

**Summary Report of the  
Panel Peer Review of the Draft NCEA Document "Approaches for the  
Application of Physiologically Based Pharmacokinetic Models and Supporting  
Data in Risk Assessment"**

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## **NOTICE**

This report was prepared by Versar, Inc., an EPA contractor (Contract No. 68-C-02-061, Task Order No. 89), as a summary of the discussion of the Panel Peer Review of the Draft NCEA Document "Approaches for the Application of Physiologically Based Pharmacokinetic Models and Supporting Data in Risk Assessment" (November 10-11, 2005). This report captures the main points and highlights of the meeting. It is not a complete record of all detailed discussion, nor does it embellish, interpret, or enlarge upon matters that were incomplete or unclear.

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## EXECUTIVE SUMMARY

The Panel Peer Review of "Approaches for the Application of Physiologically Based Pharmacokinetic Models and Supporting Data in Risk Assessment" was held on November 10-11, 2005, in Arlington, Virginia. This one and a half-day meeting was organized and hosted by Versar, Inc., for the U.S. Environmental Protection Agency's (EPA) National Center for Environmental Assessment (NCEA). A panel of five experts was convened by Versar, having broad experience and demonstrated expertise in scientific areas related to physiologically based pharmacokinetic (PBPK) modeling, toxicology, and risk assessment. The reviewers provided comments and suggestions for improvements to the document in the form of general recommendations, responses to eight charge questions, and numerous specific changes to the document's text, tables, and figures. The panel felt that these revisions will improve the clarity, accuracy, and applicability of the document to the target audience.

The reviewers found this document to be well written and noted that it should be useful for risk assessors who need to learn more about PBPK modeling and for modelers who need to understand applications for risk assessment. It makes many cogent points, describing both general principles and special considerations needed to successfully develop, evaluate, and apply PBPK models. In fact, this document appears to represent the first systematic description of PBPK modeling in risk assessment.

It does not provide much detail in any area, which makes the document easy to read cover to cover, and for the reader to get an overview of the subject matter. It does however, presuppose that the readers already have a good grasp of basic pharmacokinetic concepts. As a result, the clarity of this report to EPA scientists and risk assessors without a thorough background in these pharmacokinetic concepts may be limited. To remedy this, the document needs to expand the glossary to include definitions of many terms and principles and certain core pharmacokinetic principles such as saturation kinetics and diffusion vs. flow-limited processes, need explanation in the text.

While the document presents useful overviews of the use of PBPK modeling to address certain risk assessment issues, reviewers suggested that it could be expanded to address a broader range of PBPK modeling applications, such as: across age group extrapolations, in utero modeling, variability due to genetic polymorphisms, lactational models, interpretation of biomonitoring data, and modeling of acute exposure/risk.

Another panel suggestion is to expand introductory text to put PBPK modeling into an overall context of pharmacokinetic analysis in which classical one and two compartment models have been used for many years to provide descriptions of chemical disposition, and which have been applied to risk assessment (e.g., methyl mercury, dioxin, cadmium). The document should provide introductory material in this area and then make a transition to the current uses of PBPK modeling.

The reviewers also commented on the document's emphasis on modeling from the perspective of a certain class of chemicals, volatile organic compounds, without sufficient reference to the modeling that has been done for many other types of chemicals: persistent lipophilic compounds,

pesticides, metals, other inorganics, etc. The document needs to describe ways in which the modeling approaches for these chemicals may differ from one another. In addition, the document is not fully descriptive of chemical mixtures in terms of the types of mixtures analyses that have been conducted using PBPK models.

The appendices as now constructed are not highly useful for this audience and should not be disseminated as part of this document. The panel recommends that Appendices 1 and 3 be removed, and Appendix 2 may be retained. A new Appendix 1 is recommended in which a case study is developed which describes model development beginning with where the PK data come (both in vivo and in vitro), how they are used in the model, decisions about model structure, fitting procedures, model evaluation, interpretation and uses of model output to inform a risk assessment. The panel suggested that the recent isopropanol PBPK modeling effort (Clark, et al., 2004) be considered for the case study.

It was also noted that the document would benefit from an overview flow chart presented in the introduction that lays out the PBPK modeling process from PK data acquisition, through use of information from toxicity assessment to develop model structure and selection of dose metrics, and then into model parameterization, evaluation, interpretation, etc. In addition, the term dose metric is introduced and described adequately in various locations, however, there are numerous points where the term is left out of a discussion in which that is precisely what is being described. The panel recommends that the authors more consistently use the term dose metric after it is initially defined.

