January 27, 2005

MEMORANDUM

SUBJECT: Transmittal of Minutes of the FIFRA Scientific Advisory Panel Meeting Held December 3, 2004: N-Methyl Carbamate Cumulative Risk Assessment - Strategies and Methodologies for Exposure Assessment

TO: Joseph J. Merenda, Director
Office of Office of Science Coordination and Policy

FROM: Paul I. Lewis, Designated Federal Official
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

THRU: Larry C. Dorsey, Executive Secretary
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

Please find attached minutes of the FIFRA Scientific Advisory Panel open meeting held in Arlington,Virginia from December 3, 2004. These meeting minutes address a set of scientific issues being considered by the U.S. Environmental Protection Agency regarding n-methyl carbamate cumulative risk assessment: strategies and methodologies for exposure assessment.

Attachment

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SAP Report No. 2005-03

MEETING MINUTES

FIFRA Scientific Advisory Panel Meeting, December 3, 2004 held at the Holiday Inn-National Airport, Arlington, Virginia

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

N-Methyl Carbamate Cumulative Risk Assessment: Strategies and Methodologies for Exposure Assessment

NOTICE

These meeting minutes have been written as part of the activities of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP). This report has not been reviewed for approval by the United States Environmental Protection Agency (Agency) and, hence, the contents of this report do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

The FIFRA SAP was established under the provisions of FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, to provide advice, information, and recommendations to the Agency Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The Panel serves as the primary scientific peer review mechanism of the EPA, Office of Pesticide Programs (OPP) and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. Food Quality Protection Act Science Review Board members serve the FIFRA SAP on an ad hoc basis to assist in reviews conducted by the FIFRA SAP. Further information about FIFRA SAP reports and activities can be obtained from its website at http://www.epa.gov/scipoly/sap/ or the OPP Docket at (703) 305-5805. Interested persons are invited to contact Paul Lewis, Designated Federal Official, via e-mail at lewis.paul@epa.gov.

In preparing these meeting minutes, the Panel carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. This document addresses the information provided and presented within the structure of the charge by the Agency.

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A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

N-Methyl Carbamate Cumulative Risk Assessment: Strategies and Methodologies for Exposure Assessment

Paul I. Lewis, Ph.D.
Designated Federal Official
FIFRA Scientific Advisory Panel
Date: 1/27/05

Steven G. Heeringa, Ph.D.
FIFRA SAP Session Chair
FIFRA Scientific Advisory Panel
Date: 1/27/05

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
December 3, 2004

N-methyl Carbamate Cumulative Risk Assessment:
Strategies and Methodologies for Exposure Assessment

PARTICIPANTS

FIFRA SAP Session Chair

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PUBLIC COMMENTERS

Oral statements were presented as follows:

On behalf of the Natural Resources Defense Council:
Jennifer Sass

On behalf of the Carbamate Working Group
Ian Kelly and Muhilan Pandian

Written statements were provided by or on behalf of the following group:

Natural Resources Defense Council

Carbamate Working Group

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of a set of scientific issues being considered by the Agency pertaining to its review of the n-methyl carbamate cumulative risk assessment: strategies and methodologies for exposure assessment. Advance notice of the meeting was published in the *Federal Register* on October 19, 2004. The review was conducted in an open Panel meeting held in Arlington, Virginia, on December 3, 2004. The meeting was chaired by Steven Heeringa, Ph.D. Mr. Joseph Bailey served as the Designated Federal Official. Mr. Joseph Merenda, Jr. (Director, Office of Science Coordination and Policy, EPA) welcomed the Panel to the meeting. Randolph Perfetti, Ph.D. (Health Effects Division, Office of Pesticide Programs, EPA) offered opening remarks at the meeting. Anna Lowit, Ph.D. (Health Effects Division, Office of Pesticide Programs, EPA) and Mr. David J. Miller (Health Effects Division, Office of Pesticide Programs, EPA) highlighted the goals and objectives of the session. Christine F. Chaisson, Ph.D. (The LifeLine Group, Inc.), Ms. Claire Franklin (The LifeLine Group, Inc.) and Mr. Paul S. Price (The LifeLine Group, Inc.) discussed designing exposure models that support PBPK/PD models of cumulative risk.

SUMMARY OF PANEL DISCUSSION AND RECOMMENDATIONS

The FIFRA SAP deliberated on modifications to a computer model of pesticide exposure, originally developed by the LifeLine Group (LLG). This model is being adapted by the same group for potential future use in cumulative risk assessment with N-methylcarbamates. The Agency requested guidance on four topics: 1) the clarity and detail of a white paper on the model by the LLG; 2) the reliability and comprehensiveness of current information as a basis for anthropometric derivation of organ weights and blood flows; 3) the format and structure proposed for the model's output files; and 4) a proposal to retain only a fraction of the output records for analysis in PBPK/PD models. Each of these topics received extensive discussion as summarized below. The responses to charge questions and the Panel's specific recommendations are set out in more detail in subsequent sections of this report.

