Population Physiologically-Based Pharmacokinetic Modeling for the Human Lactational Transfer of PCB 153 with Consideration of Worldwide Human Biomonitoring Results

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Abbreviations: PBPK, PCBs, EPA, CDC

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ABSTRACT

We developed a physiologically based pharmacokinetic model of PCB 153 in women, and predict its transfer via lactation to infants. The model is the first human, population-scale lactational model for PCB 153. Data in the literature provided estimates for model development and for performance assessment. Physiological parameters were taken from a cohort in Taiwan and from reference values in the literature. We estimated partition coefficients based on chemical structure and the lipid content in various body tissues. Using exposure data in Japan, we predicted acquired body burden of PCB 153 at an average childbearing age of 25 years and compare predictions to measurements from studies in multiple countries. Forward-model predictions agree well with human biomonitoring measurements, as represented by summary statistics and uncertainty estimates. The model successfully describes the range of possible PCB 153 dispositions in maternal milk, suggesting a promising option for back estimating doses for various populations. One example of reverse dosimetry modeling was attempted using our PBPK model for possible exposure scenarios in Canadian Inuits who had the highest level of PCB 153 in their milk in the world.

INTRODUCTION

Prior to the 1970s, polychlorinated biphenyls (PCBs) had been used rather extensively in industries involving the manufacture of transformers, capacitors, and non-carbon copying papers. Despite the subsequent banning of PCBs, due to their chemical stability and lipophilicity, PCBs continued to be an environmental and human health concern through bioaccumulation and biomagnification. As humans are at the top of the food chain, it is not surprising that PCBs are consistently found in a variety of human tissues.

One of the most serious human health concerns from environmental contamination of PCBs is their presence in breast milk. Indeed, PCBs have been detected in milk samples from lactating mothers in the U.S. (Schechter *et al.*, 1998; Greizerstein *et al.*, 1999), Japan (Suzuki *et al.*, 2005; Inoue *et al.*, 2006), Spain (Ramos *et al.*, 1997; Angulo *et al.*, 1999), Taiwan (unpublished data), and all over the world (see Figure 4 and Dewailly *et al.*, 1996; Vartianen *et al.*, 1997; Glynn *et al.*, 2001; Polder *et al.*, 2003). It is a serious human health concern because milk, with its high lipid contents, represents a "concentrated delivery mechanism" of PCBs to infants. Furthermore, a number of human epidemiological and animal experimental studies have established an association between neurodevelopmental and neurobehavioral deficits and PCB exposure (Jacobson *et al.*, 1990; Tilson *et al.*, 1990; Huisman *et al.*, 1995). At the cellular and molecular levels, exposure to PCBs during the developmental stage is known to disrupt thyroid hormone homeostasis and dopamine levels in the brain (Goldey *et al.*, 1995; Seegal *et al.*, 1997).

Given these human biomonitoring levels in breast milk worldwide, how can we effectively utilize such information? In this paper, we present an approach to render such human biomonitoring results useful by using physiologically based pharmacokinetic (PBPK) modeling. We first transformed an earlier PBPK model for lactational transfer of PCB 153 in

mice (Lee *et al.*, 2007) to a PBPK model for a non-pregnant human female at an average child-bearing age of 25 years. We focused on PCB 153 because it is the most prevalent congener of PCBs detected in human tissue, often representing around 27 to 30% of the total detected PCB congeners in human tissues (Kiviranta *et al.*, 2005; Inoue *et al.*, 2006). We then predicted the body burden build up of PCB 153 from birth over a 25-year period based on realistic exposure levels found in foods, as reported for the Japanese population (Akutsu *et al.*, 2005). In doing so, we incorporated all age-related physiological changes during the first 25-year life span of a female person. Next, we transformed the PBPK model to a lactating 25-year old woman by incorporating all the physiological changes related to pregnancy and child birth. Using this model, we predict milk levels of PCB 153 using three sets of values (minimal, median, maximal) for the most sensitive parameters based on actual data reported in the literature. Model predictions of PCB 153 in mother's milk were found to bracket the human biomonitoring data found worldwide. Uncertainties and variability were propogated through the model but parameter estimation was not conducted. We were able to use this PBPK model to carry out reverse dosimetry modeling to suggest possible exposure scenarios leading to the highest concentration of milk level of PCB 153 in the world in Canadian Inuits.

MATERIALS AND METHODS

PBPK Model Development

We developed a PBPK model to predict the concentration of PCB 153 in human milk. It was derived from a model for PCB 153 transfer in pregnant and lactating mice (Lee *et al.* 2006). We limited the complexity of the human PBPK model to a five-compartment model consisting of four well-mixed tissue groups – liver, fat, mammary tissue and rest of the body – and a mixed blood compartment (Figure 1) because available human data did not justify a more refined model, nor needed for population-scale, multi-year model assessments/predictions.

All tissues in the model are flow-limited. PCB 153 is input directly into the liver. Metabolism occurs in the liver with a first-order metabolic coefficient allometrically-extrapolated from the mouse value found in Lee *et al.* (2006). Post-delivery body weight was taken from a study done at Taizhong hospital in Taiwan, which involved determining PCB concentration in milk, cord blood and maternal venous blood, using the mean body weight of 20 subjects. Postpartum weight loss was modeled via formulae from Haiek *et al.* (2000). Physiological parameters for nursing women were taken from Gentry *et al.* (2003), Fisher *et al.* (1997) and Byczkowski *et al.* (1995) (Tables 1 and 2).

