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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

November 10, 2003

MEMORANDUM

Subject: Transmission of Background Materials and Charge to the Panel for the Session of the December 11-12, 2003 FIFRA Scientific Advisory Panel Entitled "Physiologically-Based Pharmacokinetic/Pharmacodynamic Modeling: Preliminary Evaluation and Case Study of the N-Methyl Carbamate Pesticides"

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Through: Margaret Stasikowski, Director
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Attached is the document "Physiologically-Based Pharmacokinetic/ Pharmacodynamic Modeling: Preliminary Evaluation and Case Study of the N-Methyl Carbamate Pesticides." The Food Quality Protection Act (FQPA) of 1996 requires the EPA to consider the cumulative effect to human health that can result from exposure to pesticides and other substances that have a common mechanism of toxicity. Since 1996, at various stages of development of its cumulative risk assessment guidance and methodologies, the Agency has solicited scientific peer review. A research effort is under way to develop a case study for using PBPK/PD modeling in cumulative risk assessment. The development of this case study is in its early stages. At this time, the Agency is requesting the FIFRA SAP to provide comments on issues related to the model structure, data needs, and model evaluation. As the case study develops further, and in the future, the Agency expects to solicit additional review on technical aspects of PBPK/PD model development such as parameter estimation, sensitivity analysis, and uncertainty in addition to related issues such as linking estimated environmental exposures with the PBPK/PD model. (Please note, no confidential business information in contained in the attached documents.)

Charge to the Panel:

Provide comment and advice on the following questions.

Issue 1. Development of the Preliminary PBPK/PD Model Structure

Conceptually, PBPK/PD models offer great promise in cumulative risk assessment, such as the ability to incorporate species, sex, or age-specific information on biological processes and the explicit consideration of pharmacokinetic and mechanistic data. At present time, the appropriate pharmacokinetic data are not available for the majority of N-methyl carbamate pesticides. The Agency has developed preliminary model structure in two computer languages (See Section III.D, Figures 2 and 3) for this common mechanism group based on information available at present time. Specifically, the structure of the preliminary model is based on: limited available pharmacokinetic data from the literature; AChE inhibition data and rat metabolic profiles from the scientific literature and/or from studies submitted for pesticide registrations; and previous PBPK/PD models developed for organophosphorus chemicals.

Question 1.1

Please comment on the proposed PBPK/PD model structure for the N-methyl carbamate pesticides as described in the document with specific consideration of the biological and mechanistic basis for this structure.

Issue 2. Data Needs for the N-Methyl Carbamate PBPK/PD Model

The document under review describes an iterative process for model development where the model developer and laboratory scientist work collaboratively first to identify and then to fill in areas where data or information are missing for a particular chemical(s). At present time, the Agency has developed a preliminary model and has identified areas where pharmacokinetic and/or pharmacodynamic data are not available. These data needs along with the purpose of experiment in the modeling effort are described in the document.

Question 2.1

Please comment on the adequacy and appropriateness of the data needs identified for the purpose of developing PBPK/PD models for individual N-methyl carbamates and also for developing the PBPK/PD model for the common assessment group as a whole.

Question 2.2

Typically, parameter estimation is performed using a set of available physiological, pharmacodynamic, and pharmacokinetic data. Data used for model development are not used for evaluating model reliability. Instead, separate data sets are used. Given the considerable resources needed to conduct *in vivo* pharmacokinetic studies, particularly mixture pharmacokinetic studies, identification of a minimum amount of data needed to achieve an acceptable level of residual uncertainty in the PBPK/PD model for the common assessment group is preferred. Please comment on the ***types*** of data needed to evaluate model reliability.

Issue 3. Model Evaluation and Quality Control

This document outlines a five-step approach to evaluating a PBPK/PD model for use in cumulative risk assessment. These steps include: 1) determining and stating model purpose, 2) development of model structure based on characterization of the biological and toxicological profiles of the individual members and the common assessment group as a whole; 3) description of the mathematics of the model; 4) implementation in a computer language; and 5) estimation of parameters and evaluation of model fit.

Question 3.1

Please comment on this five-step approach to evaluating PBPK/PD models, with particular consideration of their use in regulatory settings. Does this approach encompass the main issues related to model evaluation and quality control? If not, what additional issues need to be considered?