Available online at www.sciencedirect.com
SCIENCE DIRECT
Toxicology 221 (2006) 241–248
TOXICOLOGY
www.elsevier.com/locate/toxicol

Bayesian analysis of physiologically based toxicokinetic and toxicodynamic models

C. Eric Hack *

Toxicology Excellence for Risk Assessment, 2300 Montana Ave, Cincinnati, OH 45211, United States

Received 10 October 2005; received in revised form 19 December 2005; accepted 21 December 2005
Available online 8 February 2006

Abstract

Physiologically based toxicokinetic (PBTK) and toxicodynamic (TD) models of bromate in animals and humans would improve our ability to accurately estimate the toxic doses in humans based on available animal studies. These mathematical models are often highly parameterized and must be calibrated in order for the model predictions of internal dose to adequately fit the experimentally measured doses. Highly parameterized models are difficult to calibrate and it is difficult to obtain accurate estimates of uncertainty or variability in model parameters with commonly used frequentist calibration methods, such as maximum likelihood estimation (MLE) or least squared error approaches. The Bayesian approach called Markov chain Monte Carlo (MCMC) analysis can be used to successfully calibrate these complex models. Prior knowledge about the biological system and associated model parameters is easily incorporated in this approach in the form of prior parameter distributions, and the distributions are refined or updated using experimental data to generate posterior distributions of parameter estimates. The goal of this paper is to give the non-mathematician a brief description of the Bayesian approach and Markov chain Monte Carlo analysis, how this technique is used in risk assessment, and the issues associated with this approach.

Keywords: Bayesian; MCMC; PBTK; PBPK

1. Introduction

Well-controlled experiments on the toxicology of bromate, a disinfection byproduct resulting from water ozonation (EPA, 2001), have been and will likely continue to be conducted in animals. Optimally, the resulting toxic doses in animals will be extrapolated to the equivalent human dose by accounting for differences in kinetics and dynamics. Physiologically based toxicokinetic (PBTK) and toxicodynamic (TD) models of bromate in animals and humans would serve as a means to accomplish this goal.

A schematic illustrating an approach for using PBTK/TD models and Bayesian analysis in risk assessment is shown in Fig. 1. The example shown gives a brief overview of an approach for calculation of a human equivalent effective dose (i.e., the dose in mg/kg/day corresponding to a specified target level of risk or response) and illustrates where Bayesian analysis fits into the process. Animal and human kinetic data may include the time-course of the concentration of the parent chemical or metabolites in plasma, tissues, urine, or other tissues. Toxicodynamic data, such as gene expression or cell proliferation data, may be collected in vitro and in vivo in

* Tel.: +1 513 542 7475.
E-mail address: hack@tera.org.

0300-483X/$ – see front matter © 2006 Aww Research Foundation. Published by Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.tox.2005.12.017

