EPA/600/R-08/090
August 2008

Uncertainty and Variability in Physiologically Based Pharmacokinetic Models: Key Issues and Case Studies

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC 20460

Uncertainty and Variability in Physiologically Based Pharmacokinetic Models: Key Issues and Case Studies

Introduction

U.S. EPA increasingly utilizes physiologically based pharmacokinetic (PBPK) models in the development of its risk assessments. As reviewed in U.S. EPA's *Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment* (U.S. EPA, 2006), these models are designed to determine the relationship between external exposure and biologically-relevant (usually internal) dose, and their predictions can be used for extrapolating across routes, levels, or patterns of exposure, and for quantitatively characterizing differences in susceptibility across species, populations, and life-stages. However, characterizing uncertainty and variability in PBPK models and their predictions has been an ongoing challenge, and this report summarizes some of the recent progress in this area that has been conducted or funded by the National Center for Environmental Assessment (NCEA). Specifically, the elements of this work are:

- Identification of (i) the key issues in characterizing uncertainty and variability in PBPK modeling; (ii) the state of the science on addressing those issues; and (iii) the key areas in need of improvement though research or enhanced implementation. These issues were discussed as a part of the International Workshop on Uncertainty and Variability in PBPK Models,[1] held on October 31 - November 2, 2006. The outcome of this workshop has been summarized by Barton et al. (2007).
- Case examples of chemical-specific applications that demonstrate the methods and issues associated with characterizing uncertainty and variability in PBPK modeling. Specifically, the following case examples were completed: (i) uncertainty and variability in the human pharmacokinetics of tetrachloroethylene (Chiu and Bois, 2006; Chiu, 2006); (ii) uncertainty in the route-to-route extrapolation of vinyl chloride pharmacokinetics (Chiu, 2006); (iii) the development of a method to characterize inter-individual variability when only pooled data (mean and standard deviation) are available, using data on 1,3-butadiene (Chiu and Bois, 2007); and (iv) evaluation of uncertainty in human dose metrics for methyl tertiary-butyl ether (MTBE) exposures (Blancato et al., 2007).

Each of the topics is discussed in greater detail below.

[1] Co-sponsored by NCEA, NCCT, NHEERL, and NIEHS, with additional support from CIIT Centers for Health Research (now The Hamner Institutes for Health Sciences), L'Institut National de l'environnement industriel et des risques (INERIS), Miami University, Summit Toxicology, and the U.K. Health and Safety Executive, Health and Safety Laboratory (HSL).

Key Issues

The key issues in characterizing uncertainty and variability in PBPK modeling are summarized in Table 1, reproduced from Barton et al. (2007).[2] Here, "model specification" refers to the process of determining the structure of the PBPK model, "model calibration" refers to the process of determining the appropriate values for the PBPK model parameters given the available data, and "model prediction" refers to the use of the model to make quantitative inferences of interest to risk assessment.

The current state of the science in addressing these issues was summarized in the background white papers and presentations that were prepared as part of the Workshop, and listed in Tables 2 and 3.

Table 1: Key Issues in Characterizing Uncertainty and Variability in PBPK Models

Model Specification

- Integration of deterministic[3] and non-deterministic[4] model development
- Specification of alternative models
- Commonality of model structures across species

Model Calibration

- Use of data for estimating parameters versus "validating" the model
- Level of depth/rigor necessary in the non-deterministic model and parameter calibration methods
- Implementation of non-deterministic models (data inclusion/exclusion criteria, sources of variance/covariance, combined analysis of data with very different experimental designs)
- Evaluation of alternative models

Model Prediction

- Changes to the models and parameters for risk assessment predictions
- Characterizing uncertainty from alternative models
- Providing feedback to data needs and experimental design

[2] URL: http://toxsci.oxfordjournals.org/cgi/content/full/99/2/395

[3] The "deterministic" model is the mathematical representation of the biological/chemical system (e.g., PBPK model and metabolic pathways).

[4] The "non-deterministic" model is the mathematical/statistical representation of the uncertainty, variability, and covariance of the data and parameters of the deterministic model (e.g., statistical model for measurement errors and population variability).