In addition to these general comments, the panel made many suggestions for specific revisions in the document's text, tables, and figures. The summary report and appendices provide additional detail on the panel's suggested revisions to the document.

## **1.0 INTRODUCTION**

### **1.1 Meeting Purpose**

The Panel Peer Review of the Draft U.S. Environmental Protection Agency (EPA), National Center for Environmental Assessment (NCEA) Document "Approaches for the Application of Physiologically Based Pharmacokinetic Models and Supporting Data in Risk Assessment" was held on November 10-11, 2005, at the Hyatt Arlington in Arlington, Virginia. This one and a half-day meeting was organized and hosted by Versar, Inc. for EPA/NCEA

Physiologically based pharmacokinetic (PBPK) data and models have important applications in risk assessment. The purpose of the meeting was to provide a peer review by a group of expert scientists on the document, which describes approaches for using PBPK data and models in human health risk assessment, to ensure the creation of a scientifically correct, high quality document.

Experts in PBPK modeling, toxicology, and risk assessment were invited to participate, and included individuals from academia, consulting, and State government. The meeting was a peer review and the participants were challenged to provide technical feedback, make recommendations, and provide input to the document in the form of suggested text amendments, deletions, and additions. EPA developed charge questions to help guide and focus the discussion. The reviewers made recommendations throughout the meeting and also responded to each charge question.

### **1.2 Meeting Participants**

A panel of five experts was convened by Versar to review and provide input on the document. Versar selected experts having broad experience and demonstrated expertise in the scientific areas related to PBPK modeling, toxicology, pharmacokinetics, and risk assessment. The reviewers certified that they had no conflicts of interest relative to this document prior to being selected by Versar for the peer review panel. The list of reviewers is presented in Appendix A.

### **1.3 Agenda**

The agenda for the peer review meeting is presented in Appendix B. The meeting began with a welcome, introductions, and outline of the goals of the meeting. Background on the document and general guidance for the discussion was provided by EPA to the reviewers and observers. The first day consisted of the panel review of the document, observer comments, and discussion of public comments. The participants discussed sections of the document and suggested revisions and additions of text, figures, and references to improve the technical content and clarity of the document. The second day was a closed meeting in which the reviewers participated in a writing session to document their comments from the first day.

## **1.4 Organization of Summary Report**

This report presents information on the presentations and discussions from the meeting.

- Section 2 of this report summarizes the opening presentations and discussion on the purpose and procedures for the conduct of the peer review workshop as well as for observer comments. Section 3 contains summaries of the reviewers' general comments and responses to charge questions.
- The appendices to this report are as follows:

Appendix A - List of Participants and Observers

Appendix B - Agenda

Appendix C - Charge Questions

Appendix D - PowerPoint Presentations

Appendix E - Written Comments from Participants

Appendix F - Observer Comments

Appendix G - Additional References and Suggestions

## **2.0 SUMMARY OF PRESENTATIONS AND DISCUSSION ON THE DOCUMENT**

This section presents summaries of the opening presentations by Versar and EPA, as well as the observer comments. Slides supporting the presentations can be found in Appendix D and observer comments are presented in Appendix F.

### **2.1 Goals of Workshop and Introductions**

Mr. David Bottimore, of Versar Inc., gave the welcoming remarks, outlining the objectives and process for the meeting. He noted that the goal was to collect input, comments, and suggestions for technical feedback on the document. He reviewed the materials that the participants should have received, which included premeeting comments from the experts, the charge questions, and agenda for the meeting. He then initiated short introductions by each of the reviewers.

Dr. Bob Sonawane, of NCEA, gave additional welcoming remarks and a brief introduction to the document. He noted that NCEA currently has three major functions including: the health risk assessment of chemicals; developing methods, models, tools and techniques for risk assessment; and supporting the EPA program offices, regulatory offices, and regions in health risk assessment of chemicals. He explained that the document has been through EPA internal review and is currently in the process of external peer review at the meeting. He requested that the reviewers provide comments and feedback on the document and hopes to have the document cleared and distributed to the public in the next six months.

Dr. Chad Thompson, of NCEA, provided general background on the document. He explained that the purpose of the document was to describe approaches for using PBPK models in risk assessment and to describe the kinds of questions that PBPK models can address. The scope of

the document included a rationale for using PBPK models in risk assessments, data needed and available resources, evaluation of PBPK models for use in risk assessment, and examples of applications of PBPK models in EPA risk assessments. He described the primary audience to be risk assessors, PBPK model developers, and the public. He outlined the organization of the document and recognized contributors to the document. Dr. Thompson also mentioned issues beyond the present scope including questioning when it is necessary to develop a PBPK model, if there is always a benefit to using a PBPK model, and cost-benefit analysis.