Akutsu *et al.* (2005) reported daily intakes of PCB 153 in Japan between 0.00125 to 0.13 µg/kg/hr (median of 0.0068 µg/kg/hr). De Amici *et al.* (2005) and Fisher *et al.* (1997) report milk production rates between 0.0033 to 0.06 l/hr (median of 0.0317 l/hr). We simulated population scale exposure by uniformly sampling from this range in intakes and milk production rates.

Our final model was coded in the statistical software R (www.r-project.org) to facilite the data and statistical analyses.

Calculation of partition coefficients

Partition coefficients (Table 1) were calculated using methods from Parham *et al.* (1997). Parham *et al.* described calculations to determine the adipose:plasma and adipose:blood coefficients for any PCB using the structural properties of that PCB. Coefficients for other tissues were determined by multiplying the adipose:blood coefficient by an adjustment factor related to the lipid composition of the target tissue. Adjustment factors, defined as Ltottissue/Ltotfat where Ltot = fraction of neutral lipids +0.3*fraction of non-neutral lipids in a tissue, were either listed in Parham *et al.* (1997) or calculated from Krishnan *et al.* (2007). The partition coefficient for the Body compartment was the average of the partition coefficients for brain, skin and muscle. The distribution of lipids of mammary tissue was obtained from Sakai *et al.* (1992). The adjustment factor was then calculated for mammary tissue.

Model Simulations to Build Up Body Burden Through Different Developmental Stages and to Incorporate Physiological Changes of Lactating Women

We simulated individuals beginning at age 0. Body weight, blood volume, fat volume and cardiac output were given five different values according to developmental stages: for a female aged 0-1 year, 1-5 year, 5-10 year, 10-15 years and 15+ years. Values were taken from Haddad *et al.* (2001) and from Price *et al.* (2003). Mammary tissue volume was given a very low, estimated value for age less than 13 years – an average value for the onset of puberty – and its final lactational value past age 13. We assumed age 25 as an average childbearing age, and thus lactation begins at this age in the simulations.

The exposure input for our PBPK modeling of a 25-year old woman throughout her life is derived as shown in Figure 2. Akutsu *et al.* (2005) reported that the exposure of

Japanese to PCBs was in the range of 0.7 to 4.4 μg/person/day of which the dominant congener was PCB 153 accounting for 9-15% of total PCBs. Thus, we derived an estimation of 0.063 to 0.66 μg/person/day exposure of PCB 153 in human, as shown in Figure 2. We assume further that this daily dose is divided evenly in the three meals and each meal takes 15 minutes (0.25 hr) to consume. Taking into consideration an average body weight of a 25-year old woman to be 63 kg, we finally derived the body-weight dependent intake rate of PCB 153 to be 0.00125 to 0.013 μg/kg BW/hr (Figure 2).

Uncertainties and variability in our PBPK model for lactational transfer of PCB 153 in women were propagated using Latin Hypercube sampling. No parameter estimation was performed in the model to data comparisons shown in Figures 3-5. Our focus of this work is to observe and comment on the fidelity of a population-scale forward model derived from independent sources of information compared to worldwide measurements of PCB 153.

RESULTS

PBPK Model Simulations of PCB 153 Contents in Serum, Plasma, Whole Blood, and Milk in Comparison With Worldwide Human Biomonitoring Data

Blood and tissue concentrations for a 25-year old woman generated by this model were found to be within ranges found in the literature. Figure 3 shows an example of one of the 1000 individuals simulated. The apparent jaggedness in the curves is caused because body parameters are re-scaled by body weight at the above mentioned times, and when mammary tissue develops. Figure 4 shows adult blood PCB 153 concentrations in various geographic locations in the world compared to simulation values.

Figure 5 shows a histogram of PCB 153 predicted in lactated milk compared to global measurements reported in the literature. The range and spread in the model simulations, caused by uncertainty only in intake and lactation rate, spans the range in the measurements. The mean model prediction, indicated by the open circle within the histogram, also appears to be quite close to many of the means reported in the literature.

Reverse Dosimetry Modeling

Another application of a PBPK model is to reconstruct, from a given tissue level of PCB 153, a possible exposure scenario. By varying or sliding the intake dose – or other relevant physiological parameter – we can obtain the PCB 153 milk concentration of interest. For example a group of Canadian Inuits was found to have a particularly high level of milk PCB 153 (16.59 μg/L) (Griezerstein *et al.*, 1999). In fact, the milk content of PCB 153 among these Canadian Inuits are among the highest in the world (Figure 5). Similarly, the serum PCB 153 concentration of a group of fishermen from the same region is 2457 ng/g lipid (DeWailly *et al.*, 1994), or 14.7 μg/L in their blood if we assume that blood is 0.6% lipid (Sakai *et al.*, 1992). We raised the oral intake dose of PCB 153 of the model until we

obtained mean milk levels and blood levels of PCB 153 close to those reported in Dewailly *et al.*, (1994) (Figure 6). More sophisticated approaches to exposure reconstruction are available (see for example Sohn et al. 2004 and Allen et al. 2007) but where not needed for this work and are beyond the scope of this paper. We were able to postulate an estimate of the daily intake dose of PCB 153 in this particular population: an intake rate of 0.374 µg/hr/kg bw yielded a mean PCB 153 milk concentration of 16.18 µg/L and a blood concentration of 15.7µg/L. Since all other factors were held constant, the postulated dose is a rough estimate. However, this intake rate generates blood and milk levels in the same vicinity as those reported for populations in this region of Canada.