Table 2: Background White Papers on Uncertainty and Variability in PBPK Models

Background White Paper and URL	Author
Model Specification[5] http://www.epa.gov/NCCT/uvpkm/files/Specification_PreMeeting_Draft.pdf	Harvey J. Clewell, III CIIT
Introduction to Statistical Population Modeling and Analysis for Pharmacokinetic Data http://www.epa.gov/NCCT/uvpkm/files/Calibration_PreMeeting_Draft.pdf	Marie Davidian Dept. Statistics, North Carolina State University
State of the Art in Issues of Uncertainty and Variability for PBPK Model Applications http://www.epa.gov/NCCT/uvpkm/files/Prediction_PreMeeting_Draft.pdf	Frédéric Bois INERIS (Institut National de L'Environnement Industriel et des Risques).

Table 3: Background Presentations on Uncertainty and Variability in PBPK Models

Presentation Title and URL	Presenter
Overview of PBPK Modeling and Its Value in Risk Assessment http://www.epa.gov/NCCT/uvpkm/files/UVPKM_2006_HClewell.pdf	Harvey J. Clewell, III CIIT
Experimental Data Used with PBPK Models http://www.epa.gov/NCCT/uvpkm/files/UVPKM_2006_HBarton.pdf	Hugh A. Barton US EPA
Mediating the Meeting between Model and Data: Statistical Issues for PBPK Modeling http://www.epa.gov/NCCT/uvpkm/files/UVPKM_2006_WSetzer.pdf	R. Woodrow Setzer US EPA
Uncertainty and Variability in PBPK models: How Do We Put It All Together for Risk Assessment? http://www.epa.gov/NCCT/uvpkm/files/UVPKM_2006_WChiu.pdf	Weihsueh Chiu US EPA
Data from Controlled Human Exposure as Basis for PBPK Modeling of Variability http://www.epa.gov/NCCT/uvpkm/files/UVPKM_2006_6Johanson.pdf	Gunnar Johanson Karolinska Institute
Discrepancies and Discovery: The Value of PBPK Modeling for Insuring Humility http://www.epa.gov/NCCT/uvpkm/files/UVPKM_2006_MAndersen.pdf	Melvin Andersen CIIT
Title: Statistical Population Modeling and Analysis of PK Data http://www.epa.gov/NCCT/uvpkm/files/UVPKM_2006_MDavidian.pdf	Marie Davidian Dept. Statistics, North Carolina State University
Accounting for Uncertainty and Variability in PBPK Modeling Predictions: Where are We Now, Where Should We Go? http://www.epa.gov/NCCT/uvpkm/files/UVPKM_2006_FBois.pdf	Frédéric Bois INERIS (Institut National de L'Environnement Industriel et des Risques).

[5] Subsequently published in Clewell and Clewell (2008).

Three major short-term needs were identified that participants indicated could make immediate impacts on the characterization of uncertainty and variability in PBPK modeling:

- Routine formation of multi-disciplinary teams to integrate the deterministic (biological) and non-deterministic (statistical) components of the modeling;
- Broader use of sensitivity analysis, particularly global sensitivity analysis in which all parameters are allowed to vary simultaneously throughout a range of values; and
- Improved documentation of model structure(s), parameter values, sensitivity and other analyses, and data so as to enhance the transparency and reproducibility of the PBPK modeling results.

Five longer-term needs were also identified that would significantly improve the ability to routinely address uncertainty and variability in PBPK modeling in the future:

- Better statistical models and methods, particularly given the constraints imposed by previously published laboratory animal studies (e.g., aggregated rather than individual data, cross-sectional rather than longitudinal data, serial correlations in closed chamber experiments);
- Better databases for physiological properties, and particularly their inter- and intra-individual variability;
- Data, models, and analyses for a wider range of chemical classes (i.e., beyond the volatile organic compounds typically studied); and
- Training, documentation, and software to disseminate the available data, methods and best practices.