- The white paper was viewed as a good beginning on a large and difficult task. The Panel, however, had many recommendations for improving the paper as a means of defining, presenting, and guiding the modeling work as it goes forward. Although the document was surprisingly understandable, considering the confusing data handling issues concerned, its language contained too much jargon, and was needlessly convoluted. Rewriting for greater clarity was encouraged. The level of detail on many topics did not satisfy the Panel. Suggestions to remedy this problem included the following: (1) include some comparisons of the projected LLG model with other exposure models now existing or in advanced stages of development; (2) consider the processes by which chemicals are introduced into non-food exposure settings and discuss mass-balance phenomena such as transport of material into, out of, and within the exposure setting; (3) present more details on the inhalation exposure pathway; (4) consider interactive effects on absorption during overlapping dermal exposure of similar chemicals; (5) offer more explicit consideration of ways in which an individual's genotype may determine how an exposure translates into "intake"; (6) give more attention to the question of appropriate interfaces between an exposure model and a PBPK/PD model and; (7) explain what such interfaces can and should accomplish in terms of improved output on the computational side, and how the performance of an interface might be evaluated.

- Regarding the anthropometric approach to estimation of physiologic and anatomical parameters, the Panel was generally supportive but felt it worthwhile to take advantage of ongoing data collection from unusual subpopulations. The model developers and users were also urged to pay more attention to small but well perfused organs of great functional and toxicologic importance, notably in the reproductive and endocrine systems. The Panel agreed that the algorithms proposed for use in estimating the flow and volume parameters for PBPK/PD modeling were good starting points. There was a consensus, however, that these algorithms may be too linear and deterministic for the long run. There is already evidence that they yield relatively poor fits with certain data sets. It was suggested that outputs of the exposure model be flagged with qualifiers to warn analysts of such problems when they occur.

- In assessing the format and structure of the Microsoft Access output files, the Panel recognized that such files are logical and simple to implement, but that almost any relational database would do as well and possibly with lower overhead in terms of file size. The Panel considered additional elements that should be included in these output files to ensure that the key variables used by later stage models will all be present. Such elements might include bodyweight and height. In addition, "tagging" of individuals to indicate their "rank" in the overall population was recommended, anticipating that analysts might wish to pay particular attention to specific "high-end" or low-end percentiles. The Panel also gave considerable attention to the potential for incorporating stochastic components into the model output and outlined two specific approaches for doing so. The first was to randomly perturb the values for flow and volume

characteristics calculated from basic biometric data. The second was to randomly perturb the parameters in the underlying biometric equations.

- Panel discussion was particularly robust over the proposal to streamline analysis by retaining only a fraction of the modeled exposure records for subsequent PBPK/PD modeling. The Panel emphatically recommended retention of ALL records, at least as an archive, so that multiple strategies can be followed in choosing which records to pass through to the next stage. This consideration is especially important since the optimal criteria for data selection can only be established after extensive experience with an actual model (not just the concept for a model). To alleviate the pressure for selection, several different strategies were suggested that would streamline the modeling process and ease computational burdens at later stages. These strategies included compression routines for storage of large records, use of flexible time steps (with very large increments during periods of zero or stable exposure risk, such as sleep), and reduction in the number of tissues modeled at the PBPK/PD stage (when warranted by available data on the agents in question).

PANEL DELIBERATIONS AND RESPONSE TO AGENCY CHARGE

The specific issues to be addressed by the Panel are keyed to the Agency's background documents, references and Agency's charge questions.

1 .The LifeLine Group's (LLG) 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 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.

Response

The assessment of cumulative exposure and risk assessment for N-methyl carbamates is a challenging task. Many conceptual and technical issues need to be addressed for the Agency to develop a reliable assessment of cumulative N-methyl carbamate exposure. The white paper *Designing Exposure Models that Support PBPK/PBPD Models of Cumulative Risk* prepared by LLG provides an introduction to many of those issues and proposes conceptual approaches to resolving them.

On the question of clarity, the Panel found areas for improvement in the LLG draft. The graphical depictions and examples are helpful up to a point, but they are too limited. More information, more examples, and more graphics would greatly improve the utility of the report as a foundation for moving forward. In particular, the comparisons to the reference values in Tables 16 and 17 of Price et al. (2003) could be shown better graphically. If possible, it would be helpful to have graphical representations of the relative differences between predictions and sets of observations where available across the domains of relevant independent variables.