DISCUSSION

Based on actual human exposure data and parameter values reported in the literature, Our PBPK model generates a range of results that encompasses human biomonitoring data of milk content of PCB 153 from all over the world. Therefore, the model has good predictive capability. Human biomonitoring data are increasingly being collected in the U.S., Canada, and other countries in large-scale field studies. These studies are modeled after the efforts of the U. S. Centers for Disease Control and Prevention (CDC), which released its Third National Report on Human Exposure to Environmental Chemicals in the summer of 2005 (CDC, 2005). The Third Report, similar to its two predecessors but with expanded effort, contains biomonitoring data for the U. S. population for 148 environmental chemicals, grouped into 14 classes, over the period 2001-2002. Given so many chemicals are detected in our body at very low levels, an interesting question to ask is "What is the health significance of these chemicals and what can we do about these data? The application of PBPK modeling and reverse dosimetry modeling in the present study may offer a glimpse of the utility of human biomonitoring data collected by CDC and others.

This model was concerned with incorporating as realistic parameters and exposure scenarios as possible. Though simplified from the mouse model (Lee *et al.*, 2006), the most relevant compartments (fat, mammary tissue for lactation, liver for metabolism) are maintained. The first-order rate constant for PCB 153 metabolism was allometrically scaled from the mouse value given in Lee *et al.* (2006) since no literature values for PCB 153 metabolism in humans were found. Oral dose of PCB 153, given as a single daily dose in the literature (Akutsu *et al.*, 2005), was divided into three meals to more accurately represent intake.

Appropriate age-dependent physiological values (body weight, blood volume, fat volume, mammary tissue volume and cardiac output) were used to simulate the period during

which body burden of PCB 153 was acquired. Time intervals of five years were chosen as small enough to convey the changes brought on by growth, but large enough to obtain literature-based values. The exception was mammary tissue volume and growth, for which no accurate values could be found in the literature. Mammary tissue volume was assigned pre- and post-puberty values, with post-puberty values given those of a lactating woman. This parameter is probably subject to a certain inaccuracy since it is unlikely that upon puberty women acquire a mammary tissue volume equal to that observed during lactation. Pregnancy was not modeled separately.

Lactation, in this model, was considered to be a uniform phenomenon for simplicity. Even though the literature suggests that milk production and content varies throughout the day, as well as throughout lactation (Mitoulas *et al.*, 2002), for the purposes of a PBPK model, lactational performance is maintained constant, even over a wide range of maternal states (Butte *et al.*, 2006). Most PBPK lactational models make similar assumptions with regard to the modeling of lactation (Fisher *et al.*, 1997; Gentry *et al.*, 2003, Lee *et al.*, 2006).

A number of data sets were used for validation of this model (Figure 7): a pseudo-time course (from different individuals) from different populations of one country (Inoue *et al.*, 2006), a pseudo-time course from different mothers of one geographical location (Greizerstein *et al.*, 1999, Taizhong hospital data) and actual time courses from individual mothers (Ramos *et al.*, 1996, Abraham *et al.*, 1997, Schechter *et al.*, 1998). Validation data were useful in verifying ranges of values but not necessarily in identifying trends of PCB 153 concentrations in milk. There is no clear trend in either the individual time courses or the population-based pseudo-time courses. This is not wholly unexpected in a population-based study, as values are usually mean values and because such a cohort is subject to great inter- and intra-individual differences. Similarly, mean values and ranges of PCB 153 milk concentrations in different areas of the world are of limited use since diet and physiological

attributes differ throughout these areas and because sample collection times and methods were not controlled. However, they are able to validate the ranges and mean values of our simulation.

The agreement between model predictions and data in Figure 5 helps to support the level of complexity employed in this PBPK model. We condensed the Lee *et al.*, (2006) PBPK model for PCB 153 in mice because the available data to parameterize an equivalent human model were unwarranted. We also felt that they were not needed to make predictions at the global scale. Uncertainties in intake and lactation rates alone are shown to cause model predictions as wide or wider than the range of concentrations reported in the literature. This suggests that the limiting factor in improving the fidelity of the PBPK model lies more on understanding the inputs of the existing model (*e.g.*, intake, lacration) than in increasing the complexity of the model by adding tissue compartments.

While this model is useful in its ability to describe the distribution, absorption, metabolism and elimination of PCB 153 in a nursing woman, it is also useful in its capacity to provide an estimate of intake dose given a certain tissue (or in this case, milk) level of PCB 153. From our model simulation, the PCB level found in the milk of the Canadian Inuits suggests an intake dose almost fifty times higher than the median value of Akutsu *et al.* (2005): 0.374 μg/kg/hr versus 0.0068 μg/kg/hr. This is probably a reflection of a high rate of consumption of fish in the Inuit diet. Similar estimations can be made if other parameters are known for a certain population/individual. Additionally, the model can be expanded to include an infant which simulates absorption, distribution, metabolism and elimination in a nursing child, such as the approach discussed by Clewell and Gearhart (2002). Finally, because this model calculated the partition coefficients for PCB 153 based on structural properties of the PCB, the model can be expanded to other PCBs. Using the formulas described in Parham *et al.*, (1997), partition coefficients can be calculated for any PCB.

