ANALYSIS OF METHYLMERCURY DISPOSITION IN HUMANS UTILIZING A PBPK MODEL AND ANIMAL PHARMACOKINETIC DATA

John F. Young
Division of Biometry and Risk Assessment, National Center for Toxicological Research, Jefferson, Arkansas, USA

Walter D. Wosilait
Department of Pharmacology, School of Medicine, University of Missouri–Columbia, Columbia, Missouri, USA

Richard H. Luecke
Department of Chemical Engineering, University of Missouri–Columbia, Columbia, Missouri, USA

Physiologically based pharmacokinetic (PBPK) models are excellent tools to aid in the extrapolation of animal data to humans. When the fate of the chemical is the same among species being compared, animal data can appropriately be considered as a model for human exposure. For methylmercury exposure, sufficient data exist to allow comparison of numerous mammalian species to humans. PBPK model validation entails obtaining blood and tissue concentrations of the parent chemical and metabolite(s) at various times following a known exposure. From ethical and practical considerations, human tissue concentrations following a known exposure to an environmental toxicant are scarce. While animal-to-human extrapolation demands that sufficient human data exist to validate the model, the validation requirements are less stringent if multiple animal models are utilized within a single model template. A versatile PBPK model was used to analyze the distribution and elimination of methylmercury and its metabolite, inorganic mercury. Uniquely, the model is formed in a generic way from a single basic template during the initial program compilation. Basic parameters are defined for different PBPK models for mammalian species that span a relatively large range of sizes. In this article, the analyses include 12 species (mouse, hamster, rat, guinea pig, cat, rabbit, monkey, sheep, pig, goat, cow, and human). Allometric (weight-based) correlations of tissue binding coefficients, metabolism rate constants, and elimination parameters for both methylmercury and inorganic mercury are presented for species for which sufficient data are available. The resulting human model, in accord with the animal models, predicts relatively high inorganic mercury levels in the kidneys long after the disappearance of methylmercury from the blood.

Received 3 May 2000; sent for revision 27 June and 6 September 2000; accepted 2 October 2000.

Address correspondence to John F. Young, PhD, Division of Biometry and Risk Assessment, National Center for Toxicological Research, 3900 NCTR Road, Jefferson, AR 72079-9502, USA. E-mail: jyoung@nctr.fda.gov
Methylmercury is an environmental toxicant that on several occasions has been disastrous to humans (Ratcliffe et al., 1996; Harada, 1978; Bakir et al., 1973; Matsumoto et al., 1965). Clarkson (1997) in a recent review suggested that the critical factors of methylmercury toxicity are the brain exposure to methylmercury and possibly inorganic mercury as well. Neurotoxicity is the predominant effect, with prenatal exposure being the most sensitive period (Clarkson, 1997).

Methylmercury is partially eliminated directly but is also converted to an inorganic form of mercury that has a distribution and toxicity of its own. The inorganic form is eliminated more slowly than the reduction rate of methylmercury. These factors make the modeling complex. Smith and Farris (1996) point out the need for including inorganic mercury in models which deal with the fate of methylmercury.

Over the past several years a physiologically based pharmacokinetic (PBPK) model has been developed to calculate and/or simulate disposition of drugs or toxicants during pregnancy. An intricate multicompartment PBPK model was constructed that has been described in detail elsewhere (Luecke et al., 1994, 1997). The model differs from most other PBPK models in that the total material balance on the disposition of the chemicals was maintained. For growth during pregnancy, it has built-in adjustments for blood flow rates, organ sizes, and growth rates in the cases of the embryo/fetus. As part of the model evolution, a mathematical description of developmental growth of the embryo/fetus was formulated as a whole, as well as of the growth of critical individual organs (Wosilait et al., 1992; Luecke et al., 1995, 1999). Flow rates of blood to various maternal and embryo/fetal organs and tissue regions were also programmed as functions that changed with growth using allometric equations. Other principal parameters in the model included organ-to-blood binding ratios, metabolic rate constants, and kinetic elimination rate constants for the liver, kidneys, and other organs where elimination reactions have been reported to occur. Also included were “diffusion factors” that were used when transport rates between the blood and the organs were limited by interactions at binding sites or diffusion within or between cells. All of these parameters were programmed as possible nonlinear functions that did not depend explicitly on time but varied implicitly with changing concentrations (Luecke et al., 1997). Organ weights, blood flow rates, and other physiological parameters were programmed as a function of total animal weight and were an integral part of this PBPK model. The model handled the conversion of one substance to a metabolite and the distribution of both among tissues as a function of time. The program was capable of managing up to 10 repeated administrations of a substance by different or the same routes, such as oral, inhalation, dermal, subcutaneous, and/or intravenous bolus or infusion.

Most of our previous effort has been concentrated on the human model due to an abundance of literature data, especially for physiological para-
meters such as fetal weights, organs weights, and blood flow rates (Luecke et al., 1994). However, one overall goal of the work has been to provide a platform for extrapolation of data from laboratory animals to humans. To that end, the model has been extended to include simulations of other species (Luecke et al., 1997; Young & Luecke, 1998).

Organ function and arrangement and general blood circulation patterns tend to be quite similar in structure for mammals. There are, of course, many important and crucial exceptions, but this PBPK model was an attempt to exploit underlying physiological similarities where they exist. When available in the literature, physiological parameters measured for each animal species were incorporated in the extended models, but allometry was required for many parameters for extending the human model to the smaller or larger laboratory animals. These models allowed comparison of internal structure, concentrations, and even responses between animal models of various sizes.

Of course, toxicological effects can not be simply interpolated or extrapolated. There are numerous cases where responses to drugs and toxicants are completely dissimilar for different species and even for different individuals of the same species. Many important differences can exist that are not related to size, circulation rates, or other parameters of a PBPK model. However, quantitative analysis can be significant even when effects between species are very dissimilar. A comparison between models may often be more revealing than simple assignment of “safety factors” to overall results. In principle, with the PBPK model described here, allometric extrapolation allowances can be contained internally within the model for each tissue and chemical, and thus the overall effects can be calculated. In fact, in the case of methylmercury studied here, there was a great deal of PBPK model similarity between species.