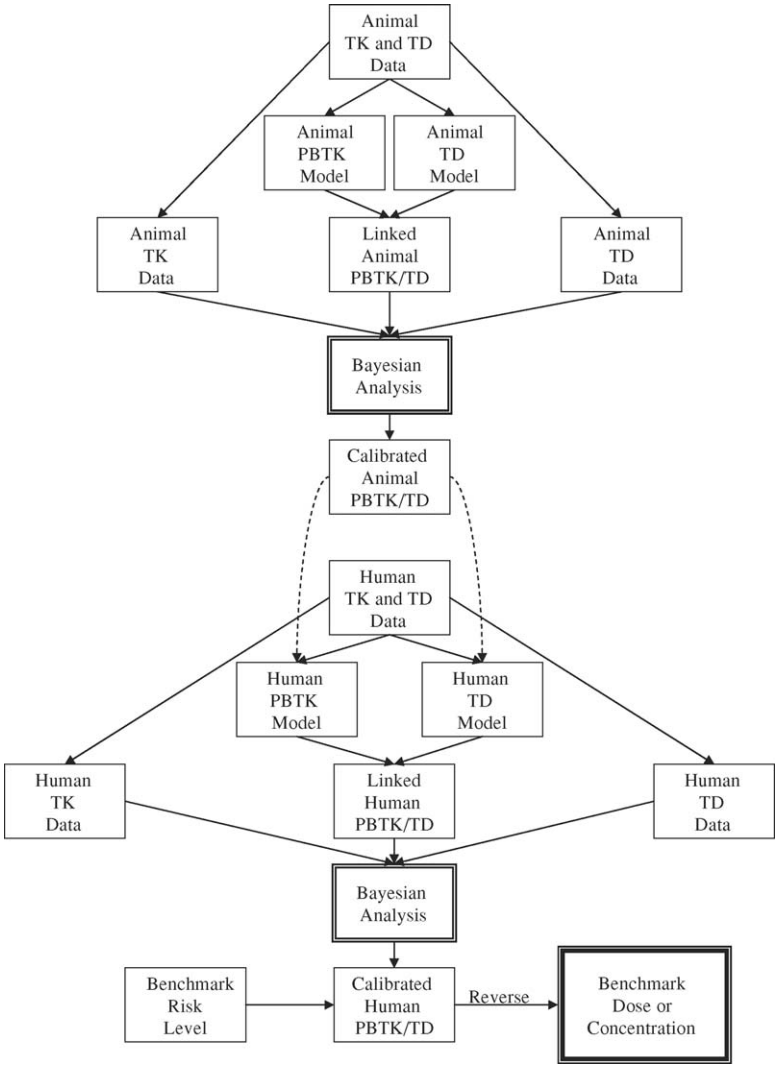

Fig. 1. The role of mathematical models and Bayesian analysis in risk assessment. An example approach for Bayesian analysis and application of a PBTK/TD model in human health risk assessment.

animals, and from in vitro experiments with human cells. The animal PBTK and TD models are developed and Bayesian analysis of the linked PBTK/TD model is performed. The human PBTK and TD models, which may be based on the structure in the animal models, are used to compute estimates of the effective dose in humans by effectively running the human model in reverse. A target risk or response level is specified, and the human PBTK/TD model is run to find the dose that will produce that level of risk or response. A detailed description of the use PBTK models in risk assessment can be found in Clewell et al. (2002).

PBTK and TD models are often highly parameterized (i.e., many parameters are required) and must be fitted or calibrated to experimental data in order to make accurate predictions of internal dose metrics or toxic response. Calibration, or model fitting, is the process of finding parameter values that result in model predictions that agree with experimentally measured values, such as tissue concentrations of bromate. Calibrating highly parameterized models and obtaining accurate estimates of uncertainty or variability in model parameters is difficult with commonly used frequentist calibration methods, such as maximum likelihood estimation (MLE) or least squared error approaches. A typical PBTK model may include several tissue compartments for the parent chemical and metabolites. It may easily require as many as 50 parameters, and population modeling (a statistical model described later in this paper) with kinetic data from 10 experimental subjects leads to more than

500 parameters. A Bayesian approach called Markov chain Monte Carlo (MCMC) analysis can be used to successfully calibrate these complex models. Often all parameters can be estimated simultaneously, even for PBTK models with several compartments. Prior knowledge about the biological system and associated model parameters is easily incorporated in the form of prior parameter distributions, and the distributions are refined or updated using experimental data.

Although MCMC is useful for calibrating PBTK models, there are issues associated with using the results in a risk assessment. Because MCMC analysis of PBTK models is a relatively new in human health risk assessment, performing an MCMC analysis involves much professional judgment in order to set up the model and interpret the results in a biologically meaningful way. Open questions regarding the interpretation of MCMC analysis must be addressed in order to use it with more confidence and to make the results more readily accepted by the risk assessment community.

Bayesian analysis is a powerful analytical tool, but it can be difficult to understand for those without mathematical training. The goal of this paper is to give the nonmathematician a description of how the technique has and can be used in risk assessment, and to describe issues associated with its application. This paper assumes the reader already has a general understanding of PBTK modeling and how such models are used in risk assessment.

