AGENDA

FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
OPEN MEETING

July 20-22, 2010

FIFRA SAP WEB SITE http://www.epa.gov/scipoly/sap/
OPP Docket Telephone: (703) 305-5805
Docket Number: EPA-HQ- OPP-2010-0383

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

Scientific Issues related to SHEDS-Multimedia version 4, Peer consult on PBPK Modeling, and a SHEDS-PBPK Permethrin Study

Please note that all times are approximate
(See note at the end of the Agenda)

Tuesday, July 20, 2010

9:00 A.M. **Opening of Meeting and Administrative Procedures by Designated Federal Official –** Sharlene Matten, Ph.D., Designated Federal Official, Office of Science Coordination and Policy, EPA

9:05 A.M. **Introduction and Identification of Panel Members –** Daniel Schlenk, Ph.D., Session Chair, FIFRA Scientific Advisory Panel

9:10 A.M. **Welcome and Opening Remarks –** Steven Bradbury, Ph.D., Director, Office of Pesticide Programs, EPA

9:20 A.M. **Goals and Objectives –** Tina Levine, Ph.D., Director, Health Effects Division, Office of Pesticide Programs, EPA

9:30 A.M **Introduction to and Overview of EPA/ORD/NERL's Stochastic Human Exposure and Dose Simulation Model for Multimedia, Multiroute/Pathway Chemicals (SHEDS-Multimedia) –** Andrew Geller, Ph.D., Office of Research and Development, EPA

10:00 A.M. **BREAK**

10:15 A.M. **SHEDS-Multimedia Dietary Module and Permethrin Case Study Results –**
Jianping Xue, M.D., M.S., **Valerie Zartarian, Ph.D.** , and Kristin Isaacs, Ph.D., Office of Research and Development, EPA;
Steve Nako, Ph.D , Office of Pesticide Programs, EPA

11:15 A\.M. **SHEDS-Multimedia Residential Module and Permethrin Case Study Results –**
Valerie Zartarian, Ph.D., Jianping Xue, M.D., M.S., and Kristin Isaacs, Ph.D., Office of Research and Development, EPA;
Graham Glen, Ph.D. and Luther Smith, Ph.D., Alion Science Technology, Inc.

12:15 P.M. **LUNCH**

1:15 P.M. **SHEDS-Multimedia Model Evaluation Efforts –**
Valerie Zartarian, Ph.D. and Jianping Xue, M.D., M.S., Office of Research and Development, EPA

2:00 P.M. **PBPK Models of Pyrethroid Pesticides –**
Rogelio Tornero-Velez, Ph.D., Jimena Davis, Ph.D. and R. Woodrow Setzer, Ph.D., Office of Research and Development, EPA

3:00 P.M. **BREAK**

3:15 P.M. **Bayesian Calibration of PBPK Models –**
Jimena Davis, Ph.D., Rogelio Tornero-Velez, Ph.D. and R. Woodrow Setzer, Ph.D., Office of Research and Development, EPA

4:00 P.M. **Extrapolation of Animal-Calibrated Models to Humans –**
Rogelio Tornero-Velez, Ph.D., Jimena Davis, Ph.D. and R. Woodrow Setzer, Ph.D., Office of Research and Development, EPA

4:45 P.M. **ADJOURN**

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Wednesday, July 21, 2010

9:00 A.M. **Opening of Meeting - Administrative Procedures by Designated Federal Official** - Sharlene Matten, Ph.D., Designated Federal Official, Office of Science Coordination and Policy, EPA

9:05 A.M. **Introduction and Identification of Panel Members –** Daniel Schlenk, Ph.D., Session Chair, FIFRA Scientific Advisory Panel

9:10 A.M. **Follow-up from Previous Day's Discussion –** Office of Pesticide Programs and Office of Research and Development, EPA

9:25 A.M. **Examining Uncertainty in the Linked Model –**
R. Woodrow Setzer, Ph.D. and Jimena Davis, Ph.D, Office of Research and Development, EPA

10:15 A.M. **BREAK**

10:30 A.M. **Permethrin SHEDS-PBPK Linked Model Case Study –**
Rogelio Tornero-Velez, Ph.D., Jianping Xue, M.D., M.S., Jimena Davis, Ph.D., R. Woodrow Setzer, Ph.D., Valerie Zartarian, Ph.D., Office of Research and Development, EPA