Simulation of pharmacokinetic data from multiple species often yields insight into the behavior of a xenobiotic that data from a single study or single species can not provide. As more data are simulated, the models become more accurate and explicit. The use of the models to fit data sets from a variety of species and the additional simulations that can be created to aid the validation of the human model are the essence of what are explored in this article.

Originally the PBPK model used in this work was created specifically to analyze data during pregnancy. The availability of prenatal concentration data for mercury compounds in the literature was, however, quite limited. The work reported in this article does not use the capability to analyze pregnancy data and focuses entirely on postnatal, primarily adult data. Future plans include further study and analyses of prenatal effects.

The ideal data set to design and test a PBPK model contains blood and tissue/organ chemical concentration values for a sufficient duration to completely define the absorption, distribution, metabolism, and elimination of the parent compound and all of its metabolites. Concentration values
are needed for all major organ/tissue groups as well as any minor groups that would be necessary to fully define the fate of the chemical. Prudence would call for too much data rather than too little data.

For methylmercury, such a near-ideal data set exists for the rat. Farris et al. (1993) collected and analyzed blood and tissue samples for methylmercury and the metabolite, inorganic mercury, at various times out to 98 d following a single dose. Their data and model indicated that metabolism of methylmercury to inorganic mercury was the main elimination pathway and that the inorganic mercury was distributed mainly to the kidneys, but also to the liver and brain, in diffusion limited transport. The inorganic mercury produced from the methylmercury persisted, particularly in the kidney tissue, for an extended period of time.

If the rat PBPK model is to be used as a paradigm for human exposure, it is critical to the human model to obtain sufficient human tissue concentrations to validate at least the brain and kidney concentration following exposure to methylmercury. Speciation of mercury, that is, measurement of methylmercury and inorganic mercury, is extremely important for model validation (Smith & Farris, 1996). However, much of the pharmacokinetic data in the literature were for total mercury, that is, unspeciated inorganic mercury and organic mercury as a single entity. Therefore, merging of literature data from several sources to obtain sufficient information to simulate appropriate models was essential for many species.

In an earlier article from our laboratory (Luecke et al., 1997), methylmercury administration to rats or humans was cited as one example of the versatility of our PBPK model. For that illustration it was assumed that the same model would hold for both species. In the present article the analysis has been extended to include 10 additional species (mouse, hamster, guinea pig, cat, rabbit, monkey, sheep, pig, goat, and cow) and has incorporated additional human data to help validate the model.

The purposes of this report are (1) to describe the utility of a PBPK model in simulating the conversion of methylmercury to inorganic mercury in 12 species of mammals and the concurrent chemical distribution among tissues, and (2) to describe the utility of a PBPK model in cross-species simulation analyses using the principles of allometry as an aid in risk assessment.

METHODS

The PBPK model used in these simulations is, in effect, four PBPK models in one: The concentrations of two chemicals can be simulated in both maternal and embryo/fetal systems. The details of model structure with equations, block diagrams, and tabulation of physiological parameters were previously described (Luecke et al., 1994). Further discussion of the model along with a description of inputs and some results also has been presented (Luecke et al., 1997). For the present work, the model was reduced to utilize only the two maternal sections of the model for methyl-
mercury and its metabolite, inorganic mercury. The embryo/fetal portions of the pregnancy model were not utilized, as all data simulated in this article were for adult, nonpregnant animals.

Uniquely, each model is formed in a generic way during the initial program compilation by defining physiological parameters (organs weights, blood flow rates, etc.) based on animal size. Different PBPK models are thereby defined from the same basic model template for animal species that span a relatively large range of sizes: human (58 kg), monkey (5 kg), rat (0.3 kg), and mouse (0.025 kg). Physiological parameters for species other than these four are interpolated using allometry between these four “standards”.

Concentration versus time data were extracted from published figures by scanning (PaperPort for WorkGroups, Version 2.0 for Windows, Visioneer, Palo Alto, CA) the published graphs and saving them as PCX files. These files were in turn imported into UN-SCAN-IT (Silk Scientific, Inc., Orem, UT), where the x,y coordinates of the data points were estimated. The concentration–time data were then used as input values for the PBPK program. Since our PBPK model could accommodate various input units, the concentration units from the original papers were kept intact as much as possible for our simulations.

Much of the data available in the literature utilizes $^{203}$Hg for analytical convenience, but several studies also reported speciated mercury data. It is only those speciated data that can be fully utilized to validate the PBPK model. The literature sources for the PBPK data simulated in this article are listed in Table 1. Included are data from mouse, hamster, rat, cat, rabbit, monkey, cow, guinea pig, pig, sheep, goat, and human. Also listed in the first part of this table are the figure and table numbers from each reference from which the data were excerpted. The animal weight, age, sex, numbers of animals, number of sacrifice times, and maximum time that the animals were observed following dosing are also included in this table.

Table 2 extends this source information to include dosing and PBPK simulation input data. Various routes of administration and dosing frequency are represented in these data sets; each can be simulated with our versatile PBPK model and program. Also listed are the tissues reported and thus available for simulation by our model. It is only these tissues that can be directly simulated and used for model validation and allometry.

In all data sets, the list of organs for which data were reported does not include all that may possibly be storage sites for mercury. In these cases, all of the pharmacokinetic parameters (binding coefficients) for the non-reported organs were regressed as a single general binding coefficient. Often the general value was found to be small since the experimentally “neglected” tissues usually tended to be those for which mercury storage was small and contributed little to the mass balance for mercury.

