

Disposition of Comments from Peer-Review of “Approaches for the Application of PBPK Models and Supporting Data in Risk Assessment

Background

The External 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) under a peer-review contract (68-C-02-061). A panel of five independently selected experts was convened in a public meeting organized by Versar, Inc. These panel members have demonstrable expertise and experience in scientific areas related to physiologically based pharmacokinetic (PBPK) modeling, toxicology, and risk assessment. The panel of experts provided comments and suggestions for improvements to the document in the form of general recommendations and numerous specific changes to the document's text, tables, and figures. In addition to comments from the expert panel, EPA also received public comments during an initial 30-day public comment period (70 FR 43692) and a subsequent 45-day extension of the public comment period (70 FR 48950).

The document "Approaches for the Application of Physiologically Based Pharmacokinetic Models and Supporting Data in Risk Assessment" is intended to be a learning tool for risk assessors less familiar with PBPK modeling. In addition, it describes approaches that those more familiar with PBPK modeling can employ when evaluating PBPK models for use in risk assessment. The theme of the document is the dose metric, and the tendency for complex dose-response relationships to become easier to understand when the applied dose is converted to an internal target tissue dose. Importantly, this simplification of the dose-response relationship aids in the various forms of extrapolations that are often required to perform a risk assessment. The document provides neither guidance nor guidelines, but rather presents generic approaches for the application of PBPK modeling and supporting data in risk assessment.

The charge to the expert panel was to carry out an independent external peer review of the draft document. This included providing review and comment on the document, as well as addressing the particular charge questions (see Final Report). In addition, it was requested that the expert panel also consider and provide remarks on the public comments.

Peer-Review Comments

General Comments

Comment 1:

The reviewers found the 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, the document appears to represent the first systematic description of PBPK modeling in risk assessment.

Response 1:

EPA thanks the Peer-Review Panel for the compliments offered regarding the quality and utility of the draft document. Importantly, the Peer-Review Panel noted that this document may be the first systematic description of PBPK model evaluation and use in risk assessment. EPA believes that the changes made to the draft version in response to comments of the Peer-Review Panel have improved the overall quality and thoroughness of the document. Of particular note, Chapter 2 has additional text regarding PBPK and other dosimetry models. Moreover, the chapter has been condensed, with important text incorporated into Chapter 4. Overall, this reduces some redundancy that was in the original draft. Also in Chapter 4, the discussion on dose metric selection has been greatly expanded. Finally, Chapter 3 has undergone several changes and provides improved text and figures regarding the evaluation (validation/calibration in particular) of PBPK models for use in risk assessment.

Comment 2:

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, modeling of acute exposure/risk, and mixtures.

Response 2:

EPA also recognizes, as does the Peer-Review Panel, that the document “could be expanded” to address a broader range of modeling applications. EPA notes, however, that the draft version contains sections addressing many of these issues. However, to further expand the final draft document, EPA has made additional changes to the document. To address age group extrapolation, section 4.3.2 “Estimating Intraspecies Variability” has been expanded, and explicitly describes how age-specific changes in physiology and biochemistry can be incorporated into existing models for adults. The section also makes reference to studies that have developed novel model structures in order to model *in utero* and lactational exposures. EPA also notes that a recently finalized EPA report “Use of Physiologically Based Pharmacokinetic Models to Quantify the Impact of Human Age and Interindividual Differences in Physiology and Biochemistry Pertinent to Risk” covers this application of PBPK models in greater detail, and this reference has been included in the final draft. In regards to intraspecies variability, EPA notes that section 4.3.2 (formerly 4.3.5) “Intraspecies Extrapolation” explicitly discusses Monte Carlo simulation for intraspecies variability. In the previous draft, however, the term “genetic polymorphisms” was not used explicitly and has now been included in this section, as well as in section 4.4.12 “Uncertainty Factors: Role of PBPK Models”. In regards to the use of PBPK models for biomonitoring, section 2.4.3 “Use of Pharmacokinetic Data and Models in Exposure Assessment” has been restructured and reference made to additional literature. In addition, new text in section 4.3 “Review of Extrapolations Possible with PBPK Models” points out that extrapolations performed with PBPK models can originate from critical studies in animals or from human epidemiology studies (e.g. biomonitoring) studies. Finally, discussion in section 4.6 “Mixtures Risk Assessment” was not expanded given the current state of development of PBPK models for mixtures.