The writing of the paper could also be clearer. The document relies excessively on jargon and acronyms that pose difficulties for readers without expertise in exposure modeling. In addition, much of the writing is needlessly complex and convoluted. For example, on page 18-19 the following lines appear. "These models begin by defining the individual's characteristics. These characteristics are those aspects of the individual that influence the probability of occurrence of an exposure opportunity and the magnitude and duration of the exposure resulting from that occurrence." The second sentence might be reworded to read: "These characteristics are those that influence the probability of an exposure, and also its magnitude and duration." Many similar examples could be cited. Overall, the Panel recommended writing more concisely and clearly for an audience of scientifically trained non-specialists.

Addressing the questions of detail, rigor and completeness, the Panel collectively expressed the following views. The LLG document outlines a strategy to assimilate cumulative risk assessment and format data that can be linked to subsequent PBPK/PD models. This paper provides a good overview of the history of exposure/risk modeling in the agency over the past 25 years and it describes an ambitious plan to change how exposure and risk modeling are conducted. The several proposed changes in risk modeling are somewhat independent of each other. Rather than moving in stepwise fashion, there is a push to accomplish four major goals together: 1) to deal effectively with multiple pesticides rather than a single index pesticide; 2) to accommodate short term units of exposure rather than the traditional daily units; 3) to incorporate multiple physiological parameters from PBPK/PD modeling; and (4) to use the PBPK/PD models to calculate internal doses as part of the same schema.

Some of the issues addressed in the white paper are developed sufficiently to provide readers with an understanding of the problem and its proposed solution. For instance, the paper adequately addresses some limitations such as missing or incomplete data sets and computational inadequacies. In addition, the paper has a wealth of detail on the proposed approach to deliver appropriate exposure metrics to the physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) model for the N-methyl carbamate group of pesticides.

In general, however, the Panel noted a lack of depth on the implementation of the proposed approaches. The Panel recognized that these details may appear later, as the proposed model is further developed. Nevertheless, an overall weakness of the paper is a

superficial treatment of certain issues. Specifically, the paper fails to address the particular ways in which the LLG approach differs from other cumulative and aggregate exposure models in terms of data computation or assimilation. The lack of attention to this issue is surprising given that the various models rely upon many of the same input data sets and have the common goal of providing exposure estimates in a format appropriate for PBPK/PD modeling. Also, the white paper does not adequately address two of the most important factors in determining target dose: 1) the occurrence of a chemical in an exposure context, and 2) the pharmacokinetic parameters for absorption, metabolism, distribution and elimination that represent the steps from exposure to dose. Among those factors, the "binary ones" are likely to be of special importance – (e.g., an exposure occurs or it does not); a gene-environment interaction leads to the presence or the absence of an important phenotype (e.g. a detoxifying enzyme). Greatly expanded discussion of such issues would make the report more useful.

Several other topics should be considered for further discussion or development including: (1) the uses and exposure pathways for N-methyl carbamates; (2) the underlying type of model envisioned; (3) the selection of time steps for modeling; (4) sources and rationales for N-methyl carbamate exposure concentrations; and (5) the interface between an exposure model and a PBPK/PD model. The Panel amplifies each of these points and provides additional guidance in the following paragraphs.

Many Panel members felt that, for an adequate simulation of exposure to the N-methyl carbamates, a cumulative exposure model should include two features. First, it should incorporate the processes by which these chemicals are introduced into residences and other exposure settings. Second, it should account for transport of the chemicals within the exposure setting and into and out of the exposure setting. From this standpoint, a detailed knowledge of the characteristics and uses of the products that contain N-methyl carbamates becomes essential for defining the exposure opportunities. Judging solely from the level of detail in this report, the Panel could not determine whether the proposed conceptual approaches for cumulative exposure assessment can meet this standard. It must be said, however, that the Panel also could not reach unanimity as to whether such a goal is feasible at present. Some agreed with the member who argued that it is premature to include fate and transport aspects associated with multiple products while aiming for a model that is simple enough to be practical.

In any case, the conceptual framework for a model designed for cumulative assessments of N-methyl carbamate exposure should fully define the model type. In this context, model type refers to steady state versus dynamic, statistical versus physical, and deterministic versus probabilistic. The white paper is clear that the model is intended to be probabilistic but other important aspects of the model format are not specified. For example, the white paper could be improved by providing information about whether and how a cumulative model for N-methyl carbamates will incorporate the principle of mass balance.

With respect to simulating temporal profiles of exposure, the white paper recommends a 10-minute "time step". This term is typically specific to dynamic mass-

balance models that track the flow of material over time. The white paper is not clear on whether the proposed modeling framework is dynamic. Therefore, "time step" may not be appropriate in this case. Rather, the time-dependent aspect of the proposed model appears to comprise a series of static representations of exposure. The interrelationship of exposure concentrations across consecutive 10-minute time increments is not described. The Panel believed that the modeling framework for cumulative exposure to n-methyl carbamates should specify the relationship of exposure concentrations over time.