Allometric (weight-based) relationships were calculated for the metabolic conversion of methylmercury to inorganic mercury, the elimination
<table>
<thead>
<tr>
<th>Source number</th>
<th>Species</th>
<th>Reference</th>
<th>Figure numbers</th>
<th>Table numbers</th>
<th>Animals</th>
<th>Sex</th>
<th>Number of animals</th>
<th>Number of sacrifice times</th>
<th>Maximum time (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mouse</td>
<td>Norseth, 1971</td>
<td>1–3</td>
<td>1 and 2</td>
<td>0.025</td>
<td>Female</td>
<td>18</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>Hamster</td>
<td>Omata et al., 1986</td>
<td>1</td>
<td>1</td>
<td>0.3</td>
<td>5–6 mo</td>
<td>Male</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Rat</td>
<td>Farris et al., 1993</td>
<td>2–3</td>
<td>5</td>
<td>0.3</td>
<td>70–90 d</td>
<td>Male</td>
<td>48</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>Cat</td>
<td>Hollins et al., 1975</td>
<td>1</td>
<td>5</td>
<td>2.8–3.4</td>
<td>Adult</td>
<td>Female</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Cat</td>
<td>Charbonneau et al., 1976</td>
<td>2</td>
<td>5</td>
<td>Adult</td>
<td>Both</td>
<td>23</td>
<td>4</td>
<td>147</td>
</tr>
<tr>
<td>6</td>
<td>Rabbit</td>
<td>Petersson et al., 1991</td>
<td>1 and 2</td>
<td>2</td>
<td>3–4</td>
<td>Adult</td>
<td>Female</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>Monkey</td>
<td>Vahter et al., 1994</td>
<td>1 and 2</td>
<td>2</td>
<td>2.4–6.1</td>
<td>7–14 yr</td>
<td>Female</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>Cow</td>
<td>Ansari et al., 1973</td>
<td>1</td>
<td>1</td>
<td>77</td>
<td>10 wk</td>
<td>Male</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>Cow</td>
<td>Ansari et al., 1973</td>
<td>1</td>
<td>1</td>
<td>72</td>
<td>10 wk</td>
<td>Male</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>Cow</td>
<td>Sell and Davison, 1975</td>
<td>1</td>
<td>1</td>
<td>680</td>
<td>6 yr</td>
<td>Female</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>Guinea pig</td>
<td>Iverson et al., 1974</td>
<td>1</td>
<td>1</td>
<td>0.35–0.40</td>
<td>Female</td>
<td>18</td>
<td>6</td>
<td>71</td>
</tr>
<tr>
<td>12</td>
<td>Pig</td>
<td>Gyrd-Hansen, 1981</td>
<td>1</td>
<td>3</td>
<td>35–50</td>
<td>Female</td>
<td>6</td>
<td>3</td>
<td>42</td>
</tr>
<tr>
<td>13</td>
<td>Sheep</td>
<td>Kostyniak, 1983</td>
<td>1</td>
<td>2</td>
<td>40.5</td>
<td>8 mo</td>
<td>Female</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>Goat</td>
<td>Sell and Davison, 1975</td>
<td>3</td>
<td>4</td>
<td>44</td>
<td>2 yr</td>
<td>Female</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>Human</td>
<td>Kitamura et al., 1976</td>
<td>Various</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Autopsy</td>
</tr>
<tr>
<td>16</td>
<td>Human</td>
<td>Yamamura et al., 1991</td>
<td>1</td>
<td>1</td>
<td>54 yr</td>
<td>Male</td>
<td>1</td>
<td>1</td>
<td>160</td>
</tr>
<tr>
<td>17</td>
<td>Human</td>
<td>Sherlock et al., 1984</td>
<td>3</td>
<td></td>
<td>52–102</td>
<td>26–62 yr</td>
<td>Both</td>
<td>20</td>
<td>200</td>
</tr>
</tbody>
</table>
rate constants for both methylmercury and inorganic mercury, and the binding coefficients for kidneys, liver, and brain for both methylmercury and inorganic mercury. The allometric equation for all of these parameters took the following form:

\[
P_{\text{PBPK}} \text{ parameter} = A \times \text{weight}^B
\]

or

\[
\log (P_{\text{PBPK}} \text{ parameter}) = \log A + B \log(\text{weight})
\]

where \(A\) and \(B\) are constants. Following the lead of Farris et al. (1993), the demethylation of methylmercury was modeled to occur in the liver. The elimination of both chemicals was modeled to be dependent on the concentration in the liver.

**RESULTS**

**Model Validation**

The ideal data set for methylmercury PBPK evaluation contained sufficient numbers of blood and tissue samples that were analyzed for methylmercury and its metabolite, inorganic mercury, to completely characterize the fate of both chemicals. Farris et al. (1993) presented and analyzed such a data set in the rat. In Farris et al. (1993), male Sprague-Dawley rats were dosed once orally with 10 µCi of radioactive mercury (\(^{203}\text{Hg}\)) as methylmercury chloride (\(\text{CH}_3\text{HgCl}\)). The animals were serially sacrificed \((n = 3\) at each data point) out to 98 d following treatment. Blood and all tissue samples were analyzed for both methylmercury and inorganic mercury, and a detailed PBPK model for the data was presented.

These data were also fitted with our model (Luecke et al., 1997), and simulated values for blood, brain, kidneys, and liver for both chemicals are presented in Figure 1 for time extended beyond the duration of the data collected. The simulation was extended past the data in order to visualize the relative decay characteristics of the tissue curves. The critical feature of these data is the maintenance of the high level of inorganic mercury, particularly in the kidneys, even as the levels in other tissues and blood fell. The higher levels of inorganic mercury in the kidneys persist even after the methylmercury blood values are reduced about 2 orders of magnitude and have decreased overall by over 3 orders of magnitude since the experiment began. By 100 d, the stored mercury in the kidneys was 95% inorganic. The PBPK simulation indicated that by 150 d, over 75% of the total stored mercury would be in the inorganic form and nearly all of this in the kidneys.

The question now becomes, does this model hold for humans? Could low or “negligible” blood or hair values from humans be giving us a false
sense of safety when actually the human body is maintaining a relatively high level of some form of mercury with the potential for long-term toxicity? Do data exist in the literature to validate or invalidate this model for humans? Do data from other animal species support and help validate this model? First to consider are the inferences from other animal species.

Norseth (1971) administered a single intravenous dose of 1 mg/kg CH$_3$HgCl labeled with $^{203}$Hg to 25-g female mice. Tissue samples were assayed for both methylmercury and inorganic mercury at each time point. Close scrutiny of the concentration curve for inorganic mercury in the kidneys showed a slow rise and a persistence that was not evident for the other tissues and blood values (Figure 2). The short time frame of these data does not allow an unambiguous interpretation or projection of these data beyond the experimental time. However, this pattern is consistent with the simulated rat model.

Male golden hamsters (5–6 mo old) were administered a single subcutaneous injection of 76 µCi $^{203}$Hg/kg as CH$_3$HgCl (10 mg/kg) (Omata et
al., 1986). The hamster data were monitored for only 16 d after administration. During this period, inorganic mercury in kidneys increased to 40%. Figure 3 shows these data and the simulations and illustrates the increasing dominance of inorganic mercury in the kidneys. Concentrations were not reported for the brain.