11:15 A.M. **Plans to Extend the SHEDS-PBPK Permethrin Case Study to Multiple Pyrethroids**
Rogelio Tornero-Velez, Ph.D., Valerie Zartarian, Ph.D., R. Woodrow Setzer, Ph.D., and Andrew Geller, Ph.D., Office of Research and Development, EPA

12:00 P.M. **LUNCH**

1:00 P.M. **PUBLIC COMMENTS**

2:00 P.M. **Charge to the Panel – Issue 1: Usability aspects of the SHEDS Dietary Module (SHEDS-Dietary v.1.0) and the SHEDS Residential Module (SHEDS-Residential v.4.0)**

A. SHEDS DIETARY

Question 1-1: *What, if any, difficulties were encountered in loading or running the SHEDS-Dietary software?*

Question 1-2: *Please comment on the organization, clarity, completeness, and usefulness of the SHEDS Dietary Technical Manual and the User Guide. Please provide any suggestions for improvement.*

Question 1-3: *Please comment on the organization and usability of the SHEDS-Dietary GUI (Graphic User Interface), and whether additional changes would be helpful the Dietary SHEDS.*

B. SHEDS RESIDENTIAL

Question 1-4: *What, if any, difficulties were encountered in loading or running the software for SHEDS-Residential software?*

Question 1-5: *Please comment on the organization, clarity, completeness, and usefulness of the SHEDS Residential Technical Manual and the User Guide? Please provide any suggestions for improvement.*

Question 1-6: *Please comment on the organization and usability of the SHEDS Residential GUI, and whether additional changes would be helpful for the Residential SHEDS.*

3:15 P.M. **BREAK**

3:30 P.M. **Charge to the Panel – Issue 2: Documentation, completeness, and clarity of technical aspects of SHEDS Dietary v. 1.0 and SHEDS Residential v. 4.0**

Question 2-1:

BACKGROUND: In August 2007, the FIFRA SAP reviewed the model and documentation for the SHEDS Residential module (then termed "SHEDS-Multimedia version 3"), plans for the dietary module, and plans for extending the model to aggregate the dietary and residential modules. The 2007 SAP report, EPA responses to the 2007 SAP comments, and specific changes from version 3 to version 4 of the Residential module have been provided to this SAP in the materials and background documents.

Please comment on whether the exposure algorithms and model components as described in the Technical Manuals are science based and technically correct for a) the Dietary module and b) the Residential module.

Question 2.2:

BACKGROUND: The 2007 FIFRA SAP, which reviewed the SHEDS Residential model and code, was provided with the SAS code and asked to comment on whether the code was consistent with the descriptions provided in the SHEDS Technical Manual, and whether the code was clear and was adequately described and annotated such that the algorithms could be followed and understood. At that time, the Panel was not provided with a code and there was no graphical user interface for the SHEDS dietary module. The 2007 SAP review of the dietary aspect of SHEDS was limited to reviewing several conceptual issues associated with dietary exposure and covered both data issues and algorithms. In the intervening three years, the Agency has updated SHEDS residential model to include applicator exposures (the 2007 version was limited to post application exposures only) and has made a number of additional changes as per the 2007 Panel review comments. Additional changes were made based on considerations that arose during review of the model and the desire to simplify the code and reduce the number of user-specified inputs. The specific changes that were made are listed and detailed in Section 1.6 of the Residential Technical Manual entitled "Changes from SHEDS-Residential version 3 to version 4". The current status of the SHEDS-Dietary module remains behind the residential module. Nevertheless, a number of advances have been made, including: (i) development of a GUI through which users can more easily develop and produce dietary exposure estimates, (ii) ability to read residue input files from another aggregate model (*.rdf), (iii) option to use the NHANES\WWEIA food consumption data (FCID recipes will be incorporated following public release), (iv) the ability to conduct Eating Occasions Analyses, (v) the ability to select among different Food Residue Options, (vi) simultaneous use of multi-chemical residue inputs for cumulative exposure assessment (i.e., pre-simulation adjustments using RPFs not required), and (vii) options for generating longitudinal (multi-day) consumption patterns. The Agency also prepared a draft User Guide and a Technical Manual for the SHEDS-

Dietary module, and we anticipate future work on both of these documents and SHEDS-dietary advances.