The Chair, Dr. Gary Ginsberg, of the Connecticut Department of Public Health, introduced himself, gave a brief overview of the meeting, and reviewed the eight charge questions (Appendix C). He noted that the group would discuss general comments, answer the charge questions for the document, and briefly discuss public comments. He added that the panel would be documenting the suggestions and recommendations in writing.

## **2.2 Observer Comments**

Two observers, Eric Hack and Russ Keenan, provided oral comments on the document at the meeting.

Eric Hack, of Toxicology Excellence for Risk Assessment (TERA), provided comments on the document. His written comments can be found in Appendix F. He stated that he was sponsored by the Department of Defense to prepare oral comments for the meeting and that the comments provided are those of TERA. He felt that the document was useful to modelers and will have merit in increasing the understanding for the need for quantitative risk assessment. The significant issues that Mr. Hack noted are found below:

There were a number of issues that were addressed briefly in Chapter 2, but presented much more thoroughly in Chapters 3 and 4. It would be useful to note in Chapter 2 that these issues are being introduced, but would be addressed in more detail later. It would also be useful to include one integrated discussion of some topics, such as the use of PBPK models for interspecies and intraspecies extrapolation or variability and uncertainty analysis. While the document does mention the term chemical-specific adjustment factors (CSAFs) in Section 2.6.3, it would be useful to discuss this term, and to cite the IPCS (2005) guidance.

In the model evaluation section, the discussion of assessing model fit is oversimplified. Visual fitting and a criterion that the predictions should be within 2 standard deviations of the mean is described, but other goodness of fit metrics also exist. The description of the 2 standard deviations rule should be offered as perhaps one measure of goodness of fit, but it is too simplistic to be relied upon to evaluate all PBPK models under all circumstances. The sections on uncertainty and variability analysis need more detail. More description would be helpful of the methods (Monte Carlo and Markov Chain Monte Carlo (MCMC)) and especially the issues associated with the interpretation of the results of these analyses and their use in risk assessment.

More discussion of the use of surrogates for target doses should be included. Using surrogates, such as blood concentrations rather than target tissue concentrations, the use of parent chemical concentrations or flux through a metabolic pathway instead of toxic metabolite concentrations, is

sometimes necessary when the knowledge of the mode of action is more detailed than the kinetic knowledge, or when the toxic moiety cannot be measured directly. Discussion of fetal or neonatal modeling should also be included in the document. This is an important contribution of PBPK modeling to the assessment of developmental toxicity.

There is a list of possible dose metrics is given in Box 2-1. This choice is critical for dose metric estimation, and more discussion of when each choice is appropriate would be helpful. Although it is mentioned later in the document, the description of the uses of PBPK models in chapter 2 should include mode of action hypothesis formulation and testing.

Russ Keenan, of AMEC Earth & Environmental, Inc., also provided oral comments on the document. He noted that his comments were posted on EPA's Docket during the public comment period. He commended EPA for the excellent job they did in producing the document. Mr. Keenan stated that his only issue dealt with application, as he looked at the document as a risk assessor who applies and uses PBPK models. He noted that the flexibility EPA provides by not prescribing when a model should be used or what type of model provides the scientific community with flexibility in the application of PBPK methods. However, he did not want to see the document inappropriately used in that risk managers blocked the acceptance of PBPK modeling. He concluded by asking the panel and EPA to address this issue in the document.

### **3.0 PEER REVIEW COMMENTS ON THE DOCUMENT**

Dr. Ginsberg requested general comments from the reviewers on the document. The reviewers prepared premeeting comments (Appendix E), which were the starting points for discussion at the meeting. The following general comments and specific responses to charge questions were developed by the panel.

#### **3.1 General Comments**

This a well written document and should be useful for risk assessors who need to learn more about PBPK modeling and for modelers who need to understand applications for risk assessment. It makes many cogent points, describing both general principles and special considerations needed to successfully develop, evaluate, and apply PBPK models. This appropriately is not a cookbook but provides general principles on how to do PBPK modeling as it applies to risk assessment. To some extent, the document has the potential to standardize modeling practice, not in terms of which parameters to use, but in terms of basic approaches and applications. One of its strong points is the clear listing of model evaluation criteria. In fact, this appears to represent the first systematic effort for this type of document.