Hollins et al. (1975) fed six adult random-bred female cats a diet made from fish containing only trace amounts of methylmercury. Each cat then received a single oral dose of 78 mg CH$_3$HgCl labeled with $^{203}$Hg. Whole-body total $^{203}$Hg analysis was conducted out to sacrifice at 156 d; tissue levels of total $^{203}$Hg were reported. In another report from the same laboratory (Charbonneau et al., 1976) using similarly treated cats, blood and tissue samples were assayed for total and inorganic mercury at four time points; methylmercury was calculated by subtracting the inorganic mercury concentration from the total mercury concentration. The speciation data of Charbonneau et al. (1976) provided binding coefficient values and tissue levels for liver, kidneys and brain that were used in the simulation of the total $^{203}$Hg data of Hollins et al. (1975). Figure 4 illustrates the simu-
ulation of the speciation of the Hollins et al. (1975) data as well as the projected inorganic and methylmercury tissue levels. At the 156-d point, both inorganic mercury and methylmercury have similar magnitudes, illustrating the conversion of methyl to inorganic mercury and persistence of the latter. The increasing percentage of inorganic mercury is consistent

FIGURE 1. Comparison of the PBPK simulation (lines) with the rat data (symbols) of Farris et al. (1993). The simulation is extended past the data in order to visualize the relative decay characteristics of the tissues curves. (Labels for all figures: MM, methylmercury; IM, inorganic mercury; Hg, total mercury (MM + IM). For most figures, heavy lines represent methylmercury simulations and thinner lines represent inorganic mercury simulations; open symbols represent methylmercury data and closed symbols represent inorganic mercury data.)
with the rat data; however, the highest retention of mercury in the cat is in the liver rather than in the kidneys. Thus, even though there was only a single time when tissue samples were obtained, the speciation calculation allowed for these data to be unique and important for model validation.

FIGURE 2. Comparison of the PBPK simulation (lines) with the mouse data (symbols) of Norseth (1971).
Female New Zealand White rabbits were administered 0.125 µmol $^{203}$Hg-labeled CH$_3$HgCl/kg body weight intravenously in the ear vein twice a week for 9 wk (Petersson et al., 1991). The model capability for repetitive injections was utilized with these data, but the simulation injections were restricted to once per wk for the 9 wk because of the model...
limitation of 10 inputs. The highest final concentration of mercury was found in the fur of the rabbit (not shown), while the kidneys retained the highest levels and percentage of inorganic mercury of any of the internal tissues analyzed (Figure 5). After a 12-wk decay, the kidneys were observed to have ~36 times greater concentration of total mercury than the

FIGURE 4. Comparison of the PBPK simulation (lines) with the cat data (symbols) of Hollins et al. (1975).
blood. Approximately 70% of the mercury in the kidneys was found to be in the inorganic form. Because of the scatter in the measured data, the simulated concentrations of inorganic mercury are uncertain. Nonetheless, both the data and the simulated values indicate reduced elimination rates for inorganic mercury in the kidneys and liver.

**FIGURE 5.** Comparison of the PBPK simulation (lines) with the repeated-dose rabbit data (symbols) of Petersson et al. (1991).
Total and inorganic mercury data were obtained from blood and brain samples from female *Macaca fascicularis* monkeys who were fed methylmercury for either 6, 12, or 18 mo or after washout for 6 mo following a 12-mo exposure (Vahter et al., 1994). At the end of the 12-mo dosing period (Figure 6), the brain concentrations of methylmercury and inorganic
mercury were about 4–5 times as high as their respective blood concentrations with the percentage of inorganic mercury about the same in both tissues (~9%). After a 6-mo washout period, the methylmercury and inorganic mercury blood concentrations decreased by ~90%. For the same time period, the methylmercury level in the brain decreased by about the same percentage as in the blood, but the inorganic mercury level in the brain decreased by only ~70% and now constituted about 26% of the total mercury in the brain. Extension of the simulation calculations predicted that inorganic mercury and methylmercury in the blood would be equal at about 265 d after the administration of mercury was stopped and would be equal in the brain after about 340 d. Subsequently, inorganic mercury would be the principal species present, both in the blood and in the brain. This type of data provides a challenge for the simulation model and is a sensitive measure for model parameters. Although measured data were not available, the kidneys levels for both chemicals were projected to be the highest at the end of the experimental period (simulated kidneys curves are not included in Figure 6).

Ansari et al. (1973) administered $^{203}\text{Hg}$ as either $\text{HgCl}_2$ or $\text{CH}_3\text{HgCl}$ orally to male Holstein calves and measured daily total $^{203}\text{Hg}$ in whole blood for 7 d. At sacrifice, tissue concentrations were also measured. This design allowed for fairly accurate assessment of the binding coefficients for inorganic mercury (Figure 7A) and also for methylmercury (Figure 7B) found in kidneys, liver, brain, muscle, and heart. The binding coefficients obtained from this study were utilized to fit the data of Sell and Davison (1975), who administered radiolabeled $\text{CH}_3\text{HgCl}$ intraruminally to a 6-yr-old Guernsey cow that was in mo 3 of lactation (Figure 7C). All of these data were for a 7-d period, which means that projection to chronic exposure would have a high degree of uncertainty. Only the speciated calf data were used for model validation; however, the PBPK model projected well to fit the adult cow data with only a weight adjustment.