Further description of the inhalation exposure pathway is especially desirable. The time-dependency suggested by use of a 10-minute time increment has particular relevance to concentrations of chemical in air compared to concentrations on surfaces and food over time. The white paper should specify whether the model simulates volatilization, condensation, deposition inter-room transport, and indoor-outdoor transport of N-methyl carbamates.

The proposed 10-minute time increment is apparently based on the biological half-life of typical N-methyl carbamates in humans. More than one Panel member pointed out that the relatively short biological and inhibition half-lives of the carbamates require correspondingly short time steps. Thirty minutes might be the absolute upper limit. The Panel even had reservations as to whether 10 minutes would be short enough for certain non-dietary exposure events – e.g., incidental ingestion of chemical residues transferred from surfaces that would occur over time intervals of seconds rather than minutes. Recognizing the difficulties of using shorter time-steps, based on the levels of precision in existing databases and on the computational demands, the Panel finds that the appropriateness of a 10-minute time step has not been fully demonstrated.

Although none of the current data sets on food consumption and activity patterns provide the needed temporal resolution, the Agency has recently funded three STAR grants (Science to Achieve Results) to collect longitudinal data on human activity and dietary consumption. The Panel encourages dialogue among researchers, model developers and the Agency to ensure that the data collected from these projects can be used optimally for robust and accurate exposure models.

The Panel suggested that the Agency explore alternative methods for obtaining high temporal resolution in the cumulative exposure assessment. For instance, the Panel suggested that the Agency identify the smallest or largest time increment (i.e. appropriate time step) that is needed for a given exposure situation rather than to rely exclusively on a fixed time increment. The Panel noted that methods for implementing variable time increments are available.

In general, it would be desirable for the white paper to include additional detail of non-dietary exposure pathways to be considered by the model with respect to the anticipated or current uses of N-methyl carbamates. It is especially important to consider the physical and chemical parameters that influence transport and fate. The white paper could be improved by the addition of details about how the model would simulate chemical movement among the relevant exposure media, chemical degradation and other

issues related to transport and fate. In addition, it would be desirable for the report to expand its discussion of the potential that environmental concentrations of carbamates may be correlated among application media and over time.

Additional information about the treatment of dermal absorption of multiple chemicals with similar structures and actions would also be useful. For instance, how will simultaneous dermal exposure to multiple N-methyl carbamates influence absorption? The white paper is not clear on how dermal absorption will be modeled. It should explain whether this absorption will be treated as a fraction of exposure, with a hybrid statistical/physical model based upon permeability coefficient approaches, or whether PBPK/PD approaches will be used for modeling.

Experience with other simulation models shows that absorption and distribution related factors at the end of a chain of complicated exposure calculations are often quite important in determining dose. Consider, for example, the enzymes important to N-methyl carbamate metabolism. The activity of such enzymes may vary between persons, or within a person over time, although one member pointed out that metabolism is so rapid that such differences may not be toxicologically significant. Other key variables are absorption, distribution, and elimination. These are mentioned as issues, but much more detail is needed for a full evaluation of the proposed modeling concepts and approaches. On the other hand, the white paper does address changes in overall blood flow (i.e., cardiac output) and changes in respiration as they relate to exposure. A major advance would be to address changes of perfusion at the organ level. Clearly there is a potential for interactions between exposure and alterations in organ perfusion/volume, which will impact the PBPK/PD model. What we lack is information on the relationship between normal and co-morbidity changes. The report offers little detail on these important issues.

Genetics is, of course, a source of variability in expression of phenotypes that influence the biological fate of N-methyl carbamates in exposed humans. It is at least as important a factor as socioeconomic status, for example. In this age of bioinformatics, the Agency should begin to address the problem of integrating genetics with pharmacokinetics and pharmacodynamics for risk assessment. The scientific community is rapidly developing the expertise and technology to determine toxicologically relevant genotypes on an individual basis. The Panel would like more discussion of the potential for an interface between the demographic and physiological data sets presented in the white paper and the informatics associated with genotype and phenotype.

One section of the white paper seems to imply that genetic variability can be captured to some extent from the physiological parameters and anthropometric factors in the proposed model structure. The Panel points out that reliance upon anthropometric factors to capture genetic and phenotypic attributes is completely unrealistic. These comments should be omitted from the report or modified to state that genetic determinants of dose will eventually be captured in the PBPK/PD portion of the model.

The white paper also implies that health effects of N-methyl carbamates are

simply additive, but we know that non-additive types of interactions are possible – because of synergism, antagonism, and competition, for example. The PBPK/PD model should address the potential for such interactions among the carbamates in more detail. To the authors' credit, the white paper dealt with the importance of kinetic, metabolic, and capacity parameters that vary across individuals as a function of age, gender, and genetics or ethnicity. However, the LLG report is probably too optimistic about the amount of data on such variation that is currently available to parameterize the models. Another limitation of the paper is an inadequate treatment of disease states. Disease states that influence tissue distribution (e.g., non-obese fatty liver) can strongly affect the dose absorbed from a given amount of exposure. Such effects deserve notice and raise questions on related considerations: (1) should they be dealt with by refinement of existing PBPK/PD models; (2) should they be dealt with in the Lifeline exposure model; or (3) should they be dealt within a specialized interface?