A. SHEDS RESIDENTIAL

Version 4 of SHEDS-Residential provides a number of additional capabilities compared to the SHEDS-Multimedia v.3 model reviewed in August, 2007. A summary the main changes from SHEDS-Residential version 3 to version 4 is provided in Section 1.6 of the Residential Technical Manual to which the Panel may wish to refer. The changes include: the ability to perform multichemical runs; the ability to reproduce (pseudo-) random number seeds; the capability of evaluating applicator (handler) exposures (and not just post application exposures); a new longitudinal diary assembly method based on the D&A statistic which supplements the 8-diary method from version 3; and a new option for evaluating uncertainty using bootstrap methods and the implementation of Sobol's method for sensitivity analysis, among numerous others.

Please comment on whether the annotated code for the SHEDS residential model (i) is sufficiently clear such that the algorithms can be followed and understood; and (ii) whether the algorithms defined in the Residential Technical Manual are consistent with those present in the code. In what ways might the code, its annotations, or the description in the Technical Manual be improved? Please consider in particular the new components of the code (i.e., added or modified since the 2007 SAP) as detailed and described in Section 1.6 of the Residential Technical Manual.

B. SHEDS DIETARY

Version 1 of SHEDS-Dietary represents the first version which provides the user with a graphical "point and click" interface and other enhancements and capabilities such as the ability to read residue input files from other aggregate models (*.rdf), the option to use the NHANES\WWEIA food consumption data, and Eating Occasions Analyses options. These are detailed in the Dietary User Guide and Dietary Technical Manual.

While the underlying SAS code has not at this time been fully annotated and/or is not as "reader-friendly" as the residential code, does the Panel have any comments or suggestions on the structure or form of the code or ways in which the code may be improved? Can the Panel identify any apparent discrepancies between the calculations described in the Dietary Technical Manual and the algorithms operating in and described by the SAS code?

5:30 P.M. Adjourn

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Thursday, July 22, 2010

9:00 A.M. **Opening of Meeting - Administrative Procedures by Designated Federal Official –** Sharlene Matten, Ph.D., Designated Federal Official, Office of Science Coordination and Policy, EPA

9:05 A.M. **Introduction and Identification of Panel Members –** Daniel Schlenk, Ph.D., Session Chair, FIFRA Scientific Advisory Panel

9:10 A.M. **Follow-up from Previous Day's Discussion –** Office of Pesticide Programs and Office of Research and Development, EPA

9:30 A.M. **Charge to the Panel – Issue 3: Strengths and Limitations of PBPK Approaches**

BACKGROUND: The FIFRA Scientific Advisory Panel (SAP) convened in August 16 - 17, 2007, to address science issues on approaches to model pyrethroids. To guide discussions, four charge questions were developed concerning: (1) application of a common model structure; (2) the parallelogram approach for extrapolation; (3) dose metric considerations; and, (4) pyrethroid stereochemistry. Recognizing that the 2007 SAP has commented on these approaches, the Agency seeks comment from the current SAP on issues concerning PBPK model calibration and the coupling of SHEDS and PBPK.

Question 3-1: *Please comment on the strengths and limitations of the pharmacokinetic modeling approach for pyrethroids with added attention to the PBPK structures for interpreting aggregate exposure data from SHEDS.*

Question 3-2: *Please comment on the Bayesian approach outlined here for calibrating the PBPK model against rodent PK data, including the use of computational and in vitro methods to develop priors for chemical-specific parameters.*

Question 3-3: *Please comment on the approach used to characterize the animal-to human extrapolation, including the uncertainty of the extrapolation.*

Question 3-4: *Please comment on the plausibility and limitations of model-predicted dose-metrics, such as area under the curve (AUC), peak tissue values, time above a toxicological threshold, or AUC above a toxicological threshold, in analyzing animal dose-response data and in extrapolation to humans.*

Question 3-5: *The presentation described methods for addressing uncertainty in model parameters and extrapolation from animals to humans. What other important sources of uncertainty need to be addressed for either the SHEDS exposure model or the PBPK model?*

10:30 A.M. BREAK

10:45 A.M. Charge to the Panel – Issue 3: Strengths and Limitations of PBPK Approaches, continued