It does not provide much detail in any area, which makes the document easy to read cover to cover, and get an overview of the subject matter. It does, however, presuppose that the readers already have a good grasp of such pharmacokinetic concepts as "first-pass effect"; zero-order, first-order, and second-order metabolic processes and metabolic saturation. The clarity of this report to EPA scientists and risk assessors without a thorough background in these pharmacokinetic concepts may be limited. To remedy this, the document needs to expand the glossary to include definitions of zero order, first order metabolic processes, etc. Additionally

the text should describe core pharmacokinetic principles that are mentioned briefly in the current version of the document, but are not well defined: saturable processes including Michaelis-Menten equation and parameters, saturable binding and transport, flow and diffusion limited processes, first pass effects, window of susceptibility, and any other governing kinetic principles.

The document focuses upon the use of PBPK modeling to address certain extrapolation issues in the setting of reference values and slope factors: cross-species, dose route, high dose to low dose, temporal adjustments, and degree of variability. However, it doesn't provide anything of substance on several other uses of PBPK modeling: across age group extrapolations, in utero modeling, variability due to genetic polymorphisms, lactational models, interpretation of biomonitoring, and modeling of acute exposure, such as in Acute Exposure Guideline Levels (AEGLs) development. A recommendation of the panel is for the document to include a section which describes these areas of special application for modeling in risk assessment. Regarding modeling of acute exposure/risk, this should have its own section in parallel to applications for RfC, RfDs, slope factors, etc.

Another area which the document does not cover is putting PBPK modeling into an overall context of pharmacokinetic analysis in which classical one and two compartment models have been used for many years to provide descriptions of chemical disposition, and which have been applied to risk assessment (e.g., methyl mercury, dioxin, cadmium). The document should provide introductory material in this area and then make a transition to the current uses of PBPK modeling.

The document describes modeling from the perspective of a certain class of chemicals, volatile organics, without sufficient reference to the modeling that has been done for many other types of chemicals: persistent lipophilic compounds, pesticides, metals, other inorganics, etc. The document needs to describe ways in which the modeling approach for these chemicals may differ from one another.

The document describes ways in which PBPK modeling relies upon information coming from toxicity assessment in several places but this information should be organized into paragraphs which risk assessors can see how toxicity assessment feeds into PBPK analysis. This would include identification of target organ, key dose metric, dose-response relationship, windows of susceptibility and other exposure timing issues.

The term dose metric is introduced and described adequately in various locations, however, there are numerous points where the term is left out of a discussion in which that is precisely what is being described. For example, Figure 4.2 is primarily about developing dose metrics but the term is not mentioned in the figure. The panel recommends that the bottom row of boxes in that figure be labeled with the descriptor dose metric and the term should also appear in the figure title. The authors should go back through the document and look for other places where the term dose metric would help to clarify what is being discussed.

The appendices as now constructed are not highly useful for this audience and should not be disseminated as part of this document. The panel recommends that Appendices 1 and 3 be removed, and Appendix 2 may be retained. A new Appendix 1 is recommended in which a case

study is developed which describes model development from where the PK data come (both in vivo and in vitro); how they are used in the model; decisions about model structure; fitting procedures; model evaluation; and interpretation and use of model output to influence a risk assessment. The computer source code should also be included. The panel suggests that the recent isopropanol PBPK modeling effort be considered in this regard (Clark, et al., 2004).

## **3.2 Response to Charge Questions**

### **3.2.1 Charge Question 1**

*What is the panel's overall view of the thoroughness, clarity, and applicability of this report?*

The panel's general comments capture our thoughts on overall document thoroughness, clarity, and applicability. The document is strong in these areas, but the points raised in the overall comments will help improve certain aspects of the document.

The document would benefit from a flow chart that lays out the PBPK modeling process from PK data acquisition, through use of information from toxicity assessment to develop a model structure and selection of dose metrics, and then into model parameterization, evaluation, interpretation, etc. A figure that could serve as a starting point for the development of an updated figure that includes the current terminology, such as dose metric, is found in Appendix G (PBPK Modeling Process Flowchart).

The document does not adequately describe the limitations inherent in PBPK modeling. Modeling is a very data intensive process which is often limited by incomplete or contradictory data. There are also limitations in trying to quantitatively describe complex physiological systems and how chemicals behave within such systems. A section describing model limitations should be included.

In addition, the document is not fully descriptive of chemical mixtures in terms of the types of mixtures analyses that have been conducted, the governing PK principles, the basic types of interactions (additivity, synergism, antagonism), and the various modeling approaches.

