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Application of pharmacokinetic modelling for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin exposure assessment

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Abstract

Polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans, and mono- and non-*ortho* polychlorinated biphenyls (dioxin-like PCBs) are identified as a family or group of organic compounds known as 'dioxins' or dioxin-like chemicals (DLCs). The most toxic member of this group is 2,3,7,8-tetrachlorodibenzo-(*p*)-dioxin (TCDD). Historically, DLCs have caused a variety of negative human health effects, but a disfiguring skin condition known as chloracne is the only health effect reported consistently. As part of translational research to make computerized models accessible to health risk assessors, the Concentration- and Age-Dependent Model (CADM) for TCDD was recoded in the Berkeley Madonna simulation language. The US Agency for Toxic Substances and Disease Registry's computational toxi- cology laboratory used the recoded model to predict TCDD tissue concentrations at different exposure levels. The model simulations successfully reproduced the National Health and Nutrition Examination Survey (NHANES) 2001–2002 TCDD data in age groups from 6 to 60 years and older, as well as in other human datasets. The model also enabled the estimation of lipid-normalized serum TCDD concentrations in breastfed infants. The model performed best for low background exposures over time compared with a high acute poisoning case that could due to the large dose and associated liver toxicity. Hence, this model may be useful for interpreting human biomonitoring data as a part of an overall DLC risk assessment.

Keywords

PBPK; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCDD; dioxins; NHANES

1. Introduction

Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and mono- and non-ortho polychlorinated biphenyls (dioxin-like PCBs) belong to a family of organic compounds called 'dioxins' or dioxin-like chemicals (DLCs) [1–3]. Human environmental exposure to dioxins may occur through several routes, but the majority of total intake

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is through the diet [4]. DLCs are highly lipid-soluble, induce hepatic enzymes that may sequester, are resistant to metabolic degradation, and tend to bioaccumulate.

PCDDs, PCDFs and dioxin-like PCBs elicit the same toxic effects through a common receptor-mediated mechanism of action. These compounds are agonists of the cytoplasmic aryl hydrocarbon receptor (AHR) [5,6], and induce the AHR to lose its chaperone proteins and bind the compounds. Following ligand binding, the AHR translocates to the nucleus and binds to AHR nuclear translocator (ARNT). The AHR–ARNT dimer can activate transcription of target genes coding for xenobiotic-metabolizing enzymes (CYP1A1, CYP1A2, CYP2B1, etc.) or con- trol complex cellular responses such as cell cycle progression and apoptosis. The affinity with which various DLCs bind to the AHR has been used to develop toxicity equivalence factors of TEFs. In general, the higher binding affinity of highly persistent AHR ligands and the sustained activation of the AHR produce overt toxicity [5]. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is considered the most toxic congener of the DLCs because it has the highest binding affinity for the AHR, and is highly persistent and bioaccumulative [3].

Most often, we measure human exposure to DLCs as lipid-normalized serum concentrations in pg/g-lipid or ppt-lipid units. Body burden often is used for risk assessment purposes and can be determined by one of several models [7–18]. We express DLC body burden as ng/kg body weight. In humans, the body burden is estimated either by accounting for the intake rate and the half-life of TCDD, or the lipid adjusted toxicity equivalent (TEQ) concen- tration in serum or adipose tissue [14].

Several pharmacokinetic models, ranging from one compartment to multi-compartments, have been developed to estimate tissue or blood levels of chemicals following exposure to chemicals through environmental media. The human pharmacokinetic (PK) model for TCDD used here is the concentration- and age-dependent model (CADM) developed by Carrier et al. [9,10] and refined by Aylward et al. [7,8].

The US Agency for Toxic Substances and Disease Registry (ATSDR) is developing a physiological-based pharmacokinetic (PBPK) toolkit wherein the best available PBPK/PK models, usually published in a variety of simulation languages, are being recoded in a single language, Berkeley Madonna. Currently this toolkit consists of a series of PBPK/PK models for volatile organic chemicals, metals and other general pollutants [15–18]. This effort focused on adding a TCDD model that best suits ATSDR's needs for interpreting human biomonitoring data to this collection.

The aim of this study was to recode an existing model using Berkeley Madonna software and to assess its predictability. For this we used reported blood and fat-tissue concentrations from several biomonitoring studies to predict doses of internal TCDD from oral intake. This model may be useful in public health risk assessment because it provides age- and gender-related information about TCDD exposures as a function of intake.

2. Methods

2.1. Model structure and physiological parameters

We reviewed previously published human dioxin toxicokinetic models [7–10, 13], selected the CADM, and recoded it using Berkeley Madonna software (version 8.01 for Windows, Kagi Shareware, Berkeley, CA). This model allows simulation of oral exposure, which can be from diet, water and breastfeeding.