2. Distributional approach

Model predictions can be made simply using the single best value for each parameter that gives the best agreement between model predictions and observations. However, due to underlying biological variability, model error and other sources of uncertainty, the parameters are not single values, but rather have distributions. For example, 70 kg is often used as the best estimate of human body weight in risk assessment, but clearly there is wide variation in body weights across the human population. Although body weight can be determined fairly accurately, other parameters in a PBTK model, such as target organ blood flows or weights are more difficult to measure and the parameter value distributions will reflect our uncertainty about the true values as well as variability from person to person. The uncertainty and variability distributions of the model parameters results in a distribution for the model predictions, and it is necessary to think in terms of distributions of parameter values in order to evaluate the uncertainty in the modeling results.

This focus on finding distributions of parameter values is not new or unique to the Bayesian approach. Parameter estimates obtained with most calibration or optimization software is accompanied by standard errors, representing the spread of the uncertainty distribution of the parameter, and Monte Carlo analyses uses parameter distributions as input to obtain estimates of the uncertainty or variability in model predictions. The difference in the Bayesian MCMC approach is that it uses prior parameter distributions as input, taking advantage of prior knowledge about parameter values, and provides updated posterior parameter distributions as output based on experimental data. While the Monte Carlo approach also uses parameter distributions that reflect prior knowledge, it does not update the distributions based on data.

In this document, calibration means finding distributions of model parameters that are consistent with the data. In fact, this is one of the advantages of MCMC in that prior estimates of parameter uncertainty are incorporated in the prior distributions, and posterior estimates are obtained that are consistent with experimental observations and the prior knowledge.

3. Model calibration

Model calibration, or model fitting, means finding distributions of model parameters that yield the best agreement between model predictions and experimental observations, such as the concentration of bromate or bromide in blood. For highly parameterized models like the proposed PBTK model for bromate, this is not trivial. Commonly used calibration algorithms utilize frequentist statistical approaches to maximize the likelihood or minimize the error between model predictions and observations. These approaches cannot feasibly estimate large numbers of parameters, and are limited to fitting a subset of the parameters while holding the values of other parameters fixed. However, Markov chain Monte Carlo, an implementation of the Bayesian approach, can be used to calibrate all parameters simultaneously.

Fitting a subset of model parameter is particularly troublesome when there is correlation among model parameters, as is the case with PBTK models (e.g., blood flow to liver and metabolism parameters). Ignoring these correlations leads to marginal distributions for the parameters (i.e., the parameters vary independently) that are narrower than the true distributions and may also be centered at incorrect values (Bernillon and Bois, 2000). For example, a narrower range of V_{max} values, the maximal metabolism rate, will be consistent with the kinetic data if a distribution of values for the blood flow to the

liver is used, rather than holding the blood flow to the liver fixed. That is, when the blood flow is allowed to vary, the model predictions can match the kinetic data using larger values of V_{max} when a small blood flow is chosen, and smaller values of V_{max} when a larger blood flow is chosen. MCMC can be used to calibrate all parameters and yield a joint probability distribution of the model parameters that describes the simultaneous variation of all parameters, and thus accounts for correlation between parameters.

4. Uncertainty analysis

PBTK and TD models are simplified representations of complex biological systems that depend on many underlying factors that vary from individual to individual. In addition to population heterogeneity and model error, uncertainty in model predictions arises from a lack of knowledge about parameter values (e.g., average body mass index, blood:air partition coefficient, or rate of metabolism), intraindividual variability or fluctuations that are not being modeled (e.g., breathing rate changes during active versus resting conditions), and measurement errors during data collection. Thus, model-based risk estimates inherit a degree of uncertainty that should be characterized to properly evaluate risk. Furthermore, some variation in parameter values is due to population heterogeneity, while some variation arises from a lack of knowledge about the true parameter value. While the population variability is real and cannot be reduced through additional data collection, the variation due to other sources of uncertainty can. If these sources of variation are separated, the portion of parameter variation that can be reduced by collecting additional data can be determined. Information of this kind can inform risk assessment decisions, such as those regarding uncertainty factors.

