AGENDA
FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
OPEN MEETING

February 15-18, 2011

FIFRA SAP WEB SITE http://www.epa.gov/scipoly/sap/
OPP Docket Telephone: (703) 305-5805
Docket Number: EPA-HQ- OPP-2010-0588

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 Chlorpyrifos PBPK-PD Modeling Linked to CARES

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

Tuesday, February 15, 2011

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

9:05 A.M. **Introduction and Identification of Panel Members**
Dr. Kenneth Portier, Chair, FIFRA Scientific Advisory Panel

9:10 A.M. **Welcome and Opening Remarks**
Dr. Steven Bradbury, Director, Office of Pesticide Programs (OPP), EPA

9:15 A.M. **Introduction**
Dr. Jack Fowle, Deputy Director, Health Effects Division, OPP, EPA

9:20 A.M. **Introduction and Regulatory Context: Linking of a Probabilistic Exposure Model and a Physiologically-based Pharmacokinetic/Pharmacodynamic Model: Chlorpyrifos Case Study**
Dr. Anna Lowit, Health Effects Division, OPP, EPA

9:50 A.M. **Overview of Modeling Approach, Chlorpyrifos Metabolism and Mode of Action, New Enzyme Data**
Dr. Mike Bartels, Dow Agrosciences

10:30 A.M. **BREAK**

10:45 A.M. **Description of the PBPK/PD Model, Development of the Lifestage Model**
Dr. Torka Poet, Battelle/Pacific Northwest National Laboratory

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

1:00 P.M. **Description of the Variation Model**
Dr. Paul Hinderliter, Battelle/Pacific Northwest National Laboratory

2:00 P.M. **Source-to-Outcome Modeling**
Mr. Paul Price, Dow AgroSciences

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

3:15 P.M. **Utility of New Animal Study Data for Model Development**
Dr. Sue Marty, Dow AgroSciences

4:00 P.M. **Use of Model Predictions in the Risk Assessment Process**
Mr. Paul Price, Dow AgroSciences

5:30 P.M. **Adjourn**

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Wednesday, February 16, 2011

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

9:05 A.M. **Introduction and Identification of Panel Members**
Dr. Kenneth Portier, Chair, FIFRA Scientific Advisory Panel

9:10 A.M. **Follow-up from Previous Day's Discussion**
Dr. Anna Lowit, Health Effects Division, OPP, EPA

9:30 A.M. **PUBLIC COMMENTS**

10:30 A.M. **BREAK**

10:45 A.M. **CHARGE QUESTIONS**
Mr. David Miller, Chief, Chemistry & Exposure Branch, Health Effects Division, OPP, EPA

Charge Question 1: Physiologically-Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) Modeling

BACKGROUND: The model(s) developed by Dr. Charles Timchalk and co-workers at the Pacific Northwest National Laboratory has been the extensively discussed in the scientific community, published

in peer reviewed journals, and improved upon by a variety of investigators. It was first published in 2002 as an adult rat and human model (Timchalk et al., 2002a) and then updated as more data became available (Poet et al. 2003; Poet et al. 2004; Slikker et al. 2005; Timchalk et al. 2002b; Timchalk et al. 2003; Timchalk et al. 2005). Timchalk et al. (2007) published a similar model for juvenile rats. DAS has recently expanded this model to address doses that vary across time and intra-individual variation in physiology, physical activity levels, and metabolism as well as variation as a function of age (Sections 3-4).

> ***QUESTION 1.1:*** *Model Structure:* Please comment on the structure of the chlorpyrifos PBPK/PD model with specific consideration of the mechanistic basis for the acetylcholinesterase (AChE) inhibiting mode of action. Please include in your comments consideration of age-dependant metabolism and the proposed approach to assess human variability.
>
> ***QUESTION 1.2****: Dose Metrics:* In Section 6, DAS proposes a number of dose metrics for use in the PBPK/PD effort. These include peak levels of blood and brain AChE inhibition, peak blood and brain levels of chlorpyrifos and its oxon metabolite, and urinary measures of 3,5,6-trichloro-2-pyridinol (TCPy), a chlorpyrifos metabolite. Please comment on the utility, strengths, and limitations of these proposed internal dose metrics.
>
> ***QUESTION 1.3****:* Although the current modeling effort focuses on AChE inhibition, there are data to suggest that chlorpyrifos exposure may also result in non-cholinergic effects. As such, and if appropriate, please provide plausible additional and/or alternative dose metrics such as area under the curve (AUC) metrics or other temporal-based internal dose metrics that may be appropriate for evaluating potential non-cholinergic effects.