Iverson and colleagues reported on the oral exposure of guinea pigs to $^{203}\text{Hg}$ as $\text{CH}_3\text{HgCl}$ (Iverson et al., 1973, 1974; Iverson & Hierlihy, 1974). Iverson and Hierlihy (1974) reported total and inorganic mercury concentrations at 6 sacrifice times out to 71 d following continuous dosing throughout the experiment. Single doses of 1 and 10 mg Hg/kg, as well as multidosing studies of 0.4, 4, 40, and 400 µg/kg, were reported. These data had diminished usefulness for purposes of the present work because only total $^{203}\text{Hg}$ was reported. However, limited speciation analysis was conducted at sacrifice at 71 d. The data of Iverson and Hierlihy (1974) also provided some speciation to calculate the binding coefficients for the guinea pig liver and kidneys. With these modifications, the single-dose total $^{203}\text{Hg}$ blood and tissue data of Iverson et al. (1973) were then simulated for the 1- and 10-mg/kg doses. All simulations of the guinea pig data used a single set of PBPK constants. The multidosing studies of Iverson et al. (1974) were simulated with the average curves and normalized data illustrated in Figure 8. The four alike
FIGURE 7. Comparison of the PBPK simulation (lines) with the calf data (symbols) of Ansari et al. (1973) following administration of (A) mercuric chloride or (B) methylmercury. (C) Comparison of the PBPK simulation (lines) with the cow data (symbols) of Sell and Davison (1975) using the same PBPK parameters as determined for the calf data of Ansari et al. (1973).
symbols at each time represent results normalized from four dose sizes. Every variation from the mean is monotone with dose size; that is, the upper point is always the largest dose, and the lowest point always represents the smallest dose. This systematic variation could not be assimilated by the model and requires further study. These results were not used in the allometric correlations of pharmacokinetic parameters.
Danish Landrace pigs (Gyrd-Hansen, 1981) and one female Corriedale sheep (Kostyniak, 1983) were administered a single intravenous dose of CH$_3$HgCl. Sell and Davison (1975) administered CH$_3$HgCl orally to a 2-yr-old Saanen goat in the early stages of lactation. These data sets were of diminished value to our study and could not be used for model validation since all of the data from the pig, sheep, and goat were limited to total mercury levels in the blood and tissues. Without speciation of methylmercury and inorganic mercury, the PBPK model can not provide a unique fit to these data. In these three animal species, the kidneys and liver mercury concentrations at sacrifice were projected to be the highest even at early times. The simulations of these data are illustrated in Figure 9 (A, pig; B, sheep; and C, goat), but none of these results were used for allometric correlation of pharmacokinetic parameters. The apparent speciation presented as part of the sheep data (Figure 9B) was obtained only after several assumptions about the original data had been made.

**Human Data**

Concentrations of methylmercury and inorganic mercury from autopsies were reported by Kitamura et al. (1976). The relative concentration values for both methylmercury and inorganic mercury from these autopsy tissue data were used to estimate binding coefficients for the human model. Since these data represent steady state, the “Time (arbitrary days)” values are shown (Figure 10A) only to illustrate that the simulation model has reached steady state. Note that at steady state in humans, the inorganic mercury tissue levels are all higher than the respective tissue methylmercury levels. The high ratios of inorganic to methylmercury observed in these data are consistent with, and even exceed, predictions from the animal models.

Yamamura et al. (1991) reported inorganic mercury levels in blood from a 54-yr-old male patient hospitalized for chronic mercury poisoning following long-term exposure to mercury vapor. In this simulation, it was assumed that only inorganic mercury was present. Utilizing the binding coefficients from the autopsy data, the inorganic mercury elimination rate constant was varied to fit these human data (Figure 10B). While the blood level decreased in the mercury-free environment, the simulation indicated that inorganic mercury in all of the tissues declined in a near-parallel manner.

Twenty human volunteers consumed contaminated halibut containing 4 different natural concentrations of methylmercury 3–4 times per week for ~96 d and then were monitored for an additional ~96 d while the mercury was eliminated (Sherlock et al., 1984). Only mean total mercury concentrations in blood were reported. The concentrations were normalized to the largest dose size so that effectively they represent percent of dose (Luecke et al., 1997). Figure 11 shows the simulation and the plasma data reported by Sherlock et al. (1984). The figure includes the simulated concentrations of inorganic mercury and methylmercury projected for the kidneys, liver and brain. This figure also shows the simulation extended to 600 d
FIGURE 9. Comparison of the PBPK simulation (lines) with the large animal data (symbols) of Gyrd-Hansen (1981) for (A) the pig, (B) sheep data of Kostyniak (1983), and (C) the goat data of Sell and Davison (1975). Hg represents total unspeciated mercury.
FIGURE 10. Comparison of the PBPK simulation (lines) with (A) the human autopsy data (symbols) from Kitamura et al. (1976) and (B) the inorganic mercury data (symbols) in humans of Yamamura et al. (1991). Time is in arbitrary units in panel (A).
and illustrates the model prediction that the kidneys still would retain relatively high levels of inorganic mercury.

**Correlation of Parameters**

Allometry has proven to be a useful tool in many cross-species studies; thus, it was of special interest to study to what degree the pharmacokinetic parameters under consideration in the present studies also followed sim-
ple allometry. Table 3 summarizes the values found in the analyses of the pharmacokinetic parameters for elimination, the conversion rate constant, and for the binding coefficients for the kidneys, liver, and brain obtained from several mammalian species. The plots of these parameters are shown in Figure 12. The allometric equations are included within each panel. The correlation lines shown on these plots are “allometric” reflecting a power relationship between these parameters and animal weight.

DISCUSSION

Physiologically based pharmacokinetic models can simulate concentration versus time data from various species including humans. However, choosing and validating the model requires sufficient data to assure the uniqueness of the model; that is, a sparse data set can be fit with almost any model! Even the richness of the Farris et al. (1993) data set has been fit with at least two models that are similar but not exactly the same (Farris et al., 1993; Luecke et al., 1997).

To broaden the range of species for comparative and allometric analysis, a survey of the literature was made for suitable data in various species exposed to methylmercury. The pharmacokinetic literature for methylmercury is fairly large, with over 240 articles (13 species) in our personal database. However, usable data that include speciation, tissue concentrations, and data from extended-time sampling to define the elimination characteristics are limited to only a few articles, which were simulated in this article. Some articles were from less commonly used laboratory animals and others were from domestic animals, thereby providing a fairly broad range of mammals.

By using the same model with different parameters for multiple animal systems, it is possible to discern similarities among various species and also to highlight differences that exist for particular species. For the methylmercury data, there are several general observations that seem to be valid for all species considered here.

1. Methylmercury is slowly converted to inorganic mercury; the carbon–mercury bond can be broken by phagocytic cells, which are located throughout the body, as well as by intestinal microflora. (Clarkson, 1997). However, following the lead of Farris et al. (1993) and consistent with the PBPK model of Clewell et al. (1999), the demethylation of methylmercury was modeled to occur mainly in the liver and was adequate to fit all data sets.