Uncertainty is commonly analyzed using Monte Carlo analysis, where parameter distributions are assigned and sampled but not updated based on data. However, these analyses often assume that all model parameters vary independently, ignoring correlations among parameters and typically exaggerating uncertainty/variability in model predictions. For example, consider the negative correlation between V_{max}, the maximal rate of metabolism, and K_m, the metabolizing enzyme's affinity for the chemical. If the distributions are sampled independently, small V_{max} values can be paired with large K_m values, producing unrealistically small rates of metabolism that may not be consistent with the kinetic data. Similarly, large V_{max} values can be paired with small K_m values, resulting in very high rates of metabolism. In this example, the estimated distribution of a dose metric, such as the parent chemical dose to the kidney will include the overly low and high metabolic rates and will tend be too wide. A Bayesian approach, Markov chain Monte Carlo analysis, can be performed to obtain a data-based joint probability distribution of all parameters that takes correlations into account and is more appropriate for conducting uncertainty analysis.

5. The statistical model

To analyze the variability or uncertainty in the model, a statistical model is needed to provide a framework within which to analyze the data. Hierarchical population models are the statistical models that have typically been used to characterize the variability and uncertainty in PBTK model predictions of dose metrics within a population based on data collected for individuals or small groups of subjects (Bois, 1999; Bernillon and Bois, 2000; Gelman et al., 1996). A diagram of a hierarchical population model is shown in Fig. 2. A population model uses the same PBTK model for all individuals in the population, while different parameter values are used for each individual to represent biological variability. For each parameter, there is a population distribution that may be characterized by a population mean and variance. However, the true mean and variance are not known precisely, so at the upper level, or the population level, the population mean is represented by an uncertainty distribution

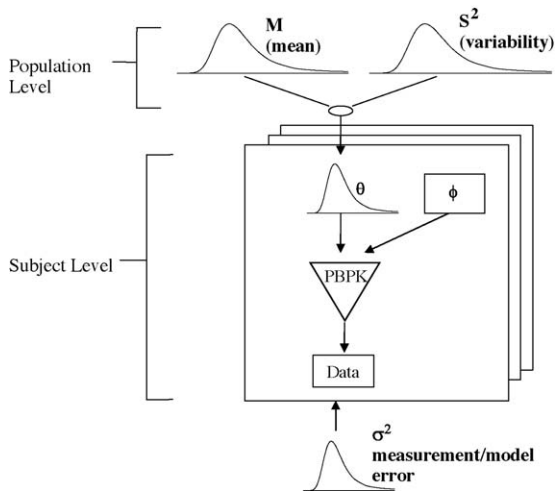

Fig. 2. A hierarchical population model. M is the population mean uncertainty distribution. S is the population variance uncertainty distribution. θ is the individual subject's parameter uncertainty distribution. φ are known parameters, such as body weight, age, sex, etc. Y are the data. σ^2 are the data error/model error. Figure adapted from Bois (2000).

and the population variance has an uncertainty distribution. A mean and variance from the population level distributions define a variability distribution that supplies subject-specific parameter values for the PBTK model to each of the individuals.

The population models require a large number of parameters to be estimated since each model parameter must be estimated for each experimental subject and for the population as a whole. For example, analysis of a PBTK model with 50 parameters and data on 10 subjects leads to more than 500 parameters. Bayesian analysis can be applied to estimate such a large number of parameters, while frequentist approaches typically cannot. This is because the Bayesian approach has the advantage that information in the prior parameter distributions helps informs the resulting posterior distributions as well as the experimental data. So, if there are little or no new data to inform the parameter distributions, the posterior distributions will draw on the information supplied in the prior distributions.