12:00 P.M. LUNCH

1:00 P.M. Charge Question 1 continued

3:00 P.M. BREAK

3:15 P.M. Charge Question 2: Longitudinal Dietary Exposure Assessment

BACKGROUND: Historically, approaches to assessing longitudinal dietary exposure (i.e., consecutive days of consumption) have been controversial due to limited information on longitudinal food consumption and the variety of ways in which the data of only several days duration can be used to develop consumption profiles for longer durations. DAS has proposed the use of its source-to-outcome model to investigate longitudinal dietary exposure in the current modeling effort. More specifically, DAS has proposed to evaluate the days immediately prior to and following a high exposure event and determine the degree to which accounting for such longitudinal exposures may affect PBPK/PD model outputs and risk.

The technical aspects of this proposal can be found in Section 5 of the DAS background document. More specifically, Section 5 discusses the use of their source-to-outcome model to investigate and characterize the impacts of longitudinal (day-to-day) dietary exposures to chlorpyrifos on (i) concentrations of the TCPy metabolite in urine and blood and (ii) inhibition of brain and blood AChE. Such a longitudinal analysis is important because the effects caused by the dose may not return to background within a 24 hour period and there thus can potentially be "carry-over" effects of AChE inhibition from previous exposures. This is because the body may not eliminate chlorpyrifos or its metabolites within 24 hours

and the effects of the dose on AChE inhibition may not be fully reversed within 24 hours. The DAS background document concludes with respect to current chlorpyrifos dietary exposures that:

1) The use of the five day exposure histories produced by CARES or other dietary exposure software models provides a reasonable basis for the evaluation of the impacts of longitudinal (multi-day) exposures, particularly for those predictions in the upper percentiles of the exposed populations. (see p. 125 of DAS background document)

2) When there is large variation in day-to-day levels of dietary doses, the impact of repeated small doses is minimal compared to a high level of exposure on a single day: if a person has a high level of exposure on a given day (e.g., top 01%), the impact on chlorpyrifos- and chlorpyrifos-oxon concentrations in blood and peak inhibition of RBC and brain AChE both on the day of initial exposure and subsequent days is determined mainly by the dose from that (high-end) day; that is, the "carry-over" effects from a previous day's exposures provide at most modest or only minimal contributions to current levels of inhibition. (see p. 125 of the DAS background document)

3) The impacts of repeated oral exposures at levels estimated to be present in the diet on blood levels of chlorpyrifos and chlorpyrifos-oxon are relatively small for high end exposures (e.g., >99th percentile). Further, the model indicates that chlorpyrifos and the chlorpyrifos-oxon do not accumulate over time and accounting for the "carry over" effects of repeated daily exposures on AChE inhibition is important only for individuals with relatively low dietary exposures (e.g., <75th percentile).

   QUESTION 2.1: Please comment on the methods used by DAS to investigate the relationships between dietary exposures and levels of chlorpyrifos and chlorpyrifos-oxon in blood. Please include in your comments discussion on the strengths, weaknesses, impacts, and utility of the DAS proposal to focus on the immediate prior and subsequent days to high-end exposures and provide alternative approaches to assessing longitudinal (multi-day) exposures, if appropriate. Under what conditions and scenarios might this focus be inadvisable and/or lead to incorrect conclusions regarding exposures, doses, and risks?

   QUESTION 2.2: Please comment on the soundness of the conclusions reached by DAS with respect to the impact and importance of accounting for longitudinal dietary exposures to chlorpyrifos at the upper ends (e.g., >99th percentile) of the exposure distribution. To what extent, if any, can the DAS conclusions be generalized to other AChE-inhibiting chemicals and under what conditions? Please suggest how this issue of generalization to other pesticides could be investigated and explored?

5:30 P.M. Adjourn

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Thursday, February 17, 2011

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

9:05 A.M. **Introduction and Identification of Panel Members**
Dr. Kenneth Portier, Chair, FIFRA Scientific Advisory Panel

9:10 A.M. **Follow-up from Previous Day's Discussion**
Mr. David Miller, Chief, Chemistry & Exposure Branch, Health Effects Division, OPP, EPA

9:30 A.M. **Charge Question 3: Model Calibration and Evaluation with Direct Dosing Human Studies**

BACKGROUND: Model calibration and evaluation is critical to ensure that simulated profiles are consistent with experimental observations and that parameter estimates are appropriate for the intended use of the model. In performing its preliminary model evaluation and in an attempt to gauge how reasonable the model predictions were, DAS compared the estimates from its source-to-outcome model – specifically blood and urinary concentration estimates – with human data. These comparisons permitted DAS to (i) evaluate how well model estimates of concentrations matched measured human data; (ii) explore and investigate reasons for any differences; and (iii) evaluate and better understand the reasons behind these differences. As part of the preliminary model evaluation procedure for the DAS source-to-outcome model, DAS has attempted to evaluate the model in a number of ways, one of which (described below) is a comparison of blood plasma and urinary TCPy concentration predictions generated by the

DAS PBPK/PD source-to-outcome model to a human volunteer study in which 12 volunteers were administered one of three doses of chlorpyrifos.

