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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

November 2, 2004

MEMORANDUM

Subject: Transmission of Background Materials and Charge to the Panel for the Session of the November 30-December 1, 2004 FIFRA Scientific Advisory Panel Entitled "Dimethoate: Issues Related to Hazard and Dose Response Assessment."

To: Myrta Christian, Designated Federal Official
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Through: George Herndon, Acting Director
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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; specifically interpretation of results from the dimethoate developmental neurotoxicity (DNT) study. Please note that no confidential business information is 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: dimethoate_appendix8_final.pdf
BMD Analysis of Pup Death Mortality Data

Appendix 9
E-file name: dimethoate_appendix9_final.pdf
BMD Analysis of Brain Cholinesterase Data

Appendix 10
E-file name: 46181001.der.2-gen repro.wpd
DATA EVALUATION RECORD. MRID 46181001. STUDY TYPE: §83-4; Multigeneration Reproduction Study in Rats.

Appendix 11
E-file name: 46348201.der.1-gen repro.wpd
DATA EVALUATION RECORD. MRID 46348201. STUDY TYPE: Non-guideline; Range-finding One-generation Reproduction Study in Rats

Appendix 12
E-file name: omethoate_reproductivetox.wpd
Results of Reproductive Toxicity Studies with Omethoate

Appendix 13
E-file name: Meta analysis report-v1 of 2.pdf AND Meta analysis report-v2 of 2.pdf
A Meta Analysis of Pup Death and Cholinesterase Inhibition Data for Dimethoate. September 1, 2004.

Appendix 14
E-file name: 46288001.der.28-day oral tox in rats.wpd
DATA EVALUATION RECORD. MRID 46288001. STUDY TYPE: Repeated Dose (28-day) Oral Toxicity Study in Rats

Charge to the Panel:

Since the release of EPA's 1999 preliminary risk assessment for dimethoate, new data related to developmental neurotoxicity and reproductive toxicity have become available. These new data have resulted in significant revisions to the hazard characterization and dose-response assessment for dimethoate. In July, 2004, EPA and PMRA jointly submitted a paper entitled "Dimethoate: Issues Related to the Hazard and Dose-Response Assessment" to the FIFRA SAP for review. This meeting was postponed, however, because additional data pertinent to the assessment were brought the Agency's attention. Furthermore, benchmark dose (BMD) analyses have been conducted on the cholinesterase (ChE) activity and pup mortality data and are now presented in the paper dated November 2, 2004.

<u>Interpretation of the cholinesterase activity and pup mortality results from the dimethoate developmental neurotoxicity (DNT) study and related studies.</u>

A few years ago, EPA developed a BMD approach for modeling the ChE inhibition caused by the OP pesticides for purposes of conducting a cumulative risk assessment (EPA, 2002). This model has been applied for dimethoate data from several studies, and the results are presented in the current paper. (It should be noted that the Agency is not requesting comment on this model per se since it received extensive comment from the FIFRA SAP in 2001 and 2002.) The calculated BMD_{10} for brain ChE inhibition following repeated dosing ranged from 0.2-1.0 mg/kg/day and the $BMDL_{10}$ ranged from 0.2-0.7 mg/kg/day. The calculated brain ChE BMDs are very consistent across age groups, between males and females, and across different studies.

In addition, the pup mortality data from the rat DNT study was also modeled using BMD analysis, with models from the EPA Benchmark Dose Software (www.epa.gov/ncea/bmds.htm). The calculated BMD_5 is 0.5 mg/kg/day and the $BMDL_5$ is 0.3 mg/kg/day.

The EPA and PMRA would like to ask the panel several questions relating to the interpretation of the pup mortality data, including the use of ChE activity data versus pup mortality data as the appropriate endpoint for use in the risk assessment on dimethoate.

Question 1.1. 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 the impact of maternal neglect/maternal toxicity on pup mortality. [Section II B and Sections II C 2, 3, 5b-d]

Question 1.2. The results of the cross fostering study suggest that the pup mortality observed at lower doses in the main DNT study may not be attributable to a single dimethoate exposure. Please comment on the evidence that supports or refutes this analysis. [Section II B 2 and II C 5 d]

Question 1.3. After considering the results of the BMD analyses for brain ChE inhibition and for pup mortality, it is proposed that brain ChE inhibition be used as the endpoint for the dimethoate risk assessment for all durations of exposure (e.g. acute, chronic). This would also be protective for the pup mortality endpoint, because available data indicate that brain ChE inhibition occurs at doses similar to or lower than those causing increases in pup mortality. A number of factors were considered in developing this proposal:

- ❏ Brain ChE inhibition occurs at doses similar to or lower than those causing ChE inhibition in other compartments;
- ❏ BMD analyses results indicate a very robust dose-response curve for brain ChE inhibition, with similar BMD_{10} values from studies with varying modes of administration (dietary or gavage) and durations (short term for DNT studies and longer term for reproduction studies);
- ❏ BMD analyses results indicate similar dose-response curves at all ages, with no difference in BMD_{10} values for different age groups following similar exposure durations;
- ❏ Comparison of BMR dose levels for brain ChE inhibition and pup mortality following repeated dosing indicates that ChE inhibition occurs at doses similar to those associated with increases in pup mortality;
- ❏ Evaluation of pup mortality data from the cross-fostering study reveals clear increases in mortality only at the highest dose following short-term exposure, indicating that increased mortality at lower doses occurs only with repeated dosing;
- ❏ Comparison of the NOAEL for increased pup mortality from limited dosing with the BMD_{10} for brain ChE inhibition following a single dose indicates that brain ChE inhibition occurs at doses below those causing a clear increase in pup mortality.

Please comment on the evidence that supports or refutes this proposal (Sections IIB 4, and II C).