2. Mercury is eliminated both as methylmercury and as inorganic mercury. Where adequate data are available to make the determination, the rate of direct elimination of methylmercury is subordinate, accounting for 2 to 25% of the total elimination. The principal route is organic → inorganic → elimination, which accounts for the major removal of mercury.
<table>
<thead>
<tr>
<th>Animal weight (kg)</th>
<th>Mouse</th>
<th>Hamster</th>
<th>Rat</th>
<th>Cat</th>
<th>Rabbit</th>
<th>Monkey</th>
<th>Cow</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.025</td>
<td>0.100</td>
<td>0.505</td>
<td>3.10</td>
<td>3.50</td>
<td>4.25</td>
<td>72</td>
<td>71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methylmercury binding coefficients</th>
<th>Mouse</th>
<th>Hamster</th>
<th>Rat</th>
<th>Cat</th>
<th>Rabbit</th>
<th>Monkey</th>
<th>Cow</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>4.59</td>
<td>6.65</td>
<td>1.57</td>
<td>6.07</td>
<td>5.40</td>
<td>26.7</td>
<td>2.09</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>1.35</td>
<td>3.85</td>
<td>0.149</td>
<td>26.1</td>
<td>3.41</td>
<td>13.8</td>
<td>4.00</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>0.497</td>
<td>0.095</td>
<td>2.32</td>
<td>1.28</td>
<td>5.78</td>
<td>3.27</td>
<td>1.59</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>0.732</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.43</td>
<td>0.836</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.4</td>
<td>0.709</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>0.778</td>
<td>2.84</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inorganic mercury binding coefficients</th>
<th>Mouse</th>
<th>Hamster</th>
<th>Rat</th>
<th>Cat</th>
<th>Rabbit</th>
<th>Monkey</th>
<th>Cow</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>25.0</td>
<td>16.9</td>
<td>322</td>
<td>34.2</td>
<td>141</td>
<td>307</td>
<td>22.4</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>5.92</td>
<td>3.88</td>
<td>10.7</td>
<td>159</td>
<td>74.2</td>
<td>84.9</td>
<td>8.88</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>0.757</td>
<td>0.821</td>
<td>4.94</td>
<td>2.38</td>
<td>6.22</td>
<td>1.12</td>
<td>1.72</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>1.54</td>
<td></td>
<td>4.94</td>
<td>2.38</td>
<td>6.22</td>
<td></td>
<td>1.25</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.79</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>1.79</td>
<td>1.57</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kinetic rate constants (1/d)</th>
<th>Mouse</th>
<th>Hamster</th>
<th>Rat</th>
<th>Cat</th>
<th>Rabbit</th>
<th>Monkey</th>
<th>Cow</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylmercury metabolism</td>
<td>0.178</td>
<td>0.101</td>
<td>1.58</td>
<td>0.019</td>
<td>0.065</td>
<td>5.26</td>
<td>0.100</td>
<td>0.107</td>
</tr>
<tr>
<td>Methylmercury elimination</td>
<td>0.276</td>
<td>0.179</td>
<td>0.038</td>
<td>0.008</td>
<td>0.759</td>
<td>0.002</td>
<td>1.90</td>
<td>0.001</td>
</tr>
<tr>
<td>Inorganic mercury elimination</td>
<td>1.14</td>
<td>0.987</td>
<td>2.38</td>
<td>0.081</td>
<td>0.073</td>
<td>0.589</td>
<td>0.245</td>
<td>0.917</td>
</tr>
</tbody>
</table>
FIGURE 12. Allometric plots of the rate constants for methylmercury metabolism and elimination of methylmercury and inorganic mercury, as well as the ratio of blood-to-tissue binding coefficients for both chemicals for kidneys, liver, and brain. The allometric equation for the best fit regression line is of the format: \( \log(PBPK \text{ parameter}) = \log A + B \log(\text{weight}) \), where \( k \) is the rate constant and \( BC \) the binding coefficient.
3. Methylmercury is distributed fairly rapidly and partitioned into various organs via the blood flow. In some cases, the rate of distribution is quite low and may require a diffusion parameter for adequate fitting of data. The diffusion factor indicates that diffusion, reaction among binding sites in the serum or in organs, or some other delay is rate limiting at the cellular level.

4. Inorganic mercury is distributed to various organs also by blood flow, but the transport is often too slow to be modeled as blood flow limited. A diffusion factor representing an approach to less than complete equilibrium is frequently required to model the distribution of methylmercury.

5. When methylmercury is administered, the concentration of inorganic mercury in the blood and in each organ is always lower than the methylmercury in the early stages except occasionally for the liver and kidneys. In most cases, the slopes of the decay curves show that the rate of elimination for the inorganic mercury is slower than for methylmercury. Using the model to extrapolate experimental results to much longer times shows in many cases that the concentrations of the inorganic mercury will surpass those of methylmercury (e.g., rat, Figure 1; hamster, Figure 3; rabbit, Figure 5; monkey, Figure 6; and guinea pig, Figure 8). The steady-state human values from cadavers shown in Figure 10A show concentrations for inorganic mercury that are dramatically higher than those of methylmercury. These values are greater than would be predicted by the model if the input were only methylmercury. While it is unknown whether inorganic mercury or methylmercury was the source of mercury for these data, the differences in elimination rates would produce a shift to the inorganic mercury form.

As indicated by the allometric plots of binding coefficients (Figure 12, D–I), the binding coefficients for inorganic mercury are higher than for methylmercury for kidneys and liver for all animal species for which speciation data are available. For these species of animals, the inorganic binding coefficients for the brain are at least as high as for the organic form. Given the reduced blood concentrations and reduced diffusion rate, the inorganic mercury in the kidneys, liver and brain will tend to persist longer than the methylmercury.

6. Allometry has been a useful tool in many areas of comparative analysis. Allometry yields interesting insight into the fate of methylmercury and inorganic mercury across species. The binding coefficients for methylmercury of the rat kidneys, liver and brain (Figure 12, D–F) indicate that the value for the rat is about 10-fold lower than the allometric regression line in all three organs. This is consistent with the species data presented by Magos (1987), which indicated that the distribution of methylmercury between the red blood cell and plasma was 12 times higher for the rat when compared to the allometric relationship for the other 7 species. The values for the rat were not used in the regression
calculation of the allometric line for the binding coefficients of methylmercury in these three organs. These same phenomena do not occur with inorganic mercury across species as the value for the rat varies around the allometric regression lines (Figure 12, G–I).