Comment 3: The document emphasizes 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.

Response 3: The document explains in the Executive Summary, section 1.1. “Scope of the Document”, and again in section 2.1 “Pharmacokinetics and Dosimetry Modeling” that many of the PBPK modeling efforts have focused on chemicals (e.g. volatile organic compounds) that distribute systemically and cause systemic effects. Each section goes on to describe that the principles are also applicable to other compounds (e.g., reactive gases) that cause effects at the portal of entry. However, section 2.1. “Pharmacokinetics and Dosimetry Modeling” has been edited to more clearly describe the historical context of model development and applicability of models for systemic distribution to gases of various reactivities that often cause respiratory tract toxicity. Finally, EPA notes that the text and the appendix contain over 900 relevant citations comprising a comprehensive list of literature regarding PBPK modeling of various classes of chemicals.

Comment 4:

It does not provide much detail in any one 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.

Response 4:

EPA agrees that certain terms (e.g. zero-order metabolic processes) were not clearly defined in the draft document. For clarity, additional terms have been added to the glossary. In addition, text was added, where appropriate, to the report. For example, there is expanded description of one- and two-compartment models in Section 2.1 “Pharmacokinetics and Dosimetry Modeling” and again in 3.2. “Model Structure”. Section 3.3 “Mathematical Presentation” describes flow-and diffusion-limited uptake, as well as zero-order, first-order, second order kinetic processes.

Comment 5:

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.

Response 5:

EPA agrees that additional discussion regarding the difference between classical compartmental models and PBPK models would improve the document. To this end, additional text has been added in section 2.1 “Pharmacokinetics and Dosimetry Modeling”.

Comment 6:

The document describes ways in which PBPK modeling relies upon information coming from toxicity assessment in several places, but this information should be organized such that 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.

Response 6:

The Peer-Review Panel provided some text in relation to the above comment. EPA agrees and has incorporated much of suggested text within an expanded section 4.2 “Evaluation of Dose Metrics for PBPK Model-based Assessments”.

Comment 7:

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.

Response 7:

EPA agrees that “modeling is a very data intensive process which is often limited by incomplete or contradictory data”, and EPA believes that the original draft extensively describes the data needs and potential limitations of PBPK modeling *throughout* the document. Much of the document is devoted to describing the types of data needed to construct and evaluate PBPK models. Such needs may also be described as limitations, as the absence of data hinders the construction of a scientifically-based risk assessment. Thus, EPA argues that ‘incomplete’ data is an inherent limitation or drawback to PBPK modeling. An alternative approach for describing these limitations, and advocated by the expert panel, would be to describe these limitations in a *stand-alone* section. EPA believes the latter approach is less informative to the general reader because a single section would describe the various limitation out of context with the advantages of PBPK modeling.

EPA agrees that there is often ‘contradictory’ data with which to build and evaluate a PBPK model. Thus, the final draft has been expanded to describe and propose some options for handling such situations; and relevant text has been added at the beginning of section 3.6 “Evaluation of Predictive Capacity”.

As for the comment that the document does not adequately describe “limitations in trying to quantitatively describe complex physiological systems”, as stated above, EPA believes that there is sufficient discussion throughout the document indicating the various types of data, and associated limitations, required to generate a PBPK model. For instance, it is pointed out in more than one place in the document that PBPK models are not presently capable of extrapolating from short term to longer term duration because physiological processes change across life stages and adaptive (often pharmacodynamic) responses change the ‘physiological system’ being modeled. For similar reasons, PBPK models can not extrapolate from LOAEL to NOAEL values due to a present lack of data and understanding of pharmacodynamic processes. There is also discussion of the various methods (experimental, fitting, algorithms) for obtaining partition coefficients and the strengths and weaknesses of each (section 3.4.2 Partition Coefficients). It may also be argued that if there are ‘limitations’ in describing physiological systems when using PBPK models, then default approaches often based on a single physiological or biochemical

component (e.g., partition coefficients) are likely to suffer the same limitations and perhaps more because (when sufficient data is available) default approaches utilize *less* information. Thus the limitations of PBPK models should be viewed in the context of available alternative approaches; and this is how the document is structured.