A major issue identified by the authors of the white paper is how to go seamlessly from the cumulative exposure assessment to the PBPK/PD models ("It is critical that the output of the exposure model defines exposure and/or dose in terms… consistent with the definitions used by the PBPK/PD model, and that there…be no gap nor can such elements be represented in both models yielding duplicative calculations for the element" p. 38). The Panel expects that the process will become evident when the modeling effort begins. Nevertheless, the white paper should address how the interface between exposure and dose models will be evaluated.

As one last reason for added detail in the white paper, the Panel believed it important to be sure that the proposed framework for the LLG model will correctly integrate exposures across time and route of exposure. One Panel member suggested consideration of the following exposure scenario. A spot urine sample was collected from a child who, 40 minutes ago, ate 8 cherries containing carbaryl residues and then played for 30 minutes on a carbaryl-treated lawn. The urine sample was analyzed for 1-naphthol. Where will this 1-naphthol data enter into the LLG framework? According to Figure 6 on page 49 in the LLG report, such data will go directly to the PBPK/PD model. Is that appropriate? It might be better to develop a computational component to convert different types of exposure data, like 1-naphthol in urine, into the common metric generated by the LL exposure model (i.e., mg/kg/day). Necessary computation could occur within the exposure model or in a specialized Interface. The conversion would require additional work on model development and compound-specific pharmacokinetics, but the reward of better quality data should justify the effort.

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. 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.

(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.

Response

The 2003 article by Price et al. considered many published studies that measure human organ sizes and related physiologic processes (e.g. blood flow and respiration rates), for the purpose of developing correlative equations that accurately predict these parameters based upon anthropomorphic data when used alone or in combination with additional indirect measures of body composition including bio-impedance, and other parameters. While the published data drawn upon for the P3M model were not numerous or, in some cases, particularly robust, Price et al. did review the studies of appropriate quality and relevance that were available at the time. However, several new papers have been published that could affect their model, including studies of obese individuals. Modifications to allow inclusion of newer data sets would be valuable refinements of the model. The authors themselves refer to ongoing efforts to keep their system "evergreen" by testing, updating, and expanding coverage to different organs and population subgroups. This enterprise is worthy of encouragement and support.

An area of concern that is not fully addressed in the Price et al. article is that of observations residing at the outer boundaries of observed variations in model parameters. While the equations are likely to perform well for most members of the population, most of the time, they are likely to return inaccurate estimates for rarer population subgroups, which may have been poorly represented in the populations studied to date. The elderly are a subpopulation of special concern. Although the modeling addresses age where appropriate, it is not clear that there is adequate representation of the growing group of elderly in the studies used to establish correlations that define organ size or function. This may not pose a significant problem for the prediction of exposure and ultimately the risk of most members of the general population. However it could be a concern if poorly represented sub-populations coincide with those who may be at particular risk for some types of exposures or effects (i.e. pregnant women, obese individuals, the very old, etc).

(B) Are there additional data or data sources for these relationships that would be

useful to include or consider?

Response

Comparisons between existing model predictions and newer published observations can provide a useful starting point for building stochastic capabilities to model uncertainty and variability within the existing framework. The existing model equations attempt to capture that portion of the variability that is "explained" by relationships with anthropometric parameters, but the equations do not fully represent other sources of variation reflected in the difference between each model's R^2 value and 1. Other new data should be gathered as published and used to update the system, particularly at the limits of existing parameters and for people with unusual determinants of exposure by reason of obesity, age, disease state, etc.

One Panel member suggested an effort to update the models based on literature documenting recent studies that may have derived more mechanistic models relating descriptive variables like body weight to organ size or tissue blood flow. Though these relationships are not themselves individual data, they may provide additional information for comparison.

Price et al. have been forward-looking and candid in identifying areas where they felt that significant gaps existed in the model system they developed. Many of the acknowledged gaps were for correlations developed for children, particularly very young children, where available data were limited in number or quality, or absent for some limited ranges altogether. These remain challenges that limit the confidence that can be placed in the model predictions for some population groups. Other areas where gaps were acknowledged were absence of data for organs of small size but of key importance. These gaps are not problematic for many expected uses of the model predictions. However, in instances where a primary target organ of toxicity is one of the organs where data are sparse or nonexistent, there are grounds for concern.

