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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

November 8, 2004

MEMORANDUM

Subject: Transmission of Background Materials and Charge to the Panel for the Session of the December 3, 2004 FIFRA Scientific Advisory Panel Entitled "The N-methyl Carbamate Cumulative Risk Assessment: Strategies and Methodologies for Exposure Assessment"

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

From: David J. Miller and Anna Lowit
Office of Pesticide Programs,
Health Effects Division (7509C)

Through: George Herndon, Acting Director
Office of Pesticide Programs,
Health Effects Division (7509C)

The December 3, 2004 FIFRA SAP meeting entitled "The N-methyl Carbamate Cumulative Risk Assessment: Strategies and Methodologies for Exposure Assessment" is the first in a series of SAP meetings planned by EPA to discuss various aspects of the N-methyl carbamate cumulative risk assessment. The primary purpose of this meeting is to discuss the concepts introduced in the white paper entitled "Designing Exposure Models that Support PBPK/PBPD Models of Cumulative Risk" and developed by the LifeLife Group Inc. In addition, this SAP meeting is meant to provide the members of the FIFRA Scientific Advisory Panel (SAP) and the public with the general framework and next steps in the development of the cumulative risk assessment for the N-methyl carbamate pesticides.

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In addition to this memo, three documents are provided to members of FIFRA Scientific Advisory Panel in preparation for the December 3, 2004 meeting:

1. A background document covering EPA activities related to the N-Methyl carbamate cumulative risk assessment

2. Attachment 1: Overview of Topics for February 2005 FIFRA SAP meeting

3. A document entitled "Designing Exposure Models that Support PBPK/PBPD Models of Cumulative Risk" developed by the LifeLife Group Inc.

Note: EPA is soliciting comment (Question 2) from the SAP on topics discussed in:

> Price, P. S., Conolly, R.B., Chaisson, C.F., Young, J.S., Mathis E.T., Tedder D.T. 2003. Modeling Inter-individual Variation in Physiological Factors Used in PBPK Models of Humans, *Critical Reviews in Toxicology* Vol. 33, (5): 469-503.

EPA is currently working with Taylor and Francis, the publisher and copyright owner of this article, to provide this paper to the panel.

As part of this SAP session, we are asking Panel members to consider the following charge and questions:

Charge and Questions to the Panel:

1. The LLG's white paper entitled "*Designing Exposure Models that Support PBPK/PBPD Models of Cumulative Risk*" presents an outline of the fundamental procedures and logic required to deliver appropriate exposure metrics to the Physiologically-based Pharmacokinetic/ Pharmacodynamic (PBPK/PD) model for the N-methyl carbamate group of pesticides. Specifically, the new exposure assessment requires an approach that will modify the exposure information that is currently produced, extend the software to provide additional information on the individuals being modeled, and define the technical process by which information will be transferred from the exposure model to the PBPK/PD model. The LLG white paper also describes the data requirements of a PBPK/PD model, briefly reviews the state of existing exposure assessment models and their outputs, and presents a both a general approach and an N-methyl carbamate-specific approach of how exposure simulation models can be adapted to meet the needs of a PBPK/PD model of cumulative risks.

Please comment on the detail and clarity of this document.

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2. A central tenet underlying aggregate and cumulative risk assessment is that exposure occurs to a hypothetical individual whose specific demographic characteristics such as age group, region of residence, race/ethnicity, sex, etc. help define exposure scenarios. The exposure pattern and other data concerning this individual should be consistent with those characteristics.

The use of PBPK/PD models in cumulative assessments adds another layer to the complexity of generating and maintaining a set of internally consistent individuals comprising a hypothetical population. In defining individuals for use in PBPK/PD models, it is necessary to maintain logical consistency and linkage between the various anatomical and physiological parameters that describe that individual. For example, given a bodyweight, age, and sex of an individual from a reference population such as Lifeline's Natality data set, it is necessary that the organ sizes, compartmental blood flows, breathing rates, etc. all be consistent.

