause(s) of the pup mortality in the dimethoate DNT study and the degree to which this information can be used to determine impact of maternal neglect on pup mortality.

Issue 2. Determination of a dermal penetration factor for dimethoate

Question 2.1

Three different studies evaluating dermal penetration are available. These include: an *in vitro* study with rat and human tissue; an *in vivo* study conducted with dimethoate prepared in water suspension; and an *in vivo* study conducted with dimethoate prepared in commercial formulations. Although each study has scientific merit, there are uncertainties associated with each study: namely, effects of different vehicle/solvent used in the *in vivo* studies and lack of accuracy of estimating *in vivo* dermal absorption by *in vitro* procedure in the rat.

Please comment on the utility of these studies for purposes of estimating a dermal absorption factor for dimethoate.