A group of small but well-perfused and important organs for which adequate models have not yet been found are the reproductive organs, the breasts, and urogenital organs other than the kidney. The endocrine organs constitute a second poorly modeled group of extreme importance. These include the adrenals, thymus, parathyroid, pineal, and pituitary gland. The Islets of Langerhans are of special interest. Surrounded by the exocrine pancreas, the Islets secrete insulin and glucagon among other hormones. Islet blood supply has a somewhat different anatomy than that in neighboring tissue, and it is regulated in a different way. Information needed for modeling this tissue and most of the listed organs may be found in the open literature on endocrine physiology and pathology.

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

Response

The model developers for the P3M/Lifeline system have a sound general approach and reasonable plans for enhancing the system to meet the future needs of PBPK/PD modelers. The model framework is deliberately designed to be highly flexible in its outputs, time steps of exposure, routes, chemicals, age groups and other demographic characteristics, organs covered in PBPK/PD modeling, exposure periods and other parameters.

It is of some concern that the current equations are strictly deterministic, and, for the most part, linear. As mentioned in response to the (B) part of this question, this means that the variability captured by the modeling will not represent the full variation of the underlying data. Hence, extreme cases that drive upper percentiles of exposure or risk may be outside the range of linearity. Therefore the Panel encourages continuing efforts to test and refine the models for different organ sizes, organ blood flow rates, alveolar ventilation and cardiac output against newly emerging data sets, including the new NHANES data. Such comparisons with external data could guide the addition of stochastic elements to the model to represent variability of estimated parameters about the mean values predicted from NHANES individual records. These comparisons will also highlight and help quantify uncertainties in the model projections.

A caveat for the analytical process being considered is that many of the blood flows and organ sizes covered by the P3M system are not key determinants of the doses and risks calculated by PBPK/PD models. Most often, the sensitive determinants of expected internal doses are the data used to calibrate rates of clearance and/or metabolic activation, and their variability. These parameters need to be evaluated in the context of each separate carbamate pesticide using observed data for distribution and presence of that chemical in sampled body locations and particular times after deliberately administered or otherwise measured or estimated exposures.

Another source of concern to the Panel was a considerable difference in the indicated quality of the fits among the prediction equations for different parameters. Although many of the regression lines showed strong correlation coefficients, others seemed to fit the data poorly. One Panel member therefore recommended that the model output be accompanied by “qualifier information” indicating the quality of the estimates of organ sizes and tissue blood flows used for prediction. Examples of qualifier information could include the following: (1) the regression line used to generate the parameter poorly fit the existing data, (2) the descriptive variable (body weight, age) is beyond the limits of the data used to generate the regression line, (3) the model developers were unable to review the raw data used to generate the regression line, and (4) the model was unable to estimate the organ size or blood flow due to insufficient information on X.

The addition of such qualifiers would force the model developers and users to explicitly assume more responsibility for the information used to generate the PBPK/PD parameter estimates. It would also increase the responsibility of the model users to correctly apply the parameter estimates. For example, if the PBPK/PD model of a particular pesticide is very sensitive to a certain organ size or tissue blood flow, the

model user should be alerted to the need to determine the potential impact of uncertainties in that parameter on predicted population distributions of internal exposure or effects.

In assessing the quality of the algorithms and the fit of the regression models, Panel members experienced difficulty due to the absence of correlation plots and a general lack of individual raw data. The Panel believed that, in cases where raw data are available, the developers should consider deriving new multi-parameter regressions across multiple data sets using body weight, age, and so forth as the explanatory co-variables. The addition of other data may lead to improved linear models, or provide an impetus for using nonlinear regression modeling to achieve better fits.

The current system of equations commendably provides for activity-related changes in breathing rates and blood flows in the light of changes in activity during the day. If the model developers are ambitious enough they might attempt to capture a similar effect in the proposed Lifeline system. This would be the effect of meals on tissue/blood partition coefficients for highly fat/soluble chemicals. Consumption of meals containing fatty foods increases the fat content of the blood and therefore systematically increases tissue/blood partition coefficients for lipophilic compounds. Observations dating from the dawn of PBPK/PD modeling (Munson et al. 1978) suggest that such effects can be appreciable (increases up to 20% or more), although their consistency and duration may not have been fully evaluated as yet.

One specific comment was offered on inhalation rates. The computation in this case follows the Layton equation--calculating the breathing rate based on the ratio of total energy expenditure to basal metabolic rate (BMR). It is noted that the value for the ratio of food energy intake to BMR ratio, "A", is taken from default parameters given in the USEPA exposure factor handbook, which is compacted for children 0.5 to 3 years old. The alternative of using a more age-specific value is recommended. Consideration should also be given to provide breathing rates that may be more appropriate for short-term exposures and would take into account the different human activity levels, specific to age for very young infants.

3. Traditional non-cancer probabilistic risk assessment methods perform a direct conversion of exposure (expressed, for example, in µg/kg day) into risk (expressed, for example, as a unit less 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.