6. The Bayesian approach

The Bayesian approach to parameter estimation is based on Bayes' theorem:

$$P(X|D) = \frac{P(X) \cdot P(D|X)}{P(D)},$$

where D denotes data and X the parameter values. $P(X|D)$ is the posterior distribution of the parameters given the data, the goal of the Bayesian analysis. $P(D)$, the total probability of the data, is often not evaluated because it does not depend on the parameter values and the parameters can be estimated without evaluating $P(D)$ (Gilks et al., 1996; Hogg and Tanis, 1993). $P(X)$ is the prior distribution of the parameters, and $P(D|X)$ is the likelihood of the data given the parameters. The MLE approach maximizes a likelihood distribution defined for the data as a function of the parameters, $P(D|X)$ (Hogg and Tanis, 1993), but no prior information is utilized. The Bayesian approach is parameter estimation based on data but anchored by prior knowledge about the parameters values. Thus, if uninformative prior distributions are used for all parameters (e.g., flat or extremely wide probability distributions with no apparent peak), the Bayesian approach will yield the same parameter means as the MLE approach because the $P(X)$ provides no information and only $P(D|X)$ affects the results. On the other hand, if little or no new data are available, then the posterior distributions will be the same as the prior distributions $P(X)$, and a Monte Carlo uncertainty analysis using the posterior distributions from the Bayesian analysis will be the same as an ordinary Monte Carlo analysis.

The Bayesian approach can be used to readily incorporate prior knowledge of the biological system being modeled in the form of prior distributions, and then refine that knowledge using experimental data to obtain posterior distributions. Prior distributions are the starting point of a Bayesian analysis, reflecting the knowledge about the parameter distributions prior to the analysis of new data. The width of the prior distributions is determined by the degree of uncertainty associated with a given parameter. In the case of PBTK models, the mean physiological parameters, such as organ volumes and blood flows, are typically well-characterized in the scientific literature and are assigned informative, or relatively narrow distributions. Mean partition coefficients are assigned informative or uninformative distributions, depending on whether or not they have been experimentally determined. Poorly characterized parameters, usually including parameters describing metabolism processes, are assigned much broader, uninformative prior distributions for the population means. The population variability is seldom known with much certainty for most parameters, and wide, uninformative uncertainty distributions are used to describe parameter variability a priori.

Posterior distributions are the result of a Bayesian analysis, reflecting refinement of prior knowledge with the new data. If informative data are used in the analysis, the posterior distribution will be narrower, representing a decrease in uncertainty. For example, analysis of time-course data on the concentration of bromate in the blood can inform the parameters describing the metabolism of bromate, and uninformative prior distributions for these parameters may be 'tightened', reflecting decreasing uncertainty. However, these data cannot inform the parameters describing the metabolism and clearance of the bromide metabolite, and uncertainty in these parameters will not be decreased.

7. MCMC

Inferences about a parameter (e.g., estimating means and variances) are made by integrating the parameter distribution. For highly parameterized models, the integration is generally too complex to perform analytically, but MCMC can be used to perform the integration numerically.

As the name implies, MCMC is Monte Carlo integration using Markov chains (Gilks et al., 1996). Monte Carlo is a method of numerical integration by drawing samples from a distribution to estimate averages. Markov chains are series of random samples where each sample

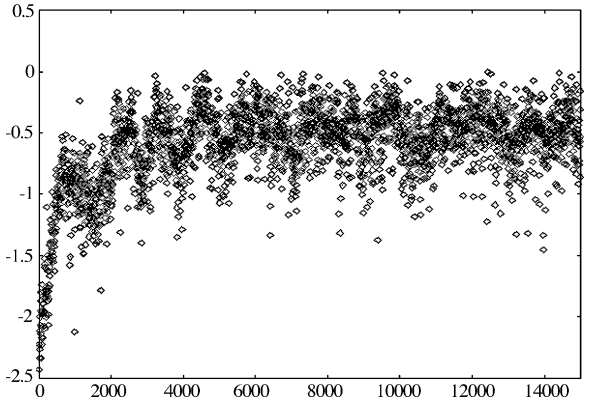

Fig. 3. A Markov chain. In this example Markov chain, the horizontal axis denotes the sample number, and the parameter values are marked on the vertical axis.

depends only on the value of the immediately preceding sample. Fig. 3 contains an illustration of a Markov chain obtained from a MCMC analysis performed using MCSim (Bois and Maszle, 1997). The chain is started by choosing a random sample from the prior distribution, and as the chain is propagated, it will eventually converge to a stationary posterior distribution that is most consistent with the prior information and the new data—this process is called convergence (Gelman and Rubin, 1992; Gelman, 1996).