Case Studies

The first case study involved the characterization of uncertainty and variability in the human pharmacokinetics of tetrachloroethylene, in particular the amount of inhaled tetrachloroethylene that is metabolized. The first part of this case study attempted a replication of Bayesian analysis of uncertainty and variability performed by Bois et al. (1996). Using updated software and greater computational resources, Chiu and Bois (2006)[6] found that the uncertainty in the results was greater than previously reported, particularly for the extrapolation to environmentally-relevant exposures (0.001 ppm exposure – as opposed to exposures of 70 ppm and higher). In particular, the 95% confidence interval for the amount of tetrachloroethylene metabolized was estimated to be 2.0%–61%, in contrast to the original Bois et al. (1996) estimate of 15%–58%. In addition, they performed an analysis that separated uncertainty from population variability, and found that in this case, the predicted population variability was greater than the inferred uncertainty. Finally, it was noted that the 95% confidence interval for the predictions at low dose encompassed predictions from all six previously published analyses (which varied by 10-fold). A subsequent analysis (Chiu, 2006) expanded on this comparison and examined the uncertainty in the values of Vmax and Km, the critical determinants of the amount metabolized. As shown in Figure 1, adapted from Chiu (2006), the point estimates from seven previously published analyses are within the envelope of the uncertainty derived by Chiu and Bois (2006). Furthermore, all these

[6] http://www.springerlink.com/content/x6khl8q47j1860m4/

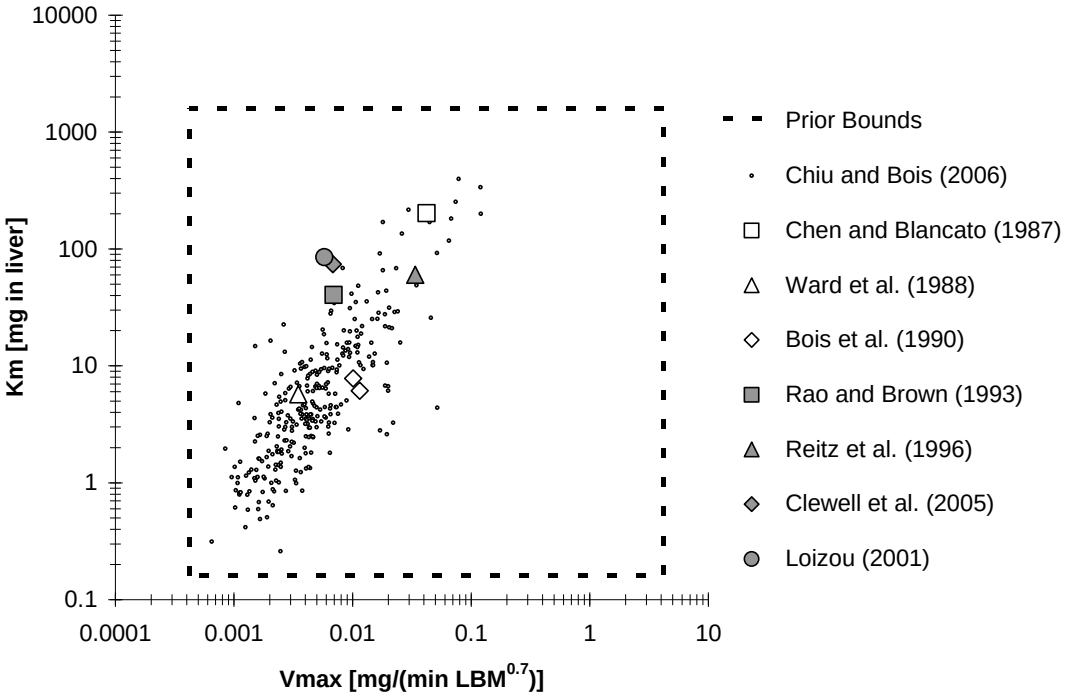

Figure 1. Vmax and Km values from eight published analyses of tetrachloroethylene pharmacokinetics. All parameters were converted to the same units as those in Chiu and Bois [note in particular that the unit for Km (mg in liver) used by Chiu and Bois (2006) is not the same as that typically used in PBPK models (mg/l in venous blood leaving liver)]. All analyses are point estimates except for Chiu and Bois (2006), which included a Bayesian analysis of uncertainty and variability. Points shown for Chiu and Bois (2006) are 300 random samples of the population means for Vmax and Km (i.e., reflecting uncertainty in the population means); the scatter would be greater if population variability were also included. Also included are the bounds on the prior distributions used in that analysis.

analyses give similar fits to the available in vivo data. Therefore, this is a case in which the available data are insufficient to highly constrain the predictions of interest, and the Bayesian methodology was able to quantify these uncertainties in a transparent and reproducible manner.