General Response

In order to use the output of an exposure model as input to a PBPK/PD model, data from the USDA's CSFII must be placed into the exposure component in a way that separates each individual's eating occasions. On the other hand, data from NHAPS and other databases will need to be entered in a way that distinguishes and separates each event occurring during a given time step. Furthermore, an appropriate link or interface between the two models is needed. The LLG white paper proposes that Lifeline be modified so an analyst can customize its output 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 to be used in creating the exposure history and will also define the overall duration of the exposure history for 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 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.

Response

The table formats are logical, simple to implement and clear. One might argue that Table 3a could be organized differently, but as long as the data are in a relational database of the type proposed, this is just a question of how the database is presented to the reader and does not reflect a limitation on the actual structure of the database. It does not seem strictly necessary to implement the database in Access™, however. The data are relatively straightforward. Table 2 contains essentially header or static information for the time series or stochastic data of Table 3a. One could just as easily implement this in SAS™ or Oracle™ data systems. It is acknowledged that the LifeLine™ developers have worked in personal computer Window™ environments and that programming staffs have extensive experience with Access™. In addition, it is a simple task to move the database from one system to the other. Thus if the PBPB/PD model were developed with software that requires an Oracle™, SAS™ or other database structure, the conversion should easily be accomplished from the Access™ structure.

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

Response

Tables 2 and Table 3a of the white paper should be considered the minimal data requirements for the output file structure. Table 3b data might be appended to Table 3a if the LifeLine™ model does the actual calculation of these physiological components. If Table 3b is not constructed in the LifeLine™ model, then Table 2 must be appended to include bodyweight and height since these two characteristics, along with gender, are the key variables that will be used by subsequent models to derive most of the flow rates and

volumes of Table 3b. In addition, it should be useful in the final presentation or data analysis of the results to examine some integration of the multiple values potentially output from the PBPK/PD model against bodyweight, as well as sex and age.

The LLG document suggests that the LifeLine™ model in its initial form will generate a distribution of individuals from which subsets can be selected for detailed analysis through the PBPK/PD model. Intelligent selection would be facilitated if the output data for each individual were tagged in some way to indicate the population percentile that he or she represents. One can envision situations where an analyst might wish to examine a plot of particular PBPK/PD (integrated) outputs against the associated percentile. For example, the analyst might choose replicate individuals at the 90^{th}, 95^{th} and 99^{th} percentiles of the exposure distribution, process them through the PBPK/PD model, collect the model outputs, and carry out statistical tests to see if inter-individual variability swamps the average level of responses. One might also wish to block percentile replicates by bodyweight class to help separate effects of bodyweight from effects based on the percentile class of exposure. This would help the assessor determine whether protection at the 99^{th} percentile of exposure is different from protection at the 90^{th} percentile when effects are modeled from a physiological perspective.

A question arises about the best way to derive flow and volume characteristics for the population of individuals to be modeled. It seems reasonable to begin with a simpler approach in which the model assigns to every individual of similar gender, bodyweight and height the same physiological flow and volume characteristics, using the equations and parameters as defined in Price et al. (2003).

For example: $BV_i = (35.5BH_i + 2.27BW_i - 3383)/0.6178$ for all individuals of same height (BH_i) and bodyweight (BW_i).

In the view of the Panel, however, stochastic components should eventually be incorporated into the derivation of individual flow and volume characteristics. There are two possible ways of accomplishing this goal within the general structure envisioned for LifeLine™:

1) Perturb the mean: Assign to individuals of similar gender, bodyweight and height different physiological flow and volume characteristics by adding a random perturbation to the values calculated using the equations and parameters of Price et. al (2003) (variability evaluation).

For example: $BV_i = \{(35.5BH_i + 2.27BW_i - 3383)/0.6178\} + z_i$, where z_i is a normally distributed random deviate with mean 0 and standard deviation s.

2) Perturb the parameters: Assign to individuals of similar gender, bodyweight and height different physiological flow and volume characteristics by perturbing the parameters used in the equations (uncertainty evaluation).

For example: $BV_i = [(35.5 \pm z_{1i})BH_i + (2.27 \pm z_{2i})BW_i - (3383 \pm z_{3i})]/(0.6178 \pm z_{4i})$

In situation 1 above, one might include in Table 2 the value of z_i that was used for each physiological component equation for that individual. In situation 2, one might include in Table 2 the values of z_1, z_2, z_3, and z_4 used for that individual for each component for that individual. That is, if a stochastic component is used in generating the physiological characteristics, analysts may want the system to keep track of the perturbations for each individual. In this way, if a really aberrant result appears, the analyst can begin to track down its cause.

(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) a user-defined percentile (e.g., 90th 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.