8. Data requirements

There are general data considerations that apply not only to Bayesian analysis, but to all mathematical modeling. Knowledge about the values of highly uncertain parameters will be refined by analyzing data that are informative. In Bayesian terminology, updating uninformative prior distributions with informative data will yield narrowed posterior distributions, representing a decrease in uncertainty. However, the converse is also true, and parameter uncertainty will not be decreased if the available data is not informative. To illustrate, suppose an animal PBTK model with two competing metabolic pathways, oxidative metabolism versus glutathione conjugation of the parent compound, is analyzed, and that test animals have received a single dose of the parent chemical and the concentration in the blood of parent has been determined. It is unlikely that uncertainty in the parameters describing the rate of GSH conjugation, a process that is typically dominated by oxidative metabolism, will be decreased by analyzing these data. More specific data is required, such as blood concentration data following dosing of animals with the oxidative pathway inhibited (e.g., through use of gene knock-outs or chemical enzyme antagonists), or through direct measurement of the pathway (e.g., through collection of glutathione depletion data).

The data needed for a Bayesian analysis of a PBTK or TD model are the same data that are required to build and validate the models. That is, kinetic data in the species of interest for PBTK modeling (e.g., concentration of bromate and metabolites in plasma), and in vitro and in vivo data for TD modeling (e.g., cell proliferation or oxidative damage data). To properly evaluate the degree of uncertainty and variability in model parameters and predictions, it is important to use individual observations. However, data are often only available in aggregate form with means and standard errors of group responses. These grouped data are useful for the Bayesian analysis, but can lead to underestimation of uncertainty in model parameters and predictions.

9. Issues

Because MCMC analysis of PBTK models is relatively new as a human health risk assessment tool (Gelman et al., 1996; Bois, 2000; Jonsson and Johanson, 2001; USAF-EPA, 2004; Marino et al., 1996; Allen et al., submitted for publication), performing an MCMC analysis involves much professional judgment in order to set up the model and interpret the results in a way meaningful for risk assessment. There are several issues regarding the proper way to model some types of data and to use the results in a risk assessment.

One question is whether the posterior parameter distributions obtained from the evaluation of specific data sets should be used in the estimation of dose metrics. One must consider whether the subject population in the MCMC data sets is representative of the population for which the risk assessment is being performed. For example, the subjects in controlled human exposures may be at rest, leading to a relatively low estimate of the ventilation rate; however, this ventilation rate would probably not be appropriate for the activity level in the general population. Therefore, calculations of dose metrics and uncertainty/variability analyses performed in support of an environmental risk assessment should use the EPA default ventilation rate or a suitable general population distribution, not the posterior obtained from the experimental subjects. For an occupational risk assessment, even higher ventilation rates would be appropriate.

What this means in practice is that the dose metric calculations and Monte Carlo uncertainty analyses must be performed separately from the Bayesian analysis. For example, in the case of methylene chloride, data from subjects in controlled exposures can be used to estimate

a posterior distribution for the rate of conjugation with glutathione using MCMC (David et al., 1996). However, in order to estimate the variability of risks across the general population due to the polymorphism in glutathione *S*-transferase (GST) using Monte Carlo analysis, it is necessary to use the empirical distributions describing the polymorphism in the general population, not the posterior distribution obtained for the controlled exposure subjects. Therefore, it is necessary to perform the Monte Carlo variability analysis where some of the parameter distributions are the posteriors from the MCMC analysis and some (GST, ventilation rate, etc.) are distributions considered to be more appropriate for the general population.