The second case study examined the uncertainty in route-to-route extrapolation using vinyl chloride as the example chemical. In particular, Chiu and White (2006)[7] showed that for a prototypical PBPK model, there is a simple relationship, depending on only four parameters, between oral dose and inhalation exposure concentrations that give the same internal dose. Chiu (2006) subsequently used Monte Carlo simulation to examine the uncertainty in this relationship due to uncertainty in the four key parameters (alveolar ventilation, cardiac output, hepatic blood flow, and the blood-air partition

[7] http://www3.interscience.wiley.com/journal/118562900/abstract?CRETRY=1&SRETRY=0

coefficient). The results showed that because all four of these parameters are fairly well measured, the route-to-route relationship has a coefficient of variation (standard deviation divided by the mean) of only 21%. Thus, this case study shows an example in which only a few model parameters determine the result, and they are all well constrained by the available data; therefore, the predictions are estimated with relatively high confidence.

The third case study addressed the critical issue of whether it is possible to characterize pharmacokinetic variability when only aggregated data in the form of mean and standard deviations, and not individual data, are available. Chiu and Bois (2007)[8] used human pharmacokinetic data on 1,3-butadiene to show that using a hierarchical Bayesian approach and several conceptually simple approximations, inter-individual variability could still be obtained from aggregated data. A comparison was made between population analysis in which individual data were available and the proposed approach using only aggregated data. It was found that the uncertainty distributions for all the pharmacokinetic parameters substantially overlapped between the two analyses, although the uncertainty from the aggregated analyses tended to be slightly larger. Importantly, the uncertainty in the model prediction of interest (i.e., the amount metabolized, as per tetrachloroethylene, above), was also quite similar, though again with somewhat higher uncertainty in the aggregated analyses. Therefore, this case study shows that aggregated data may still be informative as to population variability and is an important consideration given that individual data are often inaccessible for risk assessments.

The fourth case study considered dose metrics that may be applicable for MTBE risk assessment. A PBPK model for MTBE in rats was developed and calibrated with all known experimental data, and used to extrapolate calculations for humans to inform an uncertainty analysis (Blancato et al., 2007). This impact analysis (quantitative analysis of changes in predicted dose metrics after a change in model input values) was developed for exposure levels consistent with environmental levels. The inhalation route was examined using the following dose metrics: peak MTBE in venous blood, area under the curve (AUC) in venous blood at 24 hours, amount of MTBE metabolized in the liver at 24 hours, and peak metabolite tert-butanol (TBA) concentration in venous blood. An estimate for uncertainty in resulting dose metrics due to variability in MTBE metabolism was included in the computer simulations, consistent with variability estimates available in the literature. The impact analysis showed that TBA blood concentration varied to a greater extent than MTBE when accounting for human metabolic variability.

Conclusions

As discussed in Barton et al. (2007), current practices in characterizing uncertainty and variability in PBPK models have shown significant progress in the specification of the deterministic and stochastic model structures, the estimation of parameters using diverse data from multiple sources, and the characterization of uncertainty and variability in model parameters and predictions of interest for risk assessment. However, there are many areas in need of better methods or implementation, and the characterization of uncertainty and variability in PBPK models is not yet a sufficiently standard practice. The case studies described above demonstrate that for

[8] http://www.ingentaconnect.com/content/asa/jabes/2007/00000012/00000003/art00003

some purposes, the Bayesian approach to calibrating model parameters and characterizing the uncertainty and variability in model predictions is both feasible and transparent. However, in the route-to-route extrapolation case study with vinyl chloride, straightforward application of Monte Carlo simulation provided robust results. The MTBE case study also illustrated the value of a systematic, mathematically straightforward analysis in which impacts of variation of important parameters on estimated dose metrics for risk assessment are evaluated. Thus, the more labor-intensive Bayesian methods are not necessarily needed for all applications. While improvements in analytical methods and implementation are still needed, important applications of PBPK models can now be accompanied by systematic and transparent evaluation of the impacts of model uncertainties and inter-individual variability on risk assessment results.

Another issue is the integration of more sophisticated characterizations of PBPK model uncertainty and variability into risk assessment. For instance, Monte Carlo and Bayesian methods would fit naturally into probabilistic dose-response analyses (e.g., Hattis et al., 2002; Evans et al., 2001). However, while some example applications exist, a generally-accepted framework for such analyses has not yet been established. Moreover, even within probabilistic analyses, questions remain as to what percentiles of uncertainty and variability to use, as well as how to evaluate whether the estimates of human variability are representative of the full human population taking into account susceptible populations and life-stages. Therefore, work remains to be done on methods and approaches to integrating estimates of pharmacokinetic (and other sources of) uncertainty and variability into risk assessment.

