AGENDA

FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
OPEN MEETING

August 16-17, 2007

FIFRA SAP WEB SITE http://www.epa.gov/scipoly/sap/
OPP Docket Telephone: (703) 305-5805
Docket Number: EPA-HQ-OPP-2007-0388

U.S. Environmental Protection Agency
Conference Center - Lobby Level
One Potomac Yard (South Bldg.)
2777 S. Crystal Drive, Arlington, VA 22202

Assessing Approaches for the Development of PBPK Models of Pyrethroid Pesticides

Thursday, August 16, 2007

8:30 A.M. **Introduction and Identification of Panel Members** – Steven G. Heeringa, Ph.D. (FIFRA SAP Chair)

8:40 A.M. **Administrative Procedures by Designated Federal Official** – Mr. Steven Knott, Office of Science Coordination and Policy, EPA

8:45 A.M. **Welcome and Opening Remarks** – Debbie Edwards, Ph.D., Director, Office of Pesticide Programs, EPA

8:50 A.M. **Opening Remarks -** Tina Levine, Ph.D., Director, Health Effects Division, Office of Pesticide Programs, EPA

8:55 A.M. **Introduction** – Anna Lowit, Ph.D., Office of Pesticide Programs, Health Effects Division, EPA

9:10 A.M. **Pharmacokinetics of Pyrethroid Pesticides and Potential Dose Metrics** – Michael F. Hughes, Ph.D., Office of Research and Development, The National Health and Environmental Effects Research Laboratory, EPA

9:35 A.M. **Metabolism of Pyrethroid Pesticides in Rodents and Humans** – Edward Scollon, Ph.D., Michael DeVito, Ph.D., Office of Research and Development, The National Health and Environmental Effects Research Laboratory, EPA

10:00 A.M. **Approaches to Pharmacokinetic Modeling of Pyrethroids** – Rogelio Tornero-Velez, Ph.D., Office of Research and Development, The National Exposure Research Laboratory, EPA

10:30 A.M. **Statistical Approaches to PBPK Models** – R. Woodrow Setzer, Ph.D., Office of Research and Development, National Center for Computational Toxicology, EPA

10:40 A.M. Break
10:55 A.M. Public Comments
12:00 P.M. Lunch
1:15 P.M. Charge to Panel – Issue 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.

3:00 P.M. Break
3:15 P.M. Charge to Panel – Issue 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 to 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.

5:00 P.M. Adjournment

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8:40 A.M. **Administrative Procedures by Designated Federal Official** -
Mr. Steven Knott, Office of Science Coordination and Policy, EPA

8:45 A.M. **Follow-up from Previous Day's Discussion**

9:00 A.M. **Charge to Panel – Issue 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 the 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, could further inform the dose metric.

10:15 A.M. **Break**

10:30 A.M. **Charge to Panel – Issue 3 continued**

11:00 A.M. **Charge to Panel – Issue 4:**

Pyrethroids may have one or more chiral centers resulting in potentially

multiple stereoisomers. Some products, such as deltamethrin, are relatively pure single stereoisomers. 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?

12:00 P.M. Lunch

1:15 P.M. Charge to Panel – Issue 4 continued

2:00 P.M. Adjournment

Please be advised that agenda times are approximate; when the discussion for one topic is completed, discussions for the next topic will begin. For further information, please contact the Designated Federal Official for this meeting, Mr. Steven Knott, via telephone: (202) 564-0103; fax: (202) 564-8382; or email: knott.steven@epa.gov