The DAS manuscript describes two controlled human exposure studies available in the literature. In the Nolan et al. (1984) study, human volunteers were administered chlorpyrifos and the resultant plasma and urinary TCPy levels were measured at various time points post-dosing. These kinetic profiles were used to optimize oral absorption and TCPy compartmental parameters (See Table 1, Section 3) of the DAS PBPK/PD model. All the other parameters are presumed to be measured or estimated from respective growth functions (See Table 2, Section 3).

Model evaluation was then carried out by comparing measured plasma and urinary TCPy levels from a second chlorpyrifos human volunteer study (Kisicki et al., 1999) to the corresponding model-simulation of such study. DAS states that model predictions of blood plasma and urinary TCPy concentrations agree well and appear to be consistent with those measured in the Kisicki study as shown in Figures 23 (plasma) and 24 (urine).

> ***QUESTION 3:*** Please comment on the model evaluation approach comparing the linked CARES-PBPK/PD source-to-outcome model predictions with the Kisicki et al. 1999 study. In what ways could or should the model evaluation approach used by DAS be extended? Are there other model evaluation methods with respect to this aspect of the DAS manuscript that the Panel suggests be performed? To what extent does the Panel agree that the DAS model predictions are reasonably consistent with those of the Kisicki et al (1999) literature-reported values?

10:15 A.M. BREAK

10:30 A.M. Charge Question 4: **Comparison of Model Predictions with Human Monitoring Data**

BACKGROUND: DAS attempts to provide additional perspective on the predictions of the source-to-outcome model by comparing the model-predicted values to those measured in biomonitoring studies. These comparisons permitted DAS to evaluate how realistic model predictions are when compared to human biomonitoring data. Specifically, DAS uses the source-to-outcome model to predict (i) approximate blood levels of chlorpyrifos in pregnant women (Table 7 of the DAS manuscript) and (ii) TCPy levels in urine in adults and children (Figure 57 and Table 8 of the DAS manuscript).

With respect to the values reported for pregnant females in Eaton et al (2008), Whyatt et al. (2009) and Barr et al. (2010), DAS recognizes that the data sets are less than ideal for comparison to modeled results since the number of individuals in the studies was limited, the majority of samples in the studies were below the detection limit, and the individuals included in the studies were females who had just given birth and whose diets and ADME may differ from the general population. Nevertheless, the DAS source-to-outcome model predictions are within a factor of 2 of many of the cited literature-reported measured values. It should also be mentioned that the LifeStage model does not include pregnancy-related changes and was only used to predict the order of magnitude of blood levels for comparison to measured values.

With respect to the comparison of the model-predicted TCPy urinary concentrations to: (i) the literature-reported TCPy urinary concentrations (Curwin et al. (2007) and Lu et al. (2008)); and (ii) to the 2002 NHANES TCPy urinary concentrations, DAS recognizes and states that the use of TCPy in blood or urine as a direct measure of chlorpyrifos is complicated by the fact that TCPy is itself present in the environment, that dietary residues of TCPy *per se* occur in many foods, and that – as a result – only 5-20% of any TCPy observed in urine is as a result of dietary intake of chlorpyrifos residues. After

considering that only a fraction of any ingested CPY parent will be excreted as TCPy in the urine, DAS concludes that "the results of the comparison of TCPy provide confirmation that the dietary and pharmacokinetic portions of the source-to-outcome model are producing estimates for adults that are reasonably consistent with the reported blood concentrations in adults and children." DAS further concludes that "these results provide considerable support that the dietary and PBPK portions of the model are likely to be at the right order of magnitude in their predictions of body burdens of chlorpyrifos and its metabolites."

> ***QUESTION 4:*** Please comment on the model evaluation approach used by DAS to compare the linked DAS source-to-outcome model dose predictions to (i) Eaton et al (2008), Whyatt et al. (2009) and Barr et al. (2010), (ii) the Curwin (2007) and Lu (2008) literature values and (iii) NHANES data measurements. To what extent does the Panel agree that the DAS model predictions are reasonably consistent with those of the literature-reported values and the NHANES data? Please suggest, if appropriate, other model evaluation methods or alternative approaches for comparing model predictions with actual human exposure that the Panel recommends to further evaluate the model predictions. Please include in your comments suggestions for what additional datasets should be used for comparison.