References

Barton, HA; Chiu, WA; Setzer, RW; Andersen, ME; Bailer, AJ; Bois, FY; Dewoskin, RS; Hays, S; Johanson, G; Jones, N; Loizou, G; MacPhail, RC; Portier, CJ; Spendiff, M; Tan, YM. (2007) Characterizing uncertainty and variability in physiologically based pharmacokinetic models: State of the science and needs for research and implementation. Toxicol Sci 99(2):395–402.

Blancato, JN; Evans, MV; Power, FW; Caldwell, JC. (2007) Development and use of PBPK modeling and the impact of metabolism on variability in dose metrics for the risk assessment of methyl tertiary butyl ether (MTBE). J Environ Prot Sci 1:29–51.

Bois, FY; Gelman, A; Jiang, J; Maszle, DR; Zeise, L; Alexeef, G. (1996) Population toxicokinetics of tetrachloroethylene. Arch Toxicol 70:347–355.

Bois, FY; Zeise, L; Tozer, TN. (1990) Precision and sensitivity of pharmacokinetic models of cancer risk assessment: tetrachloroethylene in mice, rats, and humans. Toxicol Appl Pharmacol 102:300–315.

Chen, CW; Blancato, JN. (1987) Role of pharmacokinetic modeling in risk assessment: perchloroethylene as an example. In: Pharmacokinetics in risk assessment, drinking

water, and health. Vol. 8. Washington, DC: National Academy of Sciences, National Research Council; pp. 369–390.

Chiu; WA. (2006) Statistical issues in physiologically based pharmacokinetic modeling. In: Lipscomb, JC; Ohanian, EV; eds., Toxicokinetics and risk assessment, New York: Informa Healthcare, Inc.

Chiu, WA; Bois, RY. (2006) Revisiting the population toxicokinetics of tetrachloroethylene. Arch Toxicol 80(6):382–385.

Chiu, WA; Bois, FY. (2007) An approximate method for population toxicokinetic analysis with aggregated data. J Agri Biol Environ Stat 12(3):346–363.

Chiu, WA; White, P. (2006) Steady-state solutions to PBPK models and their applications to risk assessment I: Route-to-route extrapolation of volatile chemicals. Risk Anal 26(3):769–780.

Clewell, RA; Clewell, HJ. (2008) Development and specification of physiologically based pharmacokinetic models for use in risk assessment. Regul Toxicol Pharmacol 50:129–143.

Clewell, III, HJ; Gentry, PR; Kester, JE; Andersen, ME. (2005) Evaluation of physiologically based pharmacokinetic models in risk assessment: an example with perchloroethylene. Crit Rev Toxicol 35:413–33.

Evans, JS; Rhomberg, LR; Williams, PL; Wilson, AM; Baird, SJS. (2001) Reproductive and developmental risks from ethylene oxide: a probabilistic characterization of possible regulatory thresholds. Risk Anal 21:697–718.

Hattis, D; Baird, S; Goble R. (2002) A straw man proposal for a quantitative definition of the RfD. Drug Chem Toxicol 25(4):403–436.

Loizou, GD. (2001) The application of physiologically based pharmacokinetic modeling in the analysis of occupational exposure to perchloroethylene. Toxicol Lett 124:59–69.

Rao, HV; Brown, DR. (1993) A physiologically based pharmacokinetic assessment of tetrachloroethylene in groundwater for a bathing and showering determination. Risk Anal 13:37–49.

Reitz, RH; Gargas, ML; Mendrala, AL, Schumann, AM. (1996) In vivo and in vitro studies of perchloroethylene metabolism for physiologically based pharmacokinetic modeling in rats, mice, and humans. Toxicol Appl Pharmacol 136:289–306.

U.S. EPA (Environmental Protection Agency). (2006) Approaches for the application of physiologically based pharmacokinetic (PBPK) models and supporting data in risk assessment. National Center for Environmental Assessment, Washington DC;

EPA/600/R-05/043F. Available from the National Technical Information Service, Springfield, VA, and online at http://www.epa.gov/ncea.

Ward, RC; Travis, CC; Hetrick, DM; Andersen, ME; Gargas, ML. (1988) Pharmacokinetics of tetrachloroethylene. Toxicol Appl Pharmacol 93:108–117.