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

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MEMORANDUM

Subject: Transmission of Background Materials and Charge to the Panel for the **Session 2** of February 15-18, 2005 FIFRA Scientific Advisory Panel on the N-methyl carbamate cumulative risk assessment: "*PBPK/PD Modeling for Carbaryl*"

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A meeting of the FIFRA SAP is schedule for February 15-18. This meeting will focus on issues related to the N-methyl carbamate cumulative risk assessment. **Session 2** (February 16) of this meeting will focus on the paper entitled "PBPK/PD Modeling for Carbaryl." This memo contains the questions and issues posed by EPA to the panel for discussion. In addition to this memo, several documents/files are provided:

1. "Background document for the FIFRA Scientific Advisory Panel: N-Methyl Carbamate Cumulative Risk Assessment: Pilot analysis"
2. "Assessment of carbaryl exposure following turf application using a physiologically based pharmacokinetic model" is attached.
3. ERDEM Feb 2005 SAP PDF2.tmp
4. Loading and Operating Instructions for ERDEM

CHARGE AND QUESTIONS TO THE PANEL:

Issue 2.1. Data Requirements for PBPK/PD Models

The document "Assessment of carbaryl exposure following turf application using a physiologically based pharmacokinetic model" describes the application of a carbaryl specific physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) model to a case study of exposure for selected exposure scenarios involving broadcast applications of a liquid formulation of carbaryl to turf. A PBPK/PD model was developed based on available laboratory studies, then was applied to post-application exposure scenarios.

The PBPK/PD model provided a structure to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) data available for carbaryl. This case study was instructive in discovering data gaps, such as blood:brain partition coefficient values, isolated metabolism rates, and identification of specific metabolites. Data published in the open literature were generally incomplete for the purposes of PBPK/PD modeling, where simultaneous tissue concentration, excretion and effect data are ideal for model evaluation. Registrant data provided some constraints for PBPK/PD parameter values, but uncertainty remains in those values due to the dependence on fitting *in vivo* data and structure-activity methods (Poulin and Theil 2000; J Pharm Sci 89:16_35).

> *Question 2.1a: Please comment on the completeness of the data used to develop the PBPK/PD model.*
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> *Question 2.1b: Please comment on the way the data sets were used to estimate and constrain parameter values.*

Issue 2.2. PBPK/PD Model Fidelity

The PBPK/PD model was developed in the Exposure Related Dose Estimating Model (ERDEM) platform. The ERDEM platform is, by design, highly structured and flexible for adaptation to new or emerging exposure and risk assessment needs. In PBPK/PD modeling, there is a need to balance completeness regarding anatomical/physiological pathways/routes with the desire for model simplicity. The model is required to simulate the relevant dose metrics and provide the capability to extrapolate from the laboratory setting to exposure scenarios of interest. Modeling runs with the ERDEM platform are typically short;

thus computational time is not an issue. The important consideration is the *in silico* representation of the species and the connection with pathways and routes of exposure.

> *Question 2.2a: Please comment on the carbaryl PBPK/PD model structure for evaluating diverse exposure scenarios, including the exposure to children on the turf described in the report. Please include in your comments a consideration of the degree to which the compartments included in this model reasonably describe the PK and PD characteristics of carbaryl and provide the ability to extrapolate the model across species and scenarios, balanced against model simplicity.*

> *Question 2.2b: As more PK and PD data become available, the model structure from this application may be applied to other N-methyl carbamates, including mixtures. Please comment on the suitability of the carbaryl specific PBPK/PD model structure as developed in the ERDEM platform for expansion to include other N-methyl carbamates.*

Issue 2.3. Statistical Model Evaluation Considerations

Development of PBPK/PD models is an iterative process such that the model is improved and revised as more data and information become available. In a regulatory setting, it's not unusual that model development begins before all data sets have been collected. Currently when using ERDEM, an initial model structure is developed based on the species physiology and known chemistry of the chemical and metabolites. The initial model structure consists of the differential equations and variables that correspond to the relevant compartments and metabolic transformations. The initial parameter values are estimates made by the researcher, often based on models of related chemicals. The model is considered provisional until the available data are evaluated. The parameter values and model structure are then updated to reflect the available data. As new data are made available, they are evaluated concurrently with the existing data against the model simulations, and the model is revised accordingly. This iterative process has been followed for the current carbaryl PBPK/PD model, where model evaluation was based on visual inspection and linear regression between the model results and data points (not included in the report).

> *Question 2.3: Please comment on statistical or mathematical analyses which could inform the need for model revisions as new data are made available.*

Issue 2.4. Risk Metric

Historically, EPA has calculated margins of exposure (MOE) in its risk assessments for the N-methyl carbamate pesticides. These MOEs are calculated by dividing environmental exposure concentrations by a point of departure identified from toxicity studies. These points of departure are typically no-observed-adverse-effect- levels (NOAELs) or benchmark dose estimates (BMDs). For the N-methyl carbamates, these NOAELs or BMD estimates are generally based on peak cholinesterase inhibition. The use of PPBK/PD models provides the opportunity to consider toxicological endpoints other than peak cholinesterase inhibition. Some potential toxicological endpoints include 1) peak concentration of the pesticide (or key metabolite) at the site of action; 2) total pesticide (or key metabolite) at the site of action over a period of time (e.g. area under curve); 3) peak cholinesterase inhibition; 4) inhibition at or above a pre-defined level of inhibition (e.g. BMD10); 4) duration of time for inhibition at or above a pre-defined level of inhibition. The current report explicitly provides the peak concentration of carbaryl and peak cholinesterase inhibition; although the other metrics are easily accessible from a model developed in the ERDEM platform.

> *Question 2.4: Given the toxicological characteristics of carbaryl and other N-methyl carbamate pesticides, please comment on the degree to which these toxicological endpoints are appropriate for purposes of developing a risk assessment.*