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Table 1: Parameters used for lactating mother

Physiological values		
Body weight (kg)	63.9	Taizhong hospital
Body height (cm)	167	Taizhong hospital
Cardiac output fraction	18.0	Byczkowski et al. 1995
Blood volume	35.5*BH+2.278*BW-3382)*0.001/0.6178	Price et al. 2003
Tissue volume fractions of body weight		
VL (Liver)	0.04	Byczkowski et al. 1995
VF (Fat)	0.2	Byczkowski et al. 1995
VMt (Mammary Tissue)	0.02	Gentry et al. 2003
VR (Body)	0.91[a]-(VLC+VFC+VMt)	
Blood flows (fraction of cardiac output)		
QL (Liver)	0.25	Byczkowski et al. 1995
QF (Fat)	0.1	Fisher et al. 1997
QMt (Mammary Tissue)	0.07	Fisher et al.1997
QR (Body)	1-(QL+QF+QMt)	
Milk volume (Vmilk) (L)	0.25	Gentry et al. 2003
Milk production rate, Kmilk (L/hr)	0.0323	Gentry et al. 2003
Metabolic rate for PCB 153 (L/hr)	0.000163	Extrapolated from mouse value
Partition coefficients		
Fat partition coefficient PF	303	Calculated from Parham et al. 1997
Mammary Tissue coeffient PMt	302	Calculated from Parham et al. 1997
Liver partition coefficient PL	17.9	Calculated from Parham et al. 1997
Body (average of partition coefficients for brain, muscle and skin)	16.3	Calculated from Parham et al. 1997

[a] 0.91 is used instead of 1 to take into account parts of the body not included in the model, such as skeleton, hair, etc

Table 2: Parameters used for female age 0-25

Body weight (kg)		
0-1 year	9.8	Haddad et al. 2001
1-5 years	18.8	Haddad et al. 2001
5-10 years	31.9	Haddad et al. 2001
10-15 years	51.5	Haddad et al. 2001
15+ years	54.4	Haddad et al. 2001
Blood volume (L)		
0-1 year	0.3	Haddad et al. 2001
1-5 years	1.33	Haddad et al. 2001
5-10 years	2.49	Haddad et al. 2001
10-15 years	3.0	Estimate
15+ years	4.2	Haddad et al. 2001
Cardiac output (L/hr)		
0-1 year	84	Price et al. 2003
1-5 years	318.6	Price et al. 2003
5-12 years	310.8	Price et al. 2003
12-21 years	385.2	Price et al. 2003
21+ years	439.8	Price et al. 2003
Fat volume fraction[a]		
0-1 year	0.22	Haddad et al. 2001
1-5 years	0.157	Haddad et al. 2001
5-10 years	0.198	Haddad et al. 2001
10-25 years	0.33	Haddad et al. 2001
Mammary Tissue volume		
0-13 years	0.0001	Estimate
13+ years	0.02	Gentry et al. 2003
All other parameters and partition coefficients are the same as those listed in Table 1		

[a] Obtained by dividing adipose tissue weight by age-appropriate body weight

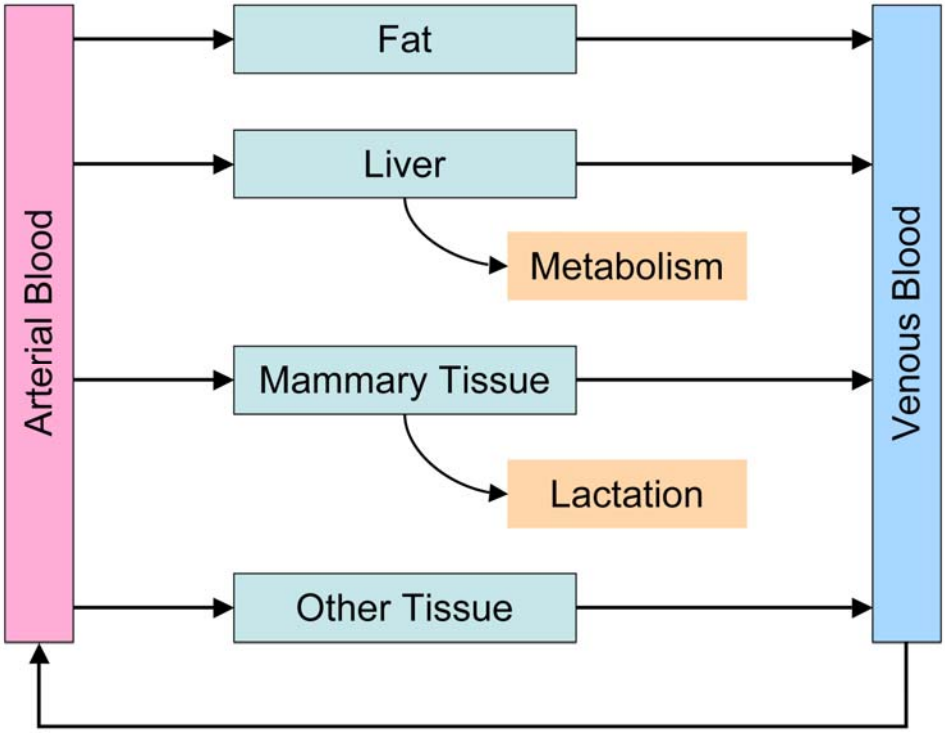


Figure 1: Five-compartment model of PCB153 transfer during lactation.