Caution is required for allometric interpretation with methylmercury because of its high and variable degree of binding by hemoglobin (Doi & Tagawa, 1983). This is important to consider because the ratios of tissue to blood values can be altered considerably from a simple allometric relationship. Clarkson (1972) reviewed the great amount of research on tissue-to-blood binding ratios and pointed out that in the case of brain, species differences would not be as great if plasma-to-brain ratios were reported. However, plasma values are not usually measured and reported, but would be useful for PBPK analysis.

7. The rate of conversion of methylmercury to inorganic mercury decreases only slightly as the species get larger. The elimination of methylmercury decreases by one to two orders of magnitude as the animal size increases. The elimination of inorganic mercury also decreases by about one order of magnitude but at a 10-fold higher rate.

The available human data are necessarily restricted for practical and ethical reasons. Only three sources of useful data were found: some limited steady-state data were found from human populations with moderately high seafood consumption (Kitamura et al., 1976); from a patient who had become ill from the effects of elevated inorganic mercury in the environment (Yamamura et al., 1991); and from some total-mercury-only blood concentrations of an experimental group that had consumed small dosages of methylmercury (Sherlock et al., 1984). The lack of human data reporting both organic and inorganic mercury concentrations over an extended time frame makes direct validation of the model problematic. However, despite these very limited data sets, the general cross-species concurrence of the fitting parameters lends considerable support to the simulation with human data.

Furthermore, by utilizing the human autopsy studies and the pharmacokinetic studies of inorganic mercury in combination with the pharmacokinetic studies of methylmercury, a viable validation scheme can be developed for the model. The human autopsy data (Kitamura et al., 1976) provide binding coefficients of inorganic and methylmercury in kidneys, brain, and liver for direct use in the model. The rate of elimination of inorganic mercury for the human can be validated from the blood decay data of Yamamura et al. (1991) (Figure 10B). Utilizing these data, it was possible to simulate the accumulation and elimination data of Sherlock et al. (1984), which provided a reasonable validation of the PBPK model to humans.

All three data sets were simulated iteratively. Each set of data contributed uniquely to the overall model. The data of Kitamura et al. (1976) de-
fined the binding coefficients; those of Yamamura et al. (1991) defined the rate constant for the elimination of the inorganic mercury; and those of Sherlock et al. (1984) defined the rate constant for the elimination of methylmercury. However, the simulation of the Kitamura et al. (1976) data must have the two elimination rate constants set to properly simulate these endpoint values; the Yamamura et al. (1991) data must have the inorganic binding coefficient before the inorganic blood values can be simulated; and to simulate the accumulation and elimination data of Sherlock et al. (1984), one must have all of the binding coefficients as well as the rate constant for the elimination of inorganic mercury. The rate constant for the elimination of methylmercury can be calculated by difference for the best fit of this data. Thus the model is a truly interactive system.

As was predicted by animal studies, Figure 11 would suggest that at extended times, as the whole blood concentration of mercury approaches low levels, the inorganic mercury level in the kidneys is still about 10-fold higher than that of methylmercury.

Model validation for methylmercury necessitates speciation in the data set. Of the more than 240 pharmacokinetic articles concerning mercury in our personal collection, only the few reported here have sufficient analytical data for both methylmercury and inorganic mercury. Even the extensive amount of data reported by Iverson et al. (1973, 1974) with the guinea pig cannot be fully utilized since they measured only total mercury. In contrast, the rather limited data of Hollins et al. (1975) in the cat can be used when combined with the companion study reported by Charbonneau et al. (1976), which analyzed for both compounds at several sacrifice times.

The cumulative studies (rabbit, monkey, and human) provide a rigorous test of the model and program and also represent a situation close to that encountered in human exposure to methylmercury. The cumulative features of the program provide reasonable fits to the experimental data. In addition, the decay curves upon cessation of exposure to methylmercury also fit the data in the simulations. Interestingly, the decay curves also fit in the autopsy cases; however, it was necessary to simulate the cumulative phase of the exposure, which again demonstrates the versatility of the model and program. These analyses show the utility of the PBPK model as a tool for human analysis where data are limited.

A great deal of research has been carried out over the years concerning the toxicity of mercury and methylmercury (Clarkson, 1997; Ratcliffe et al., 1996). Of relevance to the present studies is the capacity of methylmercury and inorganic mercury to react with sulfhydryl groups in proteins and low-molecular-weight sulfhydryl compounds. Hg$^{2+}$ combines with two sulfhydryl groups, which makes it much more stable than methylmercury in its combination with only one sulfhydryl group (Hughes, 1956–1957). The greater stability associated with the divalent bonding is reflected in a much higher association constant with sulfhydryl-containing tissue proteins and accounts for its greater persistence and longer duration
in the tissues. Thus, as methylmercury is converted to inorganic mercury, it is converted to a more persistent substance, which is reflected in a longer duration of action on a macro scale as reflected in the output of the PBPK model.

Enterohepatic recirculation is an integral and important part of the fate of methylmercury in all animal systems. However, it is not currently part of this PBPK model; nor is it necessary to model the recirculation as the net effect of biliary excretion. Intestinal conversion of methylmercury to inorganic mercury, partial reabsorption of methylmercury and inorganic mercury, and partial elimination of both compounds are modeled by the conversion rate constant as well as by the individual elimination rate constants. Enterohepatic recirculation is compensated for by the two elimination rate constants and the methylmercury to inorganic mercury conversion rate constant. Absorption and recirculation are fast when compared to conversion and elimination.

The methylmercury literature is replete with tables and discussion about various tissue ratios as well as tissue-to-blood binding values (Albert et al., 1973; Hollins et al., 1975; Omata et al., 1986). Species comparisons have been made based on some of these ratios with apparent disregard for either speciation of methylmercury to inorganic mercury or time of sampling, both of which affect these ratios. This is despite early recognition that the apparent distribution coefficient of mercury in the brain depended upon the time of sampling and number of doses (Clarkson, 1972). Lind et al. (1988) recognized that the percent of inorganic mercury in the brain increased in monkeys with increased methylmercury exposure time; they also reported that the percent of inorganic mercury in the brain further increased after exposure ceased and clearance time increased. As all of the figures in this article show, the concentration of inorganic mercury in the kidneys and/or brain would cause any ratio involving these tissues to vary with time.