12:00 P.M. LUNCH

1:00 P.M. Charge Question 5: Sensitivity Analyses, Variability, and Uncertainty

BACKGROUND: The PBPK/PD component of the DAS source-to-outcome model development efforts was comprised of three stages:

1) Development of a "Typical Adult Model" (as initially described in the Timchalk et al. 2002) to model the relationship between oral dose of chlorpyrifos and i) internal concentration of chlorpyrifos and its metabolites; and (ii) AChE inhibition;

2) The "Typical Adult Model" was expanded to a "LifeStage Model" through incorporation of age-related changes in tissue growth and enzyme ontogeny. The LifeStage model was then used to predict dose-response relationships from adults to 6 month old infants and 3 year old children;

3) The "LifeStage Model" was then further expanded to a "Variation Model" to address inter-individual variability in dose response that could be attributed to differences in physiology, physical activity, and metabolism/metabolic activity in each of the three modeled age groups above.

As described in Chapter 4 of the DAS background document, DAS used a four step procedure in developing its "Variation Model" to most appropriately address inter-individual variation: (i) sensitivity analysis was used to identify the most influential parameters that drive variation in response as predicted by the "LifeStage Model"; (ii) distributions of the identified influential parameters were assembled; (iii) attempts were made to account for and address, as appropriate, correlations between input parameters; and (iv) comparisons were made of model-predicted variability to data from human volunteer studies.

> ***QUESTION 5.1:*** The four step procedure described above was intended to permit DAS to focus on the factors that were most important in determining variation in response. Please comment on the methods used by DAS to assess variation in response (e.g., identification of sensitive factors and collection and integration of empirical data on variation). Please discuss the extent to which the methods described are appropriate and complete?

QUESTION 5.2: During the Scientific Advisory Panel meeting held in July 2010 in which EPA's Office of Research and Development SHEDS/PBPK model was presented (see http://www.epa.gov/scipoly/sap/meetings/2010/072010meeting.html), the Panel reviewed ORD's Bayesian Approach to quantitative uncertainty analysis. DAS in its source-to-outcome model did not attempt to perform a formal quantitative uncertainty analysis (QUA), but instead evaluated components of the model by performing model-to-model comparisons (e.g., multiple dietary exposure models and multiple models of longitudinal exposures) and by performing model-to-measurement comparisons for internal dose (e.g., chlorpyrifos in blood and TCPy in urine) and AChEI in blood and plasma. Since formal Bayesian QUAs are only rarely conducted, are there other methods (short of rigorous Bayesian approaches) that the SAP can recommend for characterizing uncertainty due to limited data?

3:00 P.M. BREAK

3:15 P.M. Charge Question 6: Calculating Data-Derived Extrapolation Factors

BACKGROUND: EPA typically uses standard 10x factors to address the uncertainties associated with inter- and intra-species extrapolation. Section 10 of the document describes approaches for calculating data-derived extrapolation factors informed by the current modeling effort. These approaches involve simulations of the linked models.

QUESTION 6.1: Please comment on the strengths and limitations of DAS's proposed approach to estimate an animal-to-human extrapolation factor as described in Section 10. The Agency is concerned about a component of the proposed approach involving use of the study design characteristics of a single animal study (See Section 10). The Agency generally recommends a weight of the evidence approach for determining toxicological points of departure when multiple studies are available. For chlorpyrifos, there is a large database of study results performed across different animal life stages and so it may be more appropriate to determine points of departure and extrapolation factors based on an integrated analysis of these multiple studies instead of based on a single study. In your response, please comment on the approached proposed and provide guidance and suggestions for alternative approaches, if appropriate.

QUESTION 6.2: Please comment on the strengths and limitations of proposed approach to estimate a human variability extrapolation factor as described in Section 10. Please provide alternative approaches, if appropriate.

QUESTION 6.3: The current effort by DAS is limited to food exposure and does not include all relevant exposure routes. Please comment on strengths and weaknesses of using data-derived extrapolation factors described in the current effort for lifestages (e.g., gestation or pregnancy) and/or for routes (dermal, inhalation) not considered in the current modeling effort.

5:30 P.M. ADJOURN

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Friday, February 18, 2011 (if needed)

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Dr. Sharlene Matten, Designated Federal Official, Office of Science Coordination and Policy, EPA

9:05 A.M. **Introduction and Identification of Panel Members**
Dr. Kenneth Portier, Chair, FIFRA Scientific Advisory Panel

9:10 A.M. **Follow-up from Previous Day's Discussion**
Mr. David Miller, Health Effects Division, OPP, EPA

9:30 A.M. **Charge Questions continued**

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

10:30 A.M. **Charge Questions continued**

12:00 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.