Aylward et al. [7,8] modified the structure of the Carrier et al. [9,10] model by adding a term to account for the amount of TCDD eliminated through partitioning from circulating lip- ids across the lumen of the large intestine into the fecal content. The original structure of the model predicting distribution between adipose tissue and hepatic tissue as a Michaelis-Menten type function of body concentration remains unchanged, as does the structure of the model representation of hepatic elimination rate. Figure 1(a,b) illustrates the model structure as mod- ified by Aylward et al. [7,8].

The CADM describes only liver and adipose tissue compartments, and the time unit is months. TCDD distributes relatively slowly throughout the body; hence this relatively long time unit. Additionally, and in contrast to other PBPK models, blood flow is not included explicitly. Partitioning between fat and liver is concentration dependent, and the proportion of the body burden occurring in the liver follows a Michalis-Menten relationship with body bur- den. The Aylward model was fitted to serial serum 2,3,7,8-TCDD sampling data from two Austrian study participants with a mean follow up of 2.7–3 years, and 36 study participants (19 males and 17 females) from Seveso with a mean follow up of 16 years. The Aylward model allows a good prediction of peak historical exposures using current serum 2,3,7,8- TCDD levels. Aylward et al. [8] compared the estimated peak serum 2,3,7,8-TCDD levels for the National Institute of Occupational Safety and Health (NIOSH) cohort and back-extrapo- lated assuming first-order kinetics with a fixed half-life of 7–9 years to peak levels predicted by the modified model. They found that assuming first-order kinetics resulted in an underesti- mation of maximum concentrations by several fold to an order of magnitude.

We took human physiological- and chemical-specific parameters describing the absorption, distribution, and blood and tissue partitioning of TCDD from the literature (Table 1). We obtained body weight (BW) data from McDowell et al. [19] (see in the supplementary material which is available via the multimedia link on the online article webpage). We calculated percentiles of BW and body mass index (BMI) at an age range from 1 month to 75 years from the arithmetic mean and arithmetic standard deviation assuming a lognormal distribution to avoid negative numbers. We used a logistic equation to model both BW and BMI as a function of age at the 5th, 10th, 15th, 25th, 50th, 75th, 85th, 90th and 95th percentiles.

$$\text{BW or BMI} = \frac{P1e^{P_2\partial t + P_3 P}}{1 + e^{P_4 + P_5 t}} \quad (1)$$

where BW = body weight, BMI = body mass index and P_i = parameters to be estimated.

In turn, we modeled parameters of Equation (1) as polynomial functions of percentile. We used a correlation coefficient of 0.86 to correlate BW and BMI percentiles [20]; we modeled both as percentiles by using percentage points of random normal variables. We calculated adipose weight fraction from BMI [21,22]:

$$\begin{aligned}\text{Males: Wa} &= 1.20\text{BMI} - 0.23T - 16.2\\ \text{Females: Wa} &= 1.20\text{BMI} - 0.23T - 5.4\end{aligned} \quad (2)$$

where Wa = adipose weight fraction, BMI = body mass index and T = age in years (2)

We calculated liver weight fraction from BW [22,23], assuming that liver density was that of water (1 kg/L).

$$\text{Liver volume (L)} = 0.05012\text{BW}^{0.78} \quad (3)$$

2.2. Model evaluation

We validated the recoded model by comparing simulations with other published model simu- lations and to human datasets [7,12,24–26]. We validated the model using data for four expo- sure scenarios: background; high; breastfeeding; and general US population.

We used data concerning liver and adipose tissue concentrations from the published literature and ran simulations using the recoded model to estimate the TCDD intake for various exposure scenarios [12,27,28]. We calculated the liver concentration in ng/kg wet weight and the fat concentration in ng/kg lipid weight. The adipose compartment in our recoded model is non-contiguous and represents fat all over the body, including blood lipids. Background doses of TCDD were 0.001–0.006 ng/day; these background data are within the range in published literature [29]. Similarly, the model was used to simulate liver concentration in humans aged from birth to 70 years [25]. Evaluation data from the case of Victor Yushchenko, who was exposed to high concentrations of dioxin, were used to simulate serum lipid TCDD levels [26]. Yushchenko most likely consumed 8 mg (equivalent to 275,000 ng/day) of TCDD in food.

For breastfeeding, adipose and liver concentrations were modeled for 12 months using infant intake of TCDD from breast milk as a polynomial based on published data [24]. Absorption during breastfeeding was reduced because studies indicate that TCDD is excreted in infant stools [30].

2.3. Model application

Serum TCDD levels for general US populations corresponding to National Health and Nutrition Examination Survey (NHANES) 2001–2002 were obtained from Ferriby et al. [31]. We used the recoded model to estimate the intake that could produce the NHANES data. For this simulation, we estimated the average intake for the various age groups for

NHANES 2001–2002. We used statistical and Monte Carlo methods to estimate model parameters and to characterize uncertainty in the model predictions.