Substituting general population distributions gives rise to another issue. As described in previous sections, the joint distribution obtained from the MCMC analysis takes into account the correlations between the parameters. The problem is how to insert a different distribution for one or more of the parameters without losing the information on the correlations. If the substituted distributions are sampled independently of the others, then dose metric variation will be over-estimated. Correlated distributions can be specified and sampled in Monte Carlo analysis if the amount of correlation between the parameters is known, so it is likely that a solution can be found for this problem given further research.

Though not a solution, one qualitative method of evaluating the impact of this problem is to examine the correlation coefficients between the parameter that is to be replaced and the remaining parameters in the joint distribution. The correlation coefficient is a measure of the correlation between two parameters, ranging from −1 to 1 with 0 indicating no correlation, 1 indicating perfect positive correlation and −1 indicating perfect negative correlation. Thus, if the correlation coefficients are sufficiently small, then the impact of the substitution will be small and may be neglected. Simulation experiments comparing the results of Monte Carlo analysis using the joint posterior distribution versus substituted distributions could be conducted as a sensitivity analysis to determine the impact of using substituted distributions for correlated parameters.

Another issue is the separation of data error, model error and parameter variability or uncertainty. Data error refers to measurement errors or bias arising from the limitations of instrumentation or experimental techniques. Model error is simply the result of less than perfect correspondence of the model structure to reality. When multiple data sets (i.e., multiple studies and multiple test subjects per study) are modeled, variability in physiological or toxicokinetic parameters among the individual subjects and across studies will cause different responses that cannot be predicted with the model using a single value for each parameter. If this interindividual variability were the only source of variation, the MCMC algorithm could use it to estimate the population distributions for the parameters. However, in most cases data error also contributes to the variation across individuals and studies. This data error can be systematic (i.e., there is a bias that causes data from one experiment to be higher than another), which is a particularly common problem when using data from different studies using different analytical measurement techniques. For example, mesurement of metabolic parameters (K_m and V_{max}) in different systems often gives rise to complications in this issue. Model error can also result in a systematic lack of agreement of the model predictions with the data.

An important consequence of the existence of model error is that the parameter estimates obtained by the MCMC analysis may not be valid. That is, the algorithm may estimate a value for a parameter in the model that is most likely given the comparison of model predictions and data, but due to model error, that parameter may not accurately reflect the true biochemical entity it is intended to represent. In particular for a model in which a number of parameters are to some extent collinear, a combination of changes in parameters could compensate for model error, but the resulting parameter values would not be valid representations of the underlying physicochemical quantities. An example would be estimating the rate of metabolism from data from an experiment for which model predictions are also sensitive to partition coefficients and breathing rate, and where the model is unable to accurately simulate the data because it does not model all of the tissues necessary to describe the toxicokinetics. The resulting joint estimate may be the most likely value for the parameters in the model as specified, but would not necessarily correspond to the true parameter values.

What this means in terms of the risk values generated based on the model predictions of delivered dose is that the model may appear to accurately describe the toxicokinetics based on measured tissue levels, but the predicted dose metric may be inaccurate. For example, suppose a model for a chemical that is eliminated via exhalation is calibrated using data on the levels of the chemical in blood, and a high ventilation rate is estimated to compensate for a lack of sufficient model error. Then a dose metric that was not directly used in the calibration (e.g., amount of metabolite produced per volume of liver is a common metric for reactive metabolites) may be under-estimated because the model predicts too much exhalation of the parent chemical.

This problem may be alleviated by specifying narrower, more certain distributions for the physiological parameters. In other words, this tells the MCMC algorithm that there is more information, or more weight in the prior distribution and it will be less affected by the data. This is appropriate only if the experimental population is a subgroup of the general population, such as young healthy adults or women of child-bearing age. However, this approach is unlikely to be useful for calibrating models using animal data, and it is unlikely to be applicable to partition coefficients.

The typical toxicokinetic data are mean observations for a group of animals or subjects. The variability in response and toxicokinetic parameters from one group to the next will be less than it would be from one individual to the next. At this time, a mathematically proven method for handling the grouped data in the MCMC algorithm when the grouped data must be combined with individual data or data from groups of a different size has not been formulated. A related issue is what can be done with the standard deviations that are often reported with the grouped data. No methods for utilizing this information a priori have been developed.