Methylmercury toxicity is associated with concentration of mercury in the brain, but no one knows which form is the most toxic. Acute neurotoxicity is considered to be associated with methylmercury; however, chronic toxicity is perhaps associated with inorganic mercury (Inskip & Piotrowski, 1985). Clarkson (1972) suggested that this potential toxicity is due to the observed latent period for central-nervous-system toxicity from short-chain alkyl mercurials. However, at the time he dismissed this possibility based on rat data taken over a 30-d period. Examination of the rat and/or human simulations in the present work indicates that 30 d is insufficient time to observe the conversion and accumulation. The prolonged high concentration of inorganic mercury in the kidneys can easily supply the lower, but also prolonged, concentrations of inorganic mercury to the brain.

Clarkson et al. (1988) suggested that mercury in the blood was an excellent biomarker for the body burden of methylmercury and probably the brain. This same premise was echoed by Smith and Farris (1996). If methyl-
mercury were the only chemical entity to be considered for toxicity, this simple model might be adequate. However, the continued high concentrations of inorganic mercury in the kidneys and relatively persistent level in the brain make this too simplistic a model to adequately describe the fate of methylmercury in our systems.

Scalp hair appears to be the medium of choice for monitoring human mercury exposure in both the Faroe Island (Myers & Davidson, 1998) and Seychelles Island (Myers et al., 1997) studies. However, the use of the total concentration of mercury in hair as a surrogate for methylmercury, inorganic mercury, or total mercury in the body or specific tissue levels is of questionable validity. Several authors have stated that only small amounts of inorganic mercury are found in the hair (Clarkson, 1997; Farris et al., 1993), while others report higher proportions (Bortoli et al., 1991, 32–43%). Based on human autopsy data, Suzuki et al. (1993) indicated that hair values were a good predictor of specific organ concentrations for total mercury and methylmercury, but of lesser ability for inorganic mercury levels. On the other hand, Nielsen et al. (1994) indicated that neither total mercury in blood or that in hair was a good predictor of body burden or any specific tissue/organ concentration based on their mouse data. Our PBPK model would agree with this latter work that prediction of methylmercury, inorganic mercury, or total mercury levels in the whole body or any specific organ/tissue would be inaccurate based on total blood (or hair) values due to the differing decay characteristics of each chemical in each of the organs/tissues/ fluids. Multiple samples from the same individual over an extended time would be much better and potentially more useful for risk characterization. However, more data are needed to determine if the low concentration of inorganic mercury in the hair is reflective of the blood and/or tissue levels.

Nielsen (1992) stated that the critical concentration of mercury in the blood of humans was ~200 µg/L (0.2 ppm). Berlin (1976) indicated that concentrations of mercury in the brain exceeding 1 ppm were likely to cause toxicity with some neurological signs. Based on the simulation data of Sherlock et al. (1984) illustrated in Figure 11, only methylmercury in the liver approached the 1 ppm level, and the blood level was approaching the critical concentration of 0.2 ppm when exposure ceased. The half-life for methylmercury elimination (based on the simulation from 400 to 600 d) from the plasma and tissues was approximately 53 d, about 69 d for inorganic mercury elimination from the plasma, brain, and kidneys, and 58 d for inorganic mercury decay from the liver. The total mercury in the plasma was eliminated with a half-life of about 55 d. These slight differences in the rate of elimination would eventually result in a dominance of the inorganic mercury form in all tissues.

These differing curves illustrate the problems with using hair or blood total mercury values to predict the body burden or a specific level within any specific tissue. The curvilinear characteristics of the curves for inor-
ganic mercury in the latter stages of this simulation also point out the essential nature of knowing specifically the time of exposure when trying to determine the relative concentrations within the body. The relationship among the various tissues between 100 and 200 d soon after exposure ceases is different from a similar 100-d period around 500 d, especially in relationship to the concentration of inorganic mercury in the kidneys.

CONCLUSIONS

Consistent modeling across species requires a great deal of data. For PBPK modeling of methylmercury, speciation data for extended time are necessary. Without blood and tissue data for both methylmercury and inorganic mercury for sufficient time to access the elimination portion of the curves, modeling just becomes a curve-drawing exercise; that is, many models will fit simple data. Many authors have fit total mercury data to one compartment models; however, this does not depict the true metabolism and distribution fate of this chemical. The speciation of mercury and the significant differences in binding coefficients and rates of elimination of the two forms of mercury provide a simple explanation for the differences noted in these variables when measured as “total” mercury.

The inevitable paucity of human tissue kinetic data makes it necessary to utilize any relevant data that may be useful from alternate sources such as laboratory or domestic animals. All of these, human and nonhuman, have similar anatomical, physiological, and biochemical processes, which often can be interrelated by principles of allometry. A PBPK model using allometry is a potentially useful tool to provide insight and understanding into human toxicokinetics with simulations. These simulations can be tested for validity with available, but limited, human data. The results described appear encouraging concerning the feasibility of this approach in toxicokinetics and risk assessment for methylmercury and inorganic mercury, and other toxic materials.

Simulation can be a powerful and useful tool. PBPK models are complex and the numerous equations may be difficult to visualize. However, with current computers, graphs can readily depict the complexities buried within the mathematics. Some experiments present formidable situations such as the accumulation of a toxicant over a prolonged period of time, as in the rabbit, monkey, and human studies. The data from these, and other, variable dosage experiments are difficult to analyze without a model incorporating such a feature. The fact that these experiments are linked through PBPK model structure to many other data sets is a compelling illustration of the use of the model in comparative toxicokinetics. In the case of the human autopsy data, one can not carry out controlled experiments of such human studies, but simulations provide a plausible picture of the past situation. Using a basic template in a model and program as presented here illustrates the potential of comparative toxicokinetics.
An attempt to validate this PBPK model for the human based on numerous data sets from several species was undertaken. The human model is consistent with the animal model and is supported by human autopsy data. Does this validate the model for humans? Possibly not! However, this model represents a much clearer picture of the fate and distribution of methylmercury and inorganic mercury in humans. It does indicate that future studies in any species must include measurements for both organic and inorganic mercury for extended times to be able to clearly define the disposition of this environmental toxicant.

REFERENCES