The US Centers for Disease Control and Prevention (CDC) conducts NHANES to provide a representative sample of the civilian non-institutionalized US population (NHANES information is available at http//www.cdc.gov/nchs/nhanes.htm) [32]. NHANES uses a stratified, multistage, probability cluster design to gather questionnaire data about demographics, health- related behaviors, physical exam measurements, and medical, nutritional and environmental testing on blood and urine specimens. The levels of select chlorinated dibenzo-*p*-dioxins (CDD) congeners were measured in blood samples collected as part of the NHANES (levels of 1,2,3,4,6,7,8-HpCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, OCDD, 1,2,3,7,8-PeCDD and 2,3,7,8-TCDD for the survey periods 1999–2000, 2001–2002, and 2003–2004 are presented in the latest National Report on Human Exposures to Environmental Chemicals [32]).

Patterson et al. [33,34] reported the toxic equivalents (TEQs) for dioxin-like compounds (CDDs), chlorinated dibenzofurans (CDFs), coplanar polychlorinated biphenyls (PCBs) and mono-*ortho*-substituted PCBs for survey periods 2001–2002 and 2003–2004. The blood TEQs of adults for the 2003–2004 monitoring period appear to be lower than those levels in 2001–2002.

LaKind et al. [35] examined the temporal changes in serum CDD/CDF in adults for NHANES survey periods 1999–2000, 2001–2002, and 2003–2004 and found no significant change in median (50th percentile) serum CDD/CDF levels from 1999–2000 to 2001–2002; however, serum CDD/CDF concentrations decreased significantly in the 2003–2004 survey period. When grouped by age, the participants' CDD/CDF levels decreased by 56% and 38% in the groups aged 12–19 years and 20–39 years, respectively, for the 2003–2004 survey per- iod compared with the 1999–2000 survey period. Participants' CDD/CDF levels decreased slightly and non-significantly (6%) in the group aged 40–59 years, and increased slightly (13%) in the group aged 60 years and older.

3. Results and discussion

The CADM originally developed by Carrier et al. [9,10] and modified by Aylward et al. [7,8] was successfully recoded in Berkeley Madonna. The recoded model was evaluated in several steps: background, high- and low-level dioxin exposures [7,12,24–27,36].

3.1. Modelling background exposures

First, we used human background exposure data for dioxin [12,25,27,28,36] to evaluate our model performance. The model provided a good fit for the data for continuous exposure duration in humans from birth to age 75 years, at background levels of 0.003 ng TCDD/day (Figure 2). Figure 3 shows measured and modeled liver concentration at specific dioxin exposure levels [25,27,28]. The lines show the TCDD median intake of 2.5 pg/day and the 10th and 90th percentile intakes of 0.5 and 6 pg/day, respectively, based on dietary intake in the Japanese population [29]. These data simulations from Japan show that the model

performs well for both datasets and predicts reasonably well the concentrations in liver and adipose tissues.

3.2. Modelling high exposures of Viktor Yushchenko

Dioxin is extremely poisonous and degrades very slowly. In the case of the Ukrainian president, Viktor Yushchenko, who presented to the University of Geneva Hospital with severe chloracne, Sorg et al. [26] traced the mechanisms by which dioxin is broken down and excreted by the human body. The researchers discovered in this case that the digestive tract was the main path of excretion, which was the same mechanism that dominated in animal studies. They also reported a significantly shorter elimination half-life of approximately 16 months, which was significantly less than the previously observed 5–10 years. The large amount of dioxin given to Yushchenko probably damaged the liver, caused acute liver failure, and altered significantly the disposition of dioxin to tissues and resulted in increased fecal concentrations.

The model performance of high-exposure dioxin levels was evaluated using poisoning data [26]. The model over-predicted the adipose concentrations in Yushchenko. The bolus dose of TCDD may have caused induction of enzymes that metabolized dioxin-like chemi- cals, which was not described in the model, and likely caused the model's over-prediction. In fact, both Lambert et al. [37] and Abraham et al. [38] have shown a relationship between the rate of caffeine metabolism, which measures CYP1A2 activity, and serum dioxin concentrations.

We curve fitted the hepatic elimination rate (k_e) variable (Figure 4) using mathematical optimization at Berkeley Madonna; the theoretical decay curve of dioxin for persons not at health risk is shown by the dotted line. The model predicts TCDD serum lipids levels much better using a k_e of 0.074 per month. This value is well within the range (0.04–1.00 per year) observed in humans [5]. This finding shows that the model performance is reasonably good for simulation and prediction of high-level exposures of dioxin.