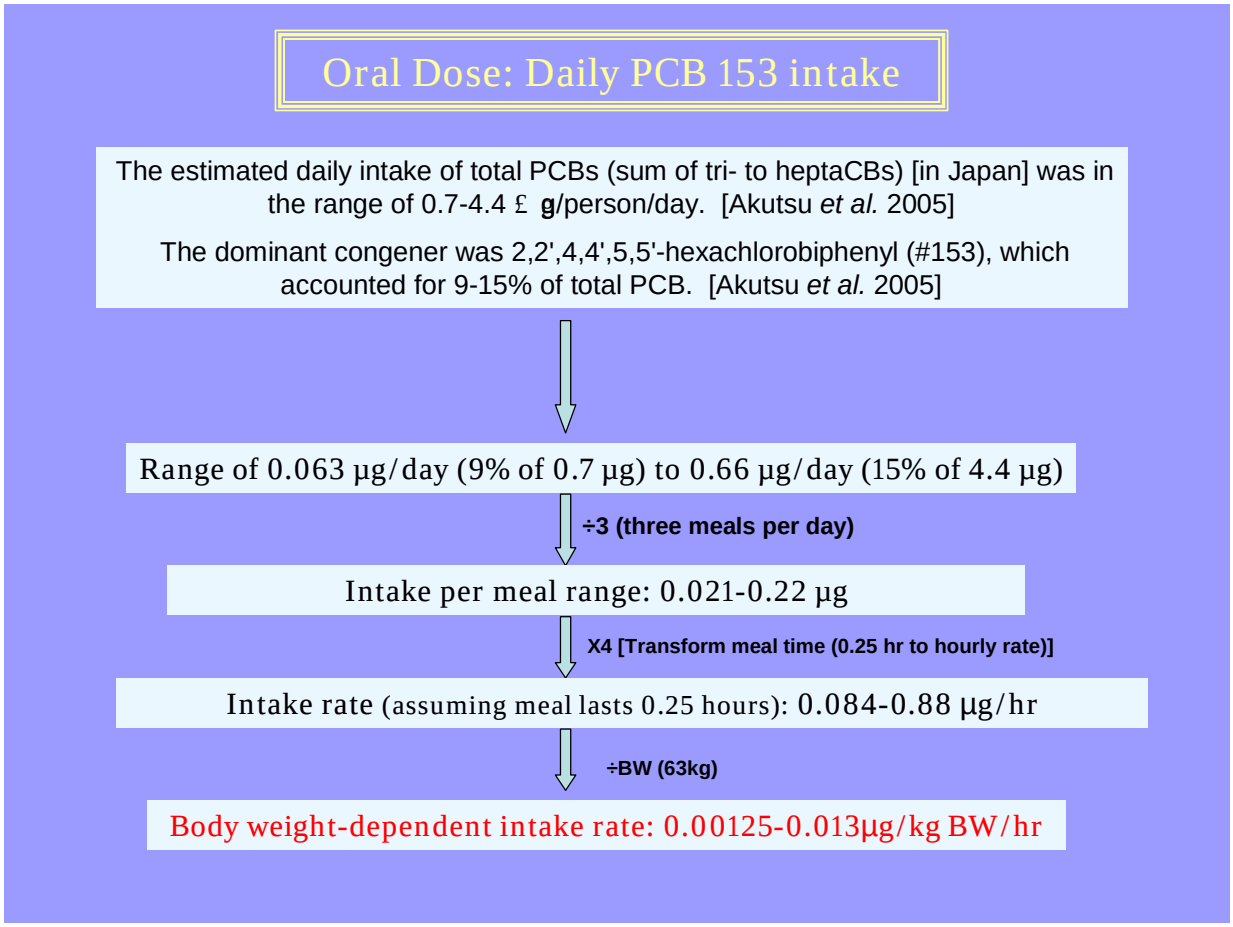


Figure 2. Derivation of input exposure dose for PBPK modeling of loading body burden of PCB 153 in a 25-year old woman.

