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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

July 19, 2007

MEMORANDUM

Subject: Transmission of Background Materials and Charge to the Panel for the August 16-17, 2007 meeting of the FIFRA Scientific Advisory Panel entitled *"Assessing Approaches for the Development of PBPK Models of Pyrethroid Pesticides."*

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

From: Michael Devito, PhD
Michael F. Hughes, PhD
Edward Scollon, PhD
National Health and Environmental Effects Research Laboratory
Office of Research and Development
Research Triangle Park, NC

Rogelio Tornero-Velez, PhD
Elin Ulrich, PhD
National Exposure Research Laboratory
Office of Research and Development
Research Triangle Park, NC

Anna Lowit, PhD
Office of Pesticide Programs,
Health Effects Division (7509C)

Through: Tina Levine, Director
Office of Pesticide Programs,
Health Effects Division (7509C)

The August 16-17, 2007 meeting of the FIFRA SAP will focus on issues related to on-going work by EPA to develop physiologically-based pharmacokinetic (PBPK) models for pyrethroid pesticides. This document provides a list of documents provided to the panel along with the charge questions.

The following documents are provided to the panel for the August 16-17 meeting:

1. Science issue paper: Assessing Approaches for the Development of PBPK Models of Pyrethroid Pesticides

2. Appendix A: *In vitro* dermal study

   In vitro dermal absorption of pyrethroid pesticides in rat and human skin, 2006. Hughes, MF and Edwards, BC. A poster presented at the 2006 Annual Meeting of the Society of Toxicology

3. Appendix B: *In vitro* metabolism studies (includes three files)

   Godin SJ, Scollon EJ, Hughes MF, Potter PM, DeVito MJ, Ross MK. Species differences in the *in vitro* metabolism of deltamethrin and esfenvalerate: Differential oxidative and hydrolytic metabolism by humans and rats. Drug Metab Dispos. 2006 Oct;34(10):1764-71.

   Godin SJ, Crow JA, Scollon EJ, Hughes MF, Devito MJ, Ross MK. Identification of rat and human cytochrome P450 isoforms and a rat serum esterase that metabolize the pyrethroid insecticides deltamethrin and esfenvalerate. Drug Metab Dispos. 2007 Jun 18; [Epub ahead of print]

   Scollon EJ, Hughes MF, DeVito MJ, et al.Oxidative and hydrolytic metabolism of type I pyrethroids in rat and human hepatic microsomes Drug Metabolism Reviews 38: 221-221 339 Suppl. 2 2006

4. Appendix C: Dose metric study

   Scollon; M. F. Hughes; J. M. Starr; K. M. Crofton; M. J. Wolansky; M. J. DeVito. Blood and Brain Concentrations of Bifenthrin Correlates with Decreased Motor Activity Independent of Time of Exposure. E. J. The Toxicologist CD — An official Journal of the Society of Toxicology, Volume 91, Number S-388, March 2007

5. Appendix D: Deltamethrin PBPK model information (includes two files)

   Model equations

   Mirfazaelian A, Kim KB, Anand SS, Kim HJ, Tornero-Velez R, Bruckner JV, Fisher JW. 2006. Development of a physiologically based pharmacokinetic model for deltamethrin in the adult male Sprague-Dawley rat. Toxicol Sci. Oct;93(2):432-42.

CHARGE AND QUESTIONS TO THE PANEL

EPA has on-going efforts to develop physiologically based pharmacokinetic (PBPK) models for pyrethroid pesticides. This model development is an important component of a significant research effort at the Agency to evaluate the toxicity, mode of action, and exposure to pyrethroids. At the present time, the Agency has preliminary PBPK models for deltamethrin and permethrin. The August, 2007 meeting of the FIFRA SAP is not meant to be a comprehensive review of these two models for use in risk assessment. Instead, this meeting is meant to focus on science issues described in the issue paper and the questions below.

Question 1:

The Agency's issue paper describes different aspects of the pharmacokinetic (PK) properties of pyrethroid pesticides. The Agency believes that the important PK properties relevant for PBPK modeling are common among all or most members of this class, such that a 'generic' or family model structure with chemical specific adjustments, as needed, can be used. *Please comment on the evidence which does and does not support the concept of using a generic model structure for the pyrethroid pesticides.*

Question 2:

In the development of PBPK models *in vivo* and *in vitro* data are acquired and used to calibrate and optimize the model. The predictions of the PBPK model are then evaluated against additional *in vivo* data sets. In the case of pyrethroids, there are limited human data available to calibrate and assess the human PBPK models. The Agency plans to develop a family modeling approach to address this issue. This approach assumes that because pyrethroids share many physical chemical and biological properties, a common model structure can be used for all pyrethroids. The family model approach allows for the assessment of the overall model structure with each iteration. The more iterations through this process, the more confidence is gained in the models predictive abilities. Thus, the rat deltamethrin model is not only assessed by data from deltamethrin, but is assessed by model fits to data for every other pyrethroid. As our confidence in the rodent family model increases across pyrethroids, our confidence in the use of this modeling approach for rodent to human extrapolation also increases. The Agency is planning to develop equivalent rodent and human *in vitro* databases for metabolic and physiological parameters. The rodent *in vitro* parameters will be assessed by comparing model predictions to *in vivo* data. It is likely that scaling factors will be used in order incorporate these *in vitro* parameters into the rodent model. When calibrating the human data, the scaling factors used in the rodent models will be used in the human models. *Please comment on this approach and other approaches that could be taken to calibrate and assess these models for use in human risk assessment.*

Question 3:

The Agency's issue paper and data provided in Appendix C show that blood and brain concentrations of parent compound in the rat correlate with pyrethroid toxicity as measured by motor activity. At present time, the Agency plans to evaluate additional metrics (e.g., area under the curve) with additional pyrethroids. Moreover, the Agency plans to test other behavioral measures (e.g., startle response). *Please comment on the available database to assess the dose metric for pyrethroids. Please also comment on what additional experiments, if any, that could further inform the dose metric.*

Question 4:

Pyrethroids may have one or more chiral centers resulting in potentially multiple stereoisomers. Some products, such as deltamethrin, are relatively pure single steroisomers. Others such as cypermethrin may contain as many as eight stereoisomers. There is limited information on the toxicity and pharmacokinetics of the different stereoisomers. The Agency is proposing to evaluate three modeling assumptions. The first approach combines all stereoisomers as one chemical. The second approach includes modeling all the diastereomers and ignores the enantiomers; the third approach includes only the toxic stereoisomers. To evaluate these approaches, the Agency is using permethrin as a model chemical. *Please comment on these three approaches. Are there additional modeling assumptions or approaches that the Agency should consider or that could simplify the modeling?*