3.3. Modelling exposures from breastfeeding

Dioxin and DLCs are lipophilic and resistant to metabolic degradation, and have a tendency to bioaccumulate. Because of the high fat content in human milk, dioxins preferentially distribute in breast milk [39,40]. Risk assessments for dioxins and DLCs in breast milk alone and in a mixture with other pollutants such as heavy metals and pesticides have been conducted [41,42]. Several studies in the late 1990s attempted to link background exposure to dioxins and adverse health effects in breastfed infants. Limited data exist regarding childhood susceptibility to DLCs [40].

Because breast milk is high in fat, some breastfed infants could receive a relatively high dose of DLCs [24,29,43,44]. The model performance was evaluated using breastfeeding data from 15 German infants; infant intake of TCDD from breast milk was modeled as a polynomial based on data in Kerger et al [24]. Absorption during breastfeeding was reduced, which is consistent with published findings [30] showing relatively high TCDD levels in infants' stools; however, absorption could have been reduced because of the high fat content of breast milk. Two datasets, liver and adipose concentrations, were obtained from Kreuzer et al. [43] and Abraham et al. [30]. These results show that the recoded model performed well

to esti- mate the internal dose for a variety of breastfeeding periods (Figure 5). That breastfeeding provides the developing infant the benefits of balanced nutrition and passive immunity against microbial infections is widely recognized. The benefits of breastfeeding outweigh the possibility that these chemicals may affect children's health or development [40].

3.4. Monte Carlo simulation of human variation in intake and pharmacokinetics and comparison with NHANES data

Human biological monitoring (biomonitoring) can be the most reliable exposure assessment method because it provides an estimate of the internal or absorbed dose of a chemical by inte- grating exposure from all routes [45]. Numerous programs, recent and ongoing, exist to evaluate environmental exposure of humans to chemicals. These programs include the Expert Team to Support Biomonitoring in Europe [46], the Consortium to Perform Human Biomonitoring on a European Scale [47], the US CDC NHANES, and the Canadian Health Measures Survey [48].

We used the elimination factor (per year), the ranges and medians from 39 persons repre- senting the medians, the 1st and 99.9th percentiles of two triangular distributions (one for males and one for females), and three values from the Vienna patients to obtain a population distribution for k_e [7]. We divided these 39 individual values by 12 to express them on a monthly basis. We best fitted the resulting bootstrapped values by a lognormal distribution with a geometric mean of 0.046 and a geometric standard deviation of 2.14.

We used the adipose clearance factor data (per year) on intake and fecal excretion of lipo- philic chemicals in 23 persons to obtain a distribution for k_a [49–51]. We divided these 23 individual values by 12 to express them on a monthly rather than a yearly basis, and fitted them to a lognormal distribution with a geometric mean of 0.0028 and a geometric standard deviation of 2.307. From various studies, we obtained the half maximal concentration for dis- tribution to liver or adipose tissue (ng/kg) and data on human liver and fat concentrations to obtain a distribution for K [9,10,28,36]. We best fitted these 35 values by a normal distribu- tion with a mean of 80.1 and a standard deviation of 18.9. We obtained BW data from McDowell et al. [19]. The adipose weight fraction was calculated from BMI [21,22] and the liver weight fraction was calculated from BW [22,23].

We run the recoded model to estimate the intakes that could produce the NHANES 2001–2002 reported serum levels. Of importance, intake estimates of TCDD and other persistent organic pollutants (POPs) have changed over the course of the 20th century. Ritter et al. [52,53] built these changes into their models. Lorber [11] and van der Molen et al. [13] pre- sented quantitative estimates of these data. We digitally extracted the NHANES 2001–2002 data from Figure 1 of Ferriby et al. [31], and corrected it to represent TCDD only by multiplying the TEQ results by the age-dependent percentages in Table 3 of Ferriby et al. [31]. We applied a natural logarithmic transformation to the dose concentrations. We set up the model to choose a single dose value to represent the lifetime average dose for a person; this is, of course, an oversimplification. Depending on dietary changes, TCDD intake changes day to day. After multiple model simulations, we estimated a daily TCDD intake range of 0.00001–0.0014 ng/kg/day. Based on NHANES TCDD serum tissue biomonitoring

data, the population can be grouped into three categories: low, medium and high exposure. In persons with high TCDD serum tissue concentrations, exposures were likely close to the ATSDR MRL of 0.001 ng/kg/day [39,40].

Figure 6 shows the estimated serum TCDD concentrations (dots) in sampled individuals in NHANES 2001–2002 and the lines representing the lifetime concentration versus time profiles for selected model simulations based on a range of average lifetime TCDD exposure levels (0.0001–0.0014 ng/kg-day), and the variation of other model parameters using Monte Carlo method.

The model could predict that the