Response

Establishing explicit criteria for data selection can be a positive development to provide choices for data retention, e.g., every Nth value, values exceeding a certain number, or the upper (or presumably lower) percentile. However, the optimal choice among records to analyze or retain can only be made after the proposed model has become available and subjected to extensive evaluation. It is difficult to reliably predict who will be in a given upper percentile of risk before applying the PBPK analysis. If only high-end values are passed through to the PBPK/PD models, there could be concerns for pathway saturation. Results based only on high-end exposures could also be misleading. Thus, a more complete exploration of the response surface for this model with regard to input is warranted.

When tagging a specific segment of the exposure record for PBPK/PD modeling,

it is important that the entire record is retained and is readily available to be retrieved for additional iterative analysis. Without the entire exposure record, the final result of such analysis would be left without context. The lack of context could cause problems when fractions of data are used two or three steps down the road for cumulative risk assessment.

The need to select only a fraction of the exposure record for PBPK/PD modeling can be practically important, given current operational limitations. However, computational memory and time requirements should not be a determining factor. The value of the full simulation data far outweighs the speed gains associated with the proposed data limitation, e.g., to retain only very high values. While manipulation of large Access™ databases may be slow, other mechanisms could be used. Computers continue to get faster and both memory and storage cheaper. With the advancement of technology and tools, this may not be a concern in the near future.

Recognizing the potential for generating huge files while modeling exposures, the Panel considered how to streamline the process without losing data. The candidate model, with its short time steps and high volume output, is designed to accommodate the pharmacokinetics of N-methyl carbamates. The short sampling time frame essential for modeling carbamate exposure will generate many data points over each 24-hour period, but many of these data points will not contain detectable pesticide. It is important to maintain the integrity of the exposure distribution at this point. However, if single data point input is the format for the PBPK/PD model, it might be prudent to devise a means that avoids multiple inputs of zero-exposure data. The Panel also offered the following three suggestions to alleviate data handling and storage issues.

First, compression routines should be considered for the storage of sizable records (e.g., in the billions). An adaptive procedure that accelerates computational analysis should be investigated and, if appropriate, implemented for periods when exposure parameters do not change, e.g., during sleep. Further, repetitive data storage techniques similar to those used in such software packages as PKZIP could be used to compress files and relieve some storage problems.

Second, the use of an Access™ database system as an interface may be a deficit in the process, although it offers certain advantages (e.g., a consistent interface). Access™ comes with a great deal of overhead that is not needed to implement a connection between an exposure model output and an input for a PBPK/PD model. It may be feasible, and even preferable, to use a simpler interface, like a simple output file for this step.

Third, the Panel questioned whether the full PBPK/PD model, incorporating all 23 organs/tissues, must be run for those pesticides that appear to have only a few sites of action. For example, if a chemical exerts toxicological effects primarily in well-perfused tissues and over a short period of time, the PBPK/PD model might exclude fatty tissues. Unburdening this model and relating it more directly to the pharmacokinetics of specific pesticide(s) might avoid the need to trim exposure data for the sole purpose of facilitating

PBPK/PD computations. This line of reasoning further raises the question of how a PBPK/PD model could accommodate such flexibility. Perhaps the task of selecting relevant toxicological or pharmacokinetic organs/tissues for PBPK/PD simulation could be done in a specialized interface. For example, one could offer the option to assign partition coefficients of zero for organs/tissues (fatty tissue, skeletal muscle, bone tissue etc) into which a given chemical does not distribute to a significant degree. One Panel member believed that computational processes should be completed in an interface before data are fed to the PBPK/PD model, to avoid further burdening the subsequent, computationally intensive steps. This individual also believed that the interface should be independent from the exposure model so that a cumulative risk assessment could also use outputs from other exposure models.

(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?

Response

The criteria for selecting exposure records for PBPK/PD modeling depend inherently on the purpose and focus for the assessment. Thus, no criteria should be hard-wired into the exposure model or its interface to the PBPK/PD model. Instead options should be offered to users who need to streamline the PBPK/PD modeling or have particular questions that need answering. These options could include the selection of specific portions of the exposure distribution or of randomly drawing from the entire distribution. Useful selections might include: mean/median; random selection; ordered selection (e.g., sorted and take every 100^{th} observation - Latin Hypercube); selection above a certain percentile; mid 50%; below a certain percentile; above a certain value; user specified weighting (e.g., weighting upper end).

A primary selection criterion should be the quality of the data. Large cohorts or GLP certification do not guarantee a better quality study. PBPK/PD modeling across all age groups is not necessarily appropriate if there are especially susceptible populations (e.g., children, elderly). Records could be selected to ask specific questions with regard to modeling such populations.

LITERATURE CITED

Munson ES, Eger EI, Tham MK, Embro WJ. 1978. Increase in anesthetic uptake, excretion, and blood solubility in man after eating. Anesth Analg. 57(2): 224-231.