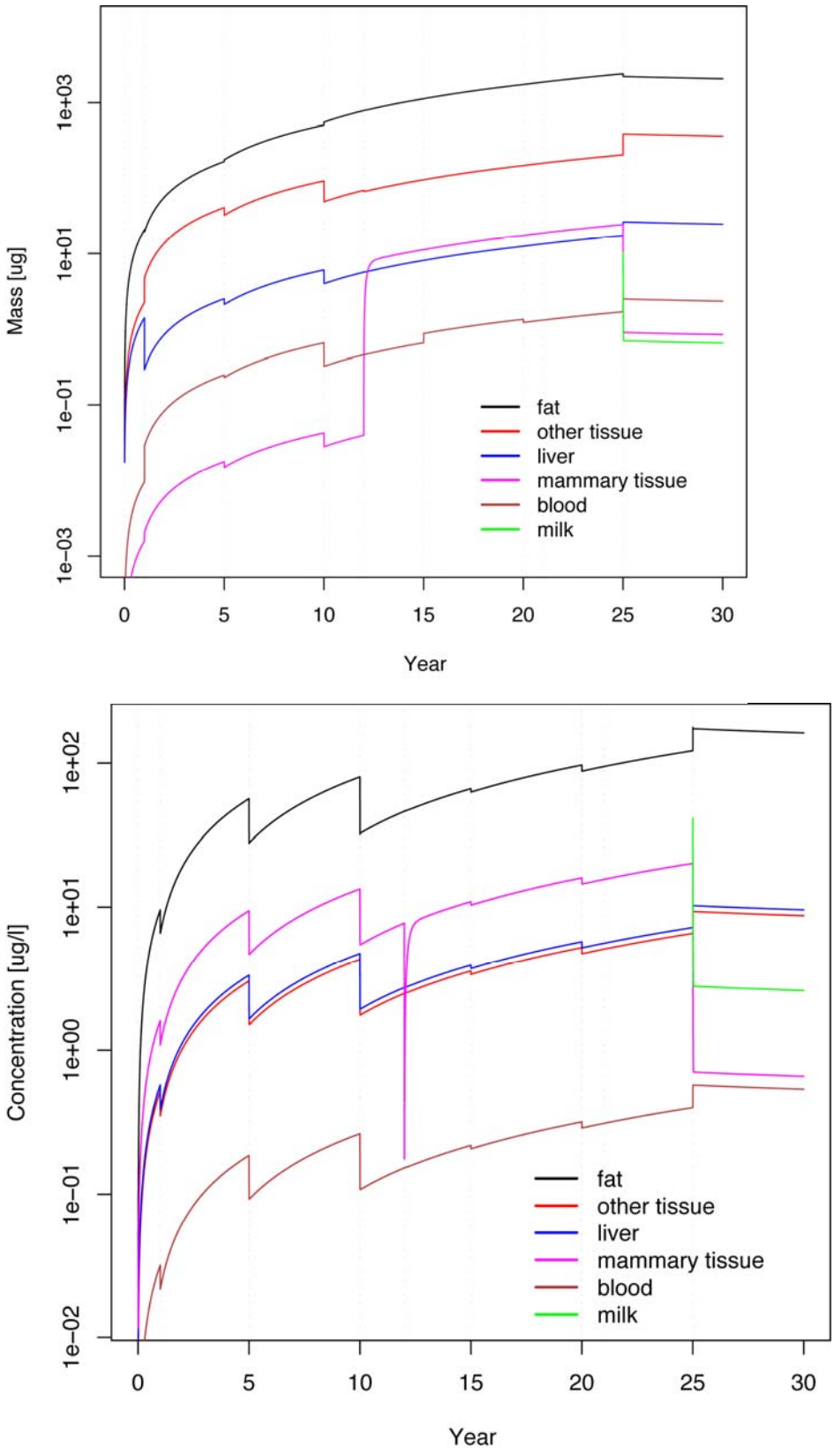
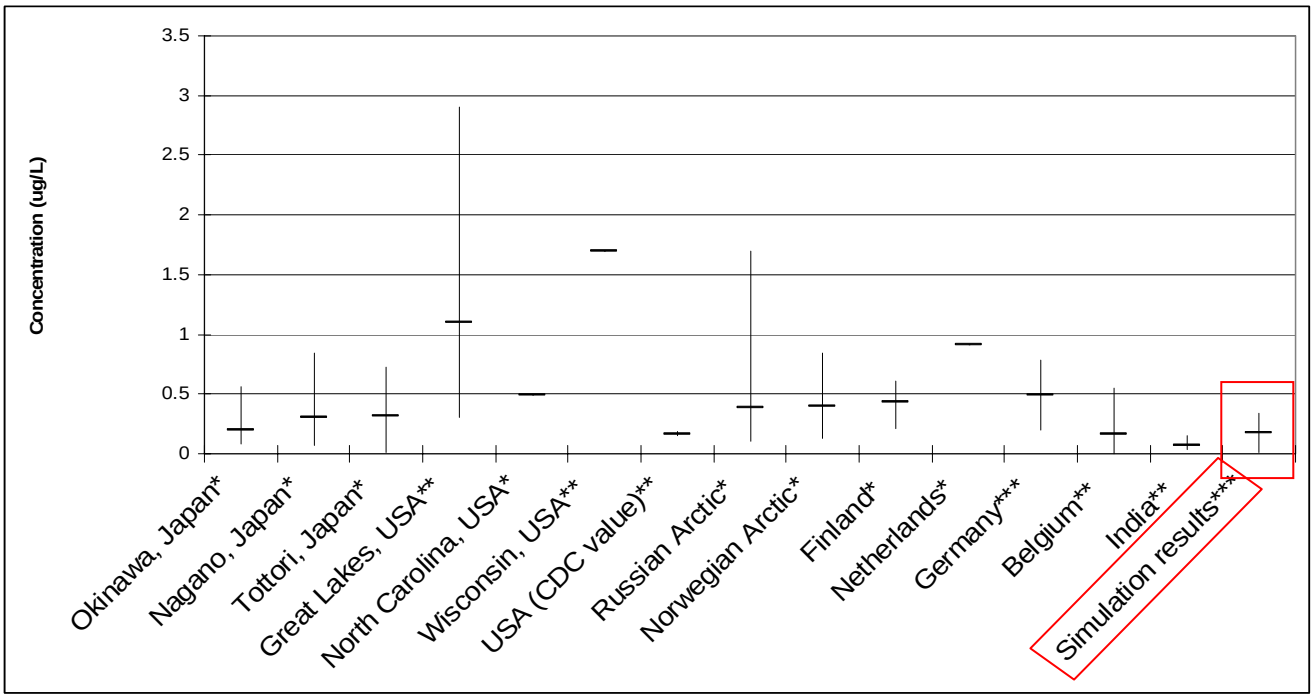


Figure 3: PCB 153 body-burden predictions for one of the 1000 model simulations. Mammary tissue develops at age 13. Lactation begins at age 25.