Finally, expanded text in section 3.7 regarding the variance and uncertainty in a model makes clear that PBPK modeling approaches have inherent limitations. Thus, EPA believes that it will be evident to most readers that construction and evaluation of PBPK models for use in risk assessment requires a relatively large amount of data (pharmacokinetic, physiological, toxicological, exposure, etc), knowledge (e.g., pharmacokinetics) and skills (e.g., computer programming) which are inherent limitations of modeling.

Comment 8:

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.

Response 8:

Additional text has been added describing CSAFs and some inherent differences in methodology between IPCS and EPA. See section 4.4.12.

Comment 9:

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).

Response 9:

EPA agrees that appendices 1 and 3 were perhaps of interest only to a minority of readers, thus the revised final draft contains only one appendix, which includes a list of PBPK publications – updated through the end of 2005. The suggestion to include an isopropanol example was considered, but it was determined that there was nothing of significant value that could be added that was not already described in the Clark et al. 2004 article. Finally, the inclusion of source code would only be interpretable by a PBPK modeler, and thus would be of little benefit to most members of the intended audience.

Specific Comments

Numerous general comments were made on improving figures and tables; and many were adopted in the final draft. Similarly, many of the specific line item edits have been included in the final draft (see attached Final PBPK Peer-review Meeting Report and Appendices). Below are the specific issues identified by the Peer-Review Panel.

Specific Comment 1:

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.

Specific Response 1:

The first paragraph to section 3.3 has been revised to address the concerns of the expert panel.

Specific Comment 2:

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.

Specific Response 2:

EPA thanks the Peer-Review Panel for pointing out this oversight. Changes have been made to section 3.5 that clearly indicate that modelers who apply a PBPK model, particularly for risk assessment, must verify that the model is free of flaws and appropriate for the specific needs of an assessment.

Specific Comment 3:

The following comments are in regards to section 3.6 "Model Evaluation", now re-titled "Evaluation of Predictive Capacity".

Comment 3.1

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.

Response 3.1

Modified text from Appendix G has been included in section 3.6.2 "Model Validation/Calibration".

Comment 3.2

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”).

Response 3.2

The issue of parameter estimation by fitting has been made clearer in the document by adding the term in the first paragraphs of sections 3.4.1 “Partition Coefficients” and 3.4.3 “Biochemical Parameters”. The issue is also discussed in section 3.7.1 “Sensitivity Analysis”. Modified text from Appendix G was included at the beginning of section 3.7 “Sensitivity, Variability, and Uncertainty Analyses”. Modified text from Appendix G was also included in section 3.6.2 “Model Validation/Calibration” where there is now some discussion about estimating parameters by fitting using Bayesian analysis.

Comment 3.3

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.

Response 3.3

EPA agrees, and the prescriptive language has been removed.

Comment 3.4

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.

Response 3.4

The original section 3.6 “Model Evaluation” has been reorganized to include subsections on “Model Verification” (i.e. evaluation of plausibility and computer code), “Model Validation/Calibration” (i.e. testing the behavior and predictive capacity), and “Model Documentation” (i.e. transparency). Note that EPA has chosen to title the section with Validation/Calibration to highlight the fact there is some disagreement between modelers about the most appropriate terminology.

Comment 3.5

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.

Response 3.5

New text has been added to the beginning of section 3.6 “Evaluation of Predictive Capacity”.

Comment 3.6

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.

Response 3.6

New text regarding Bayesian analysis, MC, and MCMC has been added to the end of section 3.6.2 “Model Validation/Calibration”, as well as in sections 3.7.1 “Sensitivity Analysis”, 3.7.2 “Variability Analysis”, and 3.7.3 “Uncertainty Analysis”.

Specific Comment 4:

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). 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.

Specific Response 4:

Modified text from Appendix G has been included in an expanded section 4.2 “Evaluation of Dose Metrics for PBPK Model-based Assessments”.

Public Comments

Comment 1:

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.