### **3.2.2 Charge Question 2**

*Are the graphical examples explaining various concepts clear and helpful? If not, do you have suggestions for improving clarity?*

In general, the graphical examples are appropriate and useful. However, several changes to improve clarity and accuracy are recommended. In addition, we recommend a new figure for the introductory section which outlines in flow chart fashion the role of PBPK modeling in risk assessment starting from PK data acquisition (in vivo, in vitro), use of toxicology information (MOA, development of model structure, selection of dose metric, critical target organs, windows of vulnerability), use of exposure information (selection of dose route), use of chemical-specific information (e.g., partition coefficients), calibrating and testing the model (use of external PK datasets) and finally application to risk assessment (RfD, RfC, cancer, acute applications). This

may be a lot for one figure but the basic elements should be presented with supporting text. A figure that could serve as a starting point is found in Appendix G (PBPK Modeling Process Flowchart).

Recommended changes:

**Figure 2-1** – y axis should read rate of metabolism; remove the word “amount” in “B”. Same comment for x axis in “C”. The text and figure legend associated with this figure needs expansion which describes the process of taking apart the external dose-response relationship and analyzing it in separate metabolism-response and then internal dose-response phases. The text should highlight the fact that in this case example the chemical is metabolically activated and that nonlinear metabolism underlies the non-linear external dose-response relationship seen in “A.”

**Figure 2-2** - The panel recommends changing this to have 3, not 2 sub-plots. The top plot can stay as is, the 2<sup>nd</sup> plot would be a human plot showing a 6 hour exposure to the same dose as in the rats but with a lower AUC to highlight the cross-species differences. The third plot can stay as is as it highlights the extrapolation in going to continuous exposure. The area that is counted as the AUC should be shaded in for clarity. A key point is that all the plots in this figure should show AUC counted to essentially “0” blood concentration. Thus, the human plot should be extended after exposure stops (beyond 24 hrs) to indicate total AUC. The equivalent AUCs should be calculated on this basis (total AUC), not when exposure stops.

**Figure 3-1** – The figure shows important modeling differences when going from one type of chemical and toxic endpoint to another. However, the text and figure legend don’t point out these key modeling differences and leads the reader to wonder what is going on (e.g., why the extra intra-organ compartments in the TCDD model, why the testes in the ETO model, etc. Also, the vinyl acetate model (D) is compressed too much and so is difficult to read. Finally, the references in the legend need to be tied to the figures.

**Figure 3-2** – The figure needs a legend, which can be adapted from the bottom of page 3-17. Panel B – this does not represent a good example of incorrect model structure as it shows a bolus exposure input to the model wherein the experimental data appears to come from an inhalation study. This is just a mistake in putting in the exposure parameters and has nothing to do with model structure. The panel recommends that it may be appropriate to consider a curve which overshoots the first two data points and then comes down too steeply to match the last 2 data points to demonstrate model structure issues.

Use of a log scale time can hide important fitting issues. This figure can handle a linear scale. The document should encourage modelers to use a linear scale when presenting fits to the data and should exemplify this in its own figures.

**Figure 3-3** – This figure also needs a legend. The sensitivity ratios are too large as one could not get a breathing rate ratio of 2. We suggest that the y axis go from –1 to +1 and all differences fit well within this scale. It may be best to select a sensitivity analysis from the literature to

exemplify this procedure and remove the identifiers (chemical name, modeling paper) to make it a generic but realistic example. Should additional parameters such as Km be shown?

**Figure 3-4** – The text supporting this figure (pg 3-24) should state that “often as many as 10,000 iterations are used to develop the simulations.”

**Figure 4-1** – This figure is a good idea but is overly simplistic. The following are the panel’s suggestions. Additionally, Appendix G to this report contains a modified Fig 4-1 for EPA’s consideration (Proposed Figure 4-1 Modification).

- Top diamond – take humans out – there are applications in which staying within the animal system is sufficient reason to do the modeling (e.g., dose route extrapolation).
- Add a box from no data to model development called “Data collection to determine parameter values”.
- The 2<sup>nd</sup> diamond needs to say “are the data needed to develop parameters for.....” It’s not a matter of whether the parameters are available but whether the data are available to develop these parameters.
- Add a line from model development to 3<sup>rd</sup> diamond showing the need to evaluate models once developed.
- From final box (lower right) – need line back up to model development.