A recent journal article by P.S. Price *et al. (2003)* appearing in *Critical Reviews in Toxicology* summarizes much of the literature in this area[1]. The article presents a number of regression and other equations which can be used to generate the linked anatomic and physiological characteristics of those individuals. [2]

a) *Please comment on the degree to which the article comprehensively summarizes the available literature concerning the anatomic and physiological relationships that exist between organ sizes and volumes, blood and other flows, breathing parameters, etc.?*

b) *Are there additional data or data sources for these relationships that would be useful to include or consider?*

c) *Please comment on algorithms provided and their potential utility in use by PBPK/PD models.*

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[1] EPA has not as of yet received permission from Taylor and Francis, the publisher and copyright owner of this article, to distribute the following study to the FIFRA SAP members. Price, P. S., Conolly, R.B., Chaisson, C.F., Young, J.S., Mathis E.T., Tedder D.T. 2003. Modeling Inter-individual Variation in Physiological Factors Used in PBPK Models of Humans, *Critical Reviews in Toxicology* Vol. 33, (5): 469-503

[2] The algorithms present in this journal article are those that are used in a model called Physiological Parameters for PBPK Modeling (P^3M) and available from http://www.thelifelinegroup.org/P3M/index.html . The model serves as a convenient tool to parameterize exposure and PBPK models The software can be downloaded from the above-indicated site and is available without charge.

3. Traditional non-cancer probabilistic risk assessment methods perform a direct conversion of exposure (expressed, for example, in ug/kg day) into risk (expressed, for example, as a unitless margin of exposure or percent of reference dose). By incorporating a PBPK/PD component into risk assessments in order to more appropriately account for temporal and other aspects of toxicity, output from the exposure component of the model must serve as input to the PBPK component. In order for this to occur, a time series of exposures must be developed for each individual considered in the assessment. Each exposure event associated with that individual that occurs during a given time step must act as a separate input to the PBPK/PD model.

   In order for this to occur, data from the USDA's CSFII must be placed into the exposure component of a model in a such a way that separates each individual's eating occasions. In addition, data from NHAPS and other databases will need to be entered in such a way that each event occurring during a given time step is distinct and separate. Furthermore, the output from this exposure model must appropriately link or interface with a PBPK/PD model. The LLG's white paper proposes that Lifeline be modified such the analyst can customize the outputs of the model for the specific PBPK/PD analysis to be run, selecting from among 23 tissues, organs, and compartments listed. The analyst will then define the duration of the time step used for creating the exposure history and the duration of the exposure history for the basis of the LifeLine™ exposure analysis metrics and output file. LifeLine™ output files will be created as Access™ files consisting of separate records for exposures of each simulated individual within the defined population of the analysis. Each individual's exposure history will be captured in a record that consists of two tables. Examples of data tables/outputs were presented in the LLG's background document.

   a) Please comment on the format and structure of the MS Access file containing the records for each individual's exposure and anatomical/physiological parameters (Table 2 and Table 3a of the LLG white paper)?

   b) Are there additional parameters or options that should be included?

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4. The suggested approach addressed in Question #3 will make resource-intensive computational demands making computer run-times impractical for regulatory purposes. The LLG white paper proposes that not every record generated or processed by the LifeLine model be saved. These limitations will require that model runs be limited to a few hundred or a thousand individuals and that only some fraction of the records be retained by software and used as input to the PBPK/PD model. The process of selecting the records to convey to the PBPK/PD model will require special attention and a transparent prioritization scheme based on explicit criteria. The specific nature of how this will be done could be based on any of several criteria. For example**:** the exposure software could create a demographic, physiological and exposure history for each individual and "tag" only those individuals with estimated exposures (or relative potency factor-adjusted exposures) greater than either 1) a certain user-defined cut-off value (e.g, >BMD_{10}) or 2) greater than a user-defined percentile (e.g., 90^{th} percentile). Only those records that were tagged in this way would be included in the interface file (MS Access™) that will be exported to the PBPK/PD model. In this way, only the records that were at the high end of the exposure distribution (however defined by the user) would be run through that model.

   a) *Please comment on the proposal to retain only a fraction of the records generated by the LL model for interface/export to the PBPK/PD model due to computational demands.*

   b) *Does the panel have any comments or suggestions on the criteria which should be used to select records for input into the PBPK/PD model?*

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