12:00 P.M. LUNCH

1:00 P.M. Charge to the Panel – Issue 4: Model Evaluation

BACKGROUND: Model evaluation is an important component of model development that helps ensure that the quality of the model meets the regulatory needs of OPP and other end-users. In performing its model evaluation, the Agency compared SHEDS model output – specifically exposure and urinary concentration estimates – with both output from other exposure assessment models and data from observational studies. These comparisons permit the SHEDS development team and model end-users to compare and contrast outputs among different models, to compare estimates with measured real-world data, to explore and investigate reasons for any differences, and to evaluate and better understand the reasons behind these differences. As part of the model evaluation procedure for SHEDS, the Agency has attempted to evaluate the SHEDS model in a number of ways. These include:

a) comparison of SHEDS-Dietary cross-sectional output to DEEM-FCIDTM; the DEEM-FCIDTM model is commonly used by OPP in its regulatory decisions and was reviewed by the SAP in 2000 (see SHEDS-Dietary Technical Manual (Section.2.8.1) and EPA 2010 Response to Comment (p.10));

b) comparison of (a) SHEDS-Dietary arsenic and permethrin estimates against duplicate diet data and (b) the predicted urinary concentrations from the SHEDPBPK linked model with the measured arsenic concentrations in urine from the 2003-2004 NHANES biomonitoring program (see SHEDS-Dietary Technical Manual and link to Xue *et al.* 2010 article provided in background materials);

c) comparison of SHEDS Residential outputs with outputs from other models or calculation methods (ORD's *Draft Protocol*, OPP's Residential Standard Operating Procedures (1997), Calendex, CARES, and ConsExpo) which was originally organized as a day long symposium at the annual meeting of ISEA in 2008 held in Pasadena, CA (see slides in background materials); and

d) following the model quality assurance procedures as detailed in Chapter 8 of the SHEDS-Residential Technical Manual and EPA's SHEDS-Multimedia Quality Assurance Project Plan (QAPP) 1 these included EPA-contractor cross-checking of the code and hand-calculation verification on a subset of data for a simulated individual to ensure the SHEDS-Residential algorithms were implemented and performing as intended.

Question 4: *Please comment on the process used to evaluate SHEDS. Are the above listed ways in which SHEDS was evaluated appropriate? In what ways could they be improved? Are there other methods through which the model should or can be evaluated? Are there other data (e.g., biomonitoring data, duplicate diet data) that the Panel is aware of through which the SHEDS model can be compared?*

3:00 P.M. BREAK

3:15 P.M. Charge to the Panel – Issue 5: SHEDS-PBPK Permethrin Case Study

Question 5-1: EPA has used a pyrethroid insecticide, permethrin, as a case study to link the SHEDS exposure model with PBPK modeling in order to be able to better interpret and understand exposure data in terms of dose and target-organ dose and assist in refining exposure estimates and associated risk.

Please comment on the approaches and offer alternatives and suggestions for:

a) linking dietary consumption diaries and residential activity information (e.g. key factors used for matching food consumption and activity pattern diaries such as caloric consumption);

1The QAPP (and additional material related to SHEDS) is available on the ORD SHEDS website at http://www.epa.gov/heasd/products/sheds_multimedia/sheds_mm.html

b) *quantification of dietary vs. residential contribution, including relative contribution of residential exposure pathways (dermal, inhalation, hand-to-mouth, object-to mouth);*

c) *D[iversity] & A[utocorrelation] longitudinal diary assembly approach (Glen et al., 2007, reviewed for residential module by 2007 SAP);*

d) *identifying significant contributors at upper percentiles of dietary exposure; and*

e) *techniques and utility of bootstrapping approaches for quantifying uncertainty and its interpretation.*

Question 5-2: *Please comment on whether the model evaluation approach comparing the linked SHEDS-PBPK dose predictions and NHANES (National Health and Nutrition Exams Survey) biomonitoring data is reasonable. Are there other model evaluation methods that the Panel would like to see the Agency perform?*

Question 5-3: *Please comment on the approaches presented to extend the SHEDS-PBPK Permethrin Case Study to include exposure to cypermethrin and cyfluthrin. Furthermore, please advise on other methodologies (e.g., cross-sectional vs. longitudinal), exposure scenarios, chemicals, and datasets which may be useful to consider in assessing SHEDSPBPK simulations of pyrethroids.*

5:30 P.M. ADJOURN

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, Dr. Sharlene Matten, via telephone: (202)-564-0130; fax: (202) 564-8382; or email: matten.sharlene@epa.gov.