Understanding the issues associated with the use of MCMC analysis is important for proper application of this tool in risk assessment. Research directed towards dealing with these issues could improve MCMC analysis and make it a more useful tool for risk assessment.

Acknowledgements

Thanks to Drs. Andrew Maier and Jay Zhao for their helpful comments on the manuscript, and to Ms. Ann Parker for her insightful suggestions for the figures. The list of issues was developed in cooperation with Harvey Clewell while at Environ International (currently at CIIT).

References

Allen et al. Use of Markov chain Monte Carlo analysis with a physiologically based pharmacokinetic model of methylmercury to estimate exposures in United States women of child-bearing age. Risk Anal., submitted for publication.

Bernillon, P., Bois, F., 2000. Statistical issues in toxicokinetic modeling: a Bayesian perspective. Environ. Health Perspect. 108 (Suppl. 5), 883–893.

Bois, F., Maszle, D., 1997. MCSIM: a simulation program. J. Stat. Software 2 (9), http://toxi.ineris.fr/activites/toxicologie_quantitative/mcsim/article3.

Bois, F.Y., 1999. Analysis of PBPK models for risk characterization. Ann. N. Y. Acad. Sci. 895, 317–337.

Bois, F., 2000. Statistical analysis of Clewell et al. PBPK model of trichloroethylene kinetics. Environ. Health Perspect. 108 (2), 307–316.

Clewell, H.J., Andersen, M.E., Barton, H.A., 2002. A consistent approach for the application of pharmacokinetic modeling in cancer and noncancer risk assessment. Environ. Health Perspect. 110 (1), 85–93.

David, R.M., Clewell, H.J., Gentry, P.R., Covington, T., Morgott, D.A., Marino, D.J., 1996. Revised assessment of cancer risk to dichloromethane using improved human metabolic parameters and Bayesian statistics, Reg. Tox. Pharm., in press.

EPA, 2001. Toxicological Review of Bromate. U.S. Environmental Protection Agency, Washington, DC.

Gelman, A., Rubin, D.B., 1992. Inference from iterative simulation using multiple sequences. Stat. Sci. 7, 457–511.

Gelman, A., 1996. Inference and monitoring convergence. In: Gilks, W.R., Richardson, S., Spiegelhalter, D.J. (Eds.), Markov Chain Monte Carlo in Practice. Chapman & Hall/CRC, Boca Raton, pp. 131–143.

Gelman, A., Bois, F., Jiang, J., 1996. Physiological pharmacokinetic analysis using population modeling and informative prior distributions. J. Am. Stat. Assoc. 91, 1400–1412.

Gilks, W.R., Richardson, S., Spiegelhalter, D.J., 1996. Introducing Markov chain Monte Carlo. In: Gilks, W.R., Richardson, S., Spiegelhalter, D.J. (Eds.), Markov Chain Monte Carlo in Practice. Chapman & Hall/CRC, Boca Raton, pp. 1–19.

Hogg, R.V., Tanis, E.A., 1993. Probability and Statistical Inference, fourth ed. Macmillan Publishing Company, New York, pp. 586–587.

Jonsson, F., Johanson, G., 2001. A Bayesian analysis of the influence of GSTT1 polymorphism on the cancer risk estimate for dichloromethane. Toxicol. Appl. Pharmacol. 174, 99–112.

Marino, D.J., Clewell 3rd, H.J., Gentry, P.R., Covington, T.R., Hack, C.E., David, R.M., Morgott, D.A., 1996. Bayesian PBPK and dose–response modeling of dichloromethane in mice. Reg. Tox. Pharm., in press.

USAF-EPA TCE PBPK Workgroup, 2004. Markov Chain Monte Carlo Analysis of Harmonized Physiologically-based Pharmacokinetic Model of Trichloroethylene and Its Metabolites, www.tera.org.