**Figure 4-2** – The table has too many boxes, some of which are not used in modeling. The 3<sup>rd</sup> line of information (Conc., Amt, Rate of Production) along with the “Quantity in Tissue” boxes can be removed. The figure is essentially about developing appropriate dose metrics but the term is not used in the figure. It should be in the title (“Measures of tissue exposure in developing dose metrics useful for risk assessment”) and the bottom row of boxes can be labeled on the side “Potential Dose Metrics.” The bottom right 2 boxes should be in units of mg/hr/vol tiss. Finally, it is suggested that a box be added under the upper right AUC box (unknown MOA) that says “Evaluate correlations to toxic response.”

**Figure 4-3** – One might expect more upward curvative in upper plot for the degree of metabolic saturation shown in lower plot. While there may be good reasons for the lack of curvative, this could take a lot of explanation. It’s probably better to show more curvative, as would be seen for styrene instead of toluene.

Page 4-12 – The second paragraph refers to Figure 2-2 as if it demonstrates a good fit to human toluene data. However, there are no data shown in this figure so it can’t be used to demonstrate goodness of fit.

**Figure 4-4** - Shade everything under the line to show portion counted as AUC. Text should highlight the fact that the peak is very different across dose routes for the same AUC – this could affect threshold phenomena.

**Figure 4-5** - Bottom is rat, not human. Simulation should be carried out after exposure ceases until chemical gone. Shade the AUC areas. The top (rat) plot should show a 4 hr not 6 hr exposure period.

**Figure 4-6** - It would be better to show the interindividual variability bracket along the x-axis than above the distribution. It's also important for the figure legend and text to acknowledge that the upper percentile cutpoint can be 95<sup>th</sup>, 99<sup>th</sup>, or some other value with citation to IPCS.

**Figure 4-7** - y axis should read GST metabolite production.

### 3.2.3 Charge Question 3

*Does this document reasonably describe the major potential uses and advantages of PBPK modeling in risk assessment, are there risk assessment applications of PBPK modeling that have not been addressed?*

Overall, the answer is yes. See answer to #1 for comments on what applications have not been fully covered. In addition, the International Programme for Chemical Safety (IPCS) document describing the use of modeling approaches by risk assessors to adjust default UFs and create chemical-specific adjustment factors (CSAFs), should be described and referenced. This is a key reference and terminology which can readily be added to sections that already describe use of PBPK models to adjust UFs.

### 3.2.4 Charge Question 4

*Are there improvements to the document that would substantially help risk assessors who are less familiar with PBPK modeling better understand the potential strengths and limitations of PBPK modeling?*

The panel has a number of specific comments that would help the document to be more useful for risk assessors.

- The first paragraph in Section 3.3 is incorrect and will confuse risk assessors trying to understand principles of PBPK models: a mass-balance differential equation consists of a series of rate terms (not clearance terms), and the units are mass per time (not volume per time). These rate terms are often calculated as the product of a clearance (in units of volume per time) and a concentration (in units of mass per volume). Also, the uptake of a chemical in systemic circulation by a tissue is proportional to its activity gradient, where the tissue:blood relationship of activities is related to the concentration difference by the partition coefficient. It just confuses things to mention Fick's law of diffusion since the transport is generally blood-flow limited, not diffusion limited.

- Section 3.5 should include a description of the process of internal verification of the model code. The suggestion in the document that the risk assessor is not responsible for ensuring that the computer implementation of the model is free from error is inappropriate. In fact this contradicts the summary (Section 3.9) which actually includes considerations relevant to internal verification (in the second to last bullet) that are not mentioned at all in this section. The document should not suggest that a risk assessor has to become well versed in model code but that he/she find someone who is to verify the acceptability of a given model.

Risk assessors need to understand the necessity of evaluating the model specifically for the dose metric that will be used in the risk assessment. For example, if the validation of the human model is based solely on parent chemical kinetic data, it may not be valid at all for a metabolism dose metric. Section 3.6 should include a discussion of this issue. The panel provides additional material on this issue (Validation of Dose Metric Prediction) in Appendix G for EPA's consideration.

- Section 4.3 should include (perhaps between sub-sections 4.3.5 and 4.3.6), a much more detailed explanation of the alternative approaches for calculating a dose metric for a repeated exposure, as discussed in Clewell et al. (2002):

- Calculation of total dose metric over entire study divided by length of study
- Single dose estimate (total AUC for single dose adjusted for exposure frequency)
- Steady-state estimate (subtraction of consecutive periods after steady state or periodicity is achieved)

The panel provides a description of dose metric calculations in Appendix G (Calculation of Dose Metrics) of this report for consideration to include in the document.

The suggestion from a public commenter that model confidence be qualitatively described as "high", "medium" or "low" seems useful and should be considered for inclusion in this document. The criteria for such categories would need to be developed.

As mentioned above, a section on interpretation of model output could be helpful for non-modeling risk assessors in reviewing the results of a modeling exercise. Areas of interpretation can be confidence in the model (extent to which it is calibrated and tested against external datasets, goodness of fit, number of parameters needing back-fit), more on sensitivity analysis (what is level of confidence and key uncertainties in the most sensitive parameters; what are reasonable bounds for these parameters; how much might they influence the assessment), more on non-linearities and how they affect results, etc.

The RfC (1994) methodology comes up in several locations. One clear presentation of the role of PBPK modeling within the RfC approach would be useful, especially in terms of simplifications taken that are not normally used in full PBPK modeling assessments. Additionally, it would be good to explain some of the differences between reactive gas and non-reactive gas models (local vs. systemic effect).

Section 2.8 – This section brings up an important and evolving use of PBPK modeling – conversion of biomonitoring data to exposure doses and application to risk assessment. This merits considerably more attention in this document. There are several case studies (dioxin, mercury, PFOA, phthalates) where this approach is used.

The differences between flow-limited and diffusion-limited uptake kinetics as introduced on the bottom of Page 3-3 should be spelled out more fully.

Page 3-17, 2nd full paragraph – near the end – “PBPK modeling is not a fitting exercise” – this is debatable since some parameters are typically fitted to an initial dataset. We agree that PBPK modeling is not a stochastic modeling exercise in which all parameters are fit to the data based solely on statistical criteria. However, its important to admit that there are usually some parameters that are derived by backfit. Once this is admitted, the document should then describe how fitting is done and what some of the issues are in this procedure. For example, when fitting multiple parameters one is not certain that the model fit obtained is because both parameters are accurately described or both may be off by compensating degrees (you get the right answer for the wrong reason). Some additional thoughts on model evaluation that should be considered for inclusion in this section are found in Appendix G (Model Evaluation).

An additional reason why this could happen is that the parameter is not adequately identifiable from the data because of co-linearity. The panel provides in Appendix G a description of this issue (Parameter “Fitting”).

Same paragraph on page 3-17 – The rule mentioned about goodness of fit involving 2 standard deviations (SD) is too proscriptive and limiting. The panel prefers that this be mentioned along with other options, e.g., that many risk assessors use a 2-fold differential on average as a general rule of thumb. It was pointed out in a public comment that a form of this latter rule of thumb has been formalized in consent agreements between the agency and the regulated community. However, the document should not proscribe a particular evaluation criterion. It is appropriate to state that the models should strive to achieve the best fit to all underlying calibration datasets.

Issue of model calibration vs. validation (e.g., Page 3-19) - its confusing to say that a model which has been cross-checked against external datasets isn’t really “validated” but is only “calibrated.” In fact, there is a definition of model validation that is applicable to PBPK models. Model validation involves substantiating that the model, within its domain of applicability, behaves with satisfactory predictive accuracy. The document should not derive a new way of describing this process using terms such as calibration and predictive capability.

Related to this, the document omits a key term, model verification. Elements of this process are presented in Sections 3.6. The panel recommends that this material be organized into a separate Model Verification section where it is made clear that the risk assessor (with the help of his associates in modeling) independently verify the model. Some additional aspects of model verification not included in the text are provided by the panel in Appendix G (Model Verification). The panel also provides in Appendix G (Model Documentation) a description of model documentation which is needed to accompany model verification.

More on model calibration - Page 3-21 – top section – should discuss the not unusual case where underlying PK datasets disagree with one another and it’s not possible to adequately simulate all the data. The document should describe the role of professional judgment in evaluating the underlying datasets to determine which are most appropriate for modeling purposes.

Page 3-21 – The point of using Bayesian methods for model calibration can lead to improper estimates of parameters leading to inaccurate predictions. Since this is not primarily a fitting technique, the discussion of the Bayesian approach should be moved to sections dealing with

model uncertainty (3.7.2, 3.7.3). In addition, issues with using this technique are identified by the panel and included in Appendix G (Model Calibration) for EPA's consideration.

Description of PBPK for Mixtures - Page 4-21 – this section would be helped by citing examples where mixtures were analyzed with PBPK models and how this was accomplished (cite work by Ray Yang), and by expanding the description of the HI approach. This appears to be a simple addition approach to HIs for multiple contaminants in a mixture in which the PBPK model is used to adjust the ingredient concentration as influenced by the other chemicals. The description should include how chemicals may interact (at metabolic enzymes or binding sites) and how this can be simulated in a model. Further, the description at the top of Page 4-22 is confusing due to the word "POD." It should be replaced with "environmental exposure concentration." Under mixtures, the equation on Page 4-22 should be updated with the relevant section from the final cancer guidelines which replaces the concept of  $q^*$ .

### **3.2.5 Charge Question 5**

*Do you think that PBPK modelers outside the EPA, and those less familiar with risk assessment practices, would find this document useful as far as fostering the kinds of research and model development useful for risk assessment?*

Yes, the panel believes that the document is valuable for those who would like to develop a PBPK model for a chemical that would be of value to the agency for a risk assessment. Some of the points raised in the previous question can assist modelers as well as risk assessors in using this document. In addition, the following point is worth noting.

Section 2.5.5 (p. 2-11) incorrectly states that "The IVF of 10 conventionally used in RfC derivation implies that for the same level of response or nonresponse, the potential doses among individuals may differ by as much as – but not more than – an order of magnitude." This is a common misunderstanding. In fact, the IVF of 10 is associated with the potential ratio of the equitoxic doses for an average individual as compared to a sensitive individual. Therefore, an IVF of 10 is consistent of a range of equitoxic doses across the population of about two orders of magnitude.

### **3.2.6 Charge Question 6**

*Are there current research needs and data gaps not highlighted in this report that would improve the utilization of PBPK models in risk assessment?*

This is not a document that talks much about research needs and so the panel does not have comments that pertain specifically to the document in this area. In fact, the panel does not believe this is the type of document that should describe research needs as it is a basic principles/users guide. If research needs are included, the panel identified the following: scaling from in vitro metabolism parameter estimates to in vivo. Use of recombinant systems in particular can give results that are of uncertain correspondence to intact systems. Further research in this area as well as scaling up from other in vitro systems (microsomes, hepatocytes) can be mentioned.

The panel recommends that EPA consider updates to this document as technologies emerge (innovative computational biology and its application to risk assessment). Key among the areas with rapid growth occurring are acute dosimetry, point-of-contact dosimetry, whole-life and developmental modeling, maternal-fetal dosimetry, and metabolic network modeling to identify sensitive subpopulations. There are substantial research needs in these areas.

### 3.2.7 Charge Question 7

*Are there future reports that you could envision which would compliment or expand upon the topics covered in the current document? For example, would a report focused on dosimetry models for reactive gases be helpful? Or a report focused on extrapolation across life stages using PBPK modeling?*

Yes. The panel believes that this document is useful in describing the general case of PBPK use in risk assessment. However, there are a number of special cases which may merit treatment in one, two, or three separate documents: 1) PBPK modeling for sensitive subpopulations (pharmacogenetics, life stage-specific models), 2) contact site modeling which can include special considerations of acute dosing, and 3) the PBPK-PD linkage.

### 3.2.8 Charge Question 8

*Do you have additional comments/suggestions that were not covered in the above questions?*

Not really. We do note that the 6<sup>th</sup> bullet on Section 3-9 is confusing and should be deleted.

EPA should review the detailed comments listed on a line-by-line basis in Appendix E to improve accuracy and clarity of the report.

**Appendix** - Table 3-1: I would remove the subscripts for current and previous simulation time. These subscripts are only accurate for explicit integration algorithms such as the Euler method. They are not correct for the case of implicit algorithms such as the Gear (backward differentiation) method.

**Appendix** - Similarly, specifying the “integration interval” is only relevant to constant step-size algorithms. For variable step-size algorithms, the appropriate element is the “error criteria”. There are a number of places in the document where this oversight should be corrected.

### 3.2.9 Responses/Reactions to Public Comments

The panel stated their reactions to the public comments that were submitted to EPA during the public comment period (July 28, 2005 to October 14, 2005) and posted to EPA’s e-docket (<http://www.epa.gov/edocket/>). The Sapphire Group’s comments were generally on target and helpful, with the panel noting that it may be useful to construct a model confidence scheme as proposed in their comments. The panel also felt that the extrapolation issues mentioned by The Sapphire Group were important and should be addressed. Similar to The Sapphire Group, the

panel had comments on the Bayesian analysis which they stated in their response to Charge Question 4. The panel also agreed with The Sapphire Group's recommendations to expand the Executive Summary and Section 2.8 to incorporate how to best use epidemiology data.

The panel also discussed that the methanol rat data/case example from the American Forest and Paper Association shows the potential utility of applying a human model to interpret rat toxicity data in concert with human biomonitoring data. The panel suggests that EPA review the publication describing this research and consider amending the document where methanol was mentioned.