Belgium : Covaci et al. 2002
India : Rusiecki et al. 2005
All other data taken cited in Minh et al. 2005

Figure 4: Range and mean concentrations of PCB 153 in plasma (*), serum (**) and whole blood (***) of populations from worldwide geographic locations

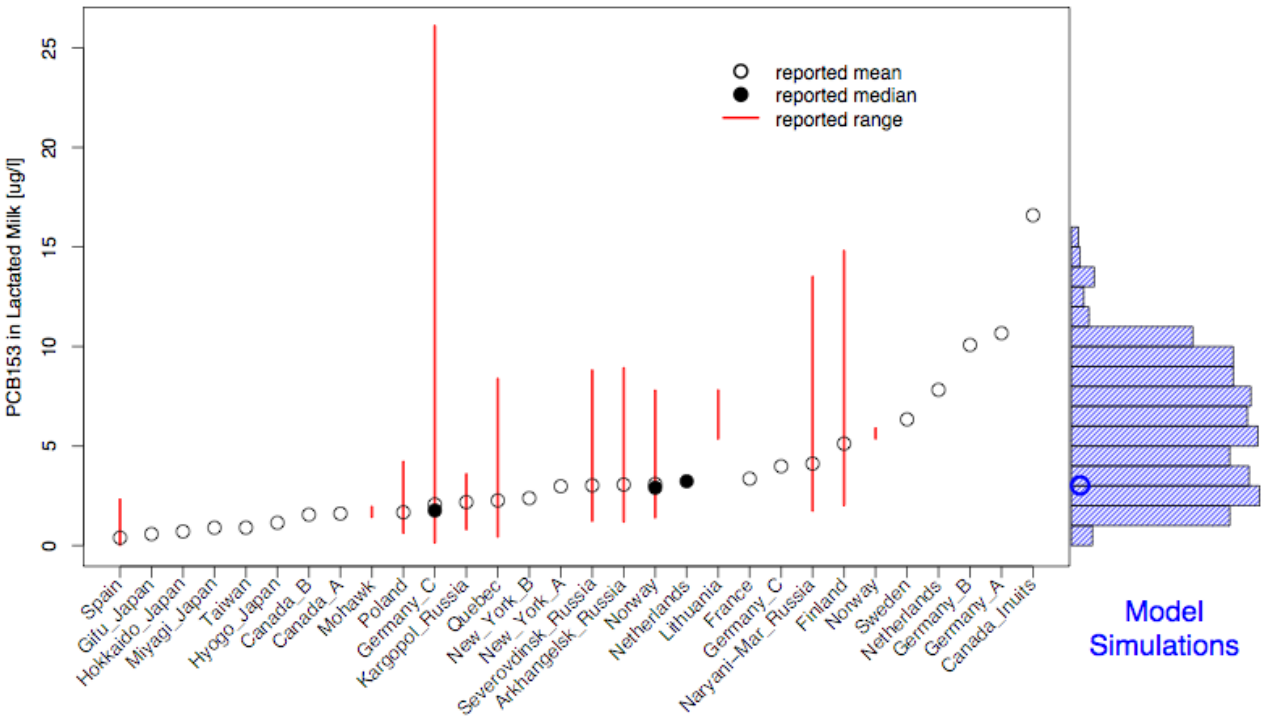


Figure 5: Histogram of model simulations compared to global measurements of PCB 153 in lactated milk. The uncertainty in the model predictions results from uncertainty in the daily PCB 153 intake and in milk lactation rate. The open circle is the mean prediction.