Response 1:

EPA agrees with this public comment. The draft document contained somewhat specific and technical information regarding dose-response value determination in chapters 2 and 4. The text was slightly repetitive, yet different enough that it was decided to provide a more abbreviated introduction to the use of PBPK models in risk assessment in chapter 2, and move much of the more detailed text to chapter 4. Specifically, the discussions in sections 2.5 through 2.8 have been incorporated into appropriate locations within sections 4.3 through 4.5.

Comment 2:

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.

Response 2:

EPA agrees with these comments. Additional discussion regarding model fit has been added to section 3.6.2 “Model Validation/Calibration”. In addition, section 3.7. “Sensitivity, Variability, and Uncertainty Analyses” has been expanded, and includes more detail on Monte Carlo simulation and Markov Chain Monte Carlo (MCMC).

Comment 3:

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. 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.

Response 3:

EPA agrees that more discussion of the dose metric could be included in the document. To this end, expanded discussion has been included in section 4.2 “Evaluation of Dose Metrics for PBPK Model-Based Risk Assessment”. This new section includes discussion of when a particular dose metric is most appropriate based on MOA information. As for hypothesis testing, this is now explicitly stated at the end of section 2.2. “Dose-Response and Measures of Delivered Dose”, is discussed in sections 3.1 “Model Purpose”, 4.2. “Evaluation of Dose Metrics for PBPK Model-Based Risk Assessment”, and 4.7 “Linkage to Pharmacodynamic Models”. Moreover, the use of PBPK models in dose metric selection is highlighted in the dichloromethane example in section 4.5.5 “Example of PBPK Model in Cancer Risk Assessment”.

Comment 4:

There were two comments specifically related to risk communication and risk management. There was a suggestion that EPA create a “confidence statement” (e.g., low, med, high) for communicating to risk managers the confidence one has in a model. There was also a comment that the document perhaps provided too much flexibility for risk managers to not use PBPK models because the document avoided prescribing when a model should be used in risk assessment.

Response 4:

In principle, EPA agrees with these comments; however, the scope of the document is not intended to address risk communication, but rather serve as a learning tool for risk assessors. There is ongoing research into developing quantitative evaluations (e.g., uncertainty analysis) of PBPK models. Such methods may improve the ability to communicate the confidence one has in a model but, at this time, EPA is not recommending other scaled means of communicating confidence for individual PBPK models. In regards to the non-prescriptive tone in the report, the focus of the current document is the potential applications of PBPK models in risk assessment, thus no prescriptive guidance is included.

Comment 5:

It was suggested that extrapolations afforded by PBPK models be presented in a hierarchical fashion or, at the very least, inter- and intra-species extrapolations be placed above others.

Response 5:

In response to this comment, inter- and intra-species extrapolations has generally been presented above others in the text; though the remaining forms of extrapolation (i.e. route, duration, and low-dose) are not obviously distinguishable by importance. Exception to this hierarchical presentation occurs in section 4.4, where the extrapolation order is changed to more closely parallel the RfC derivation process.

Comment 6:

It was suggested that EPA review the text concerning methanol and a publication describing the potential utility of applying a human model to interpret rat methanol toxicity.

Response 6:

EPA agrees that there may be instances where interspecies extrapolation can be done using PBPK models without an animal model. The methanol example is valid because critical toxicity studies also included pharmacokinetic data regarding a potential dose metric. Subsequently a human PBPK model was used to predict the inhaled dose that results in the same internal dose metric as in the animal study. This text has been added at the end of section 4.3.1.

Comment 7:

It is suggested that the authors evaluate the framework proposed in the new Cancer Guideline (U.S. EPA 2005), for applicability to noncarcinogen MOAs.

Response 7:

EPA agrees that this important framework on MOA should be brought to the attention of the reader, as well as its general applicability to noncancer outcomes. Thus additional text has been included in section 4.2 “Evaluation of Dose Metrics for PBPK Model-based Assessments”.

Comment 8:

It is suggested that a list of programs within regulatory agencies that would benefit from PBPK modeling should be included in this document.

Response 8:

EPA believes that the document, as written, highlights the potential benefits from using PBPK models for risk assessment for risk assessors within and outside the Agency, and it will be available to all programs and regions, as well as public, on the EPA website; therefore, listing of programs within regulatory agencies was deemed unnecessary.