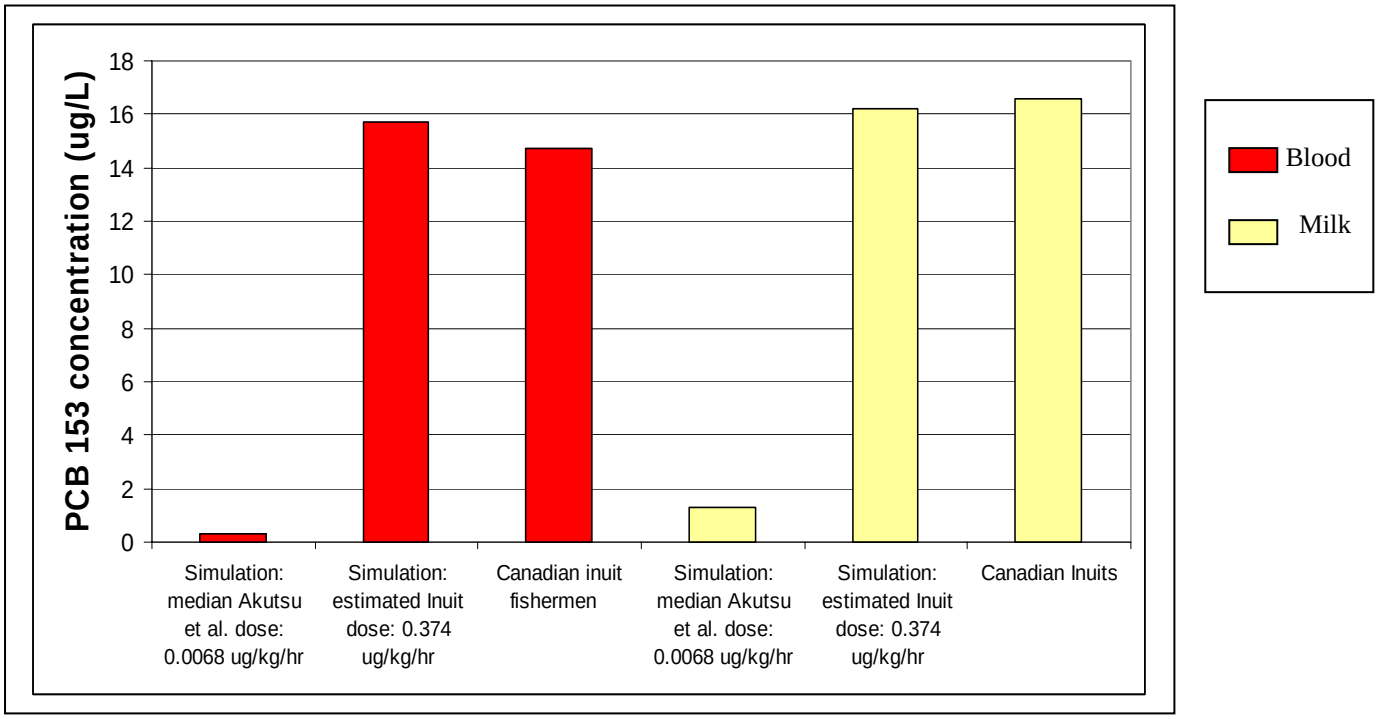


Figure 6: Blood and milk PCB 153 concentrations from Canadian inuit populations compared to simulation PCB 153 milk and blood concentrations generated with varying oral intake dose of PCB 153

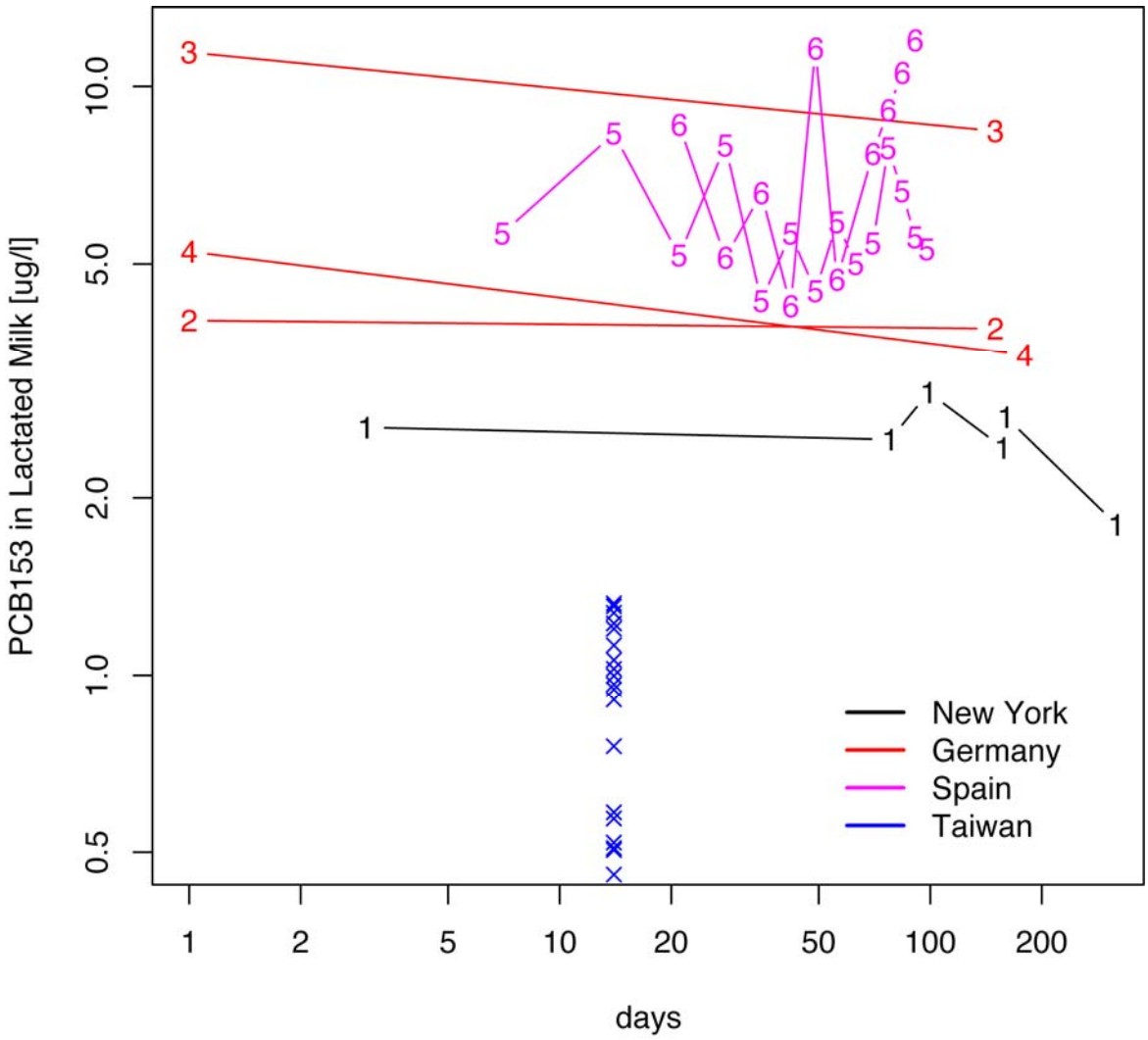


Figure 7: PCB 153 concentrations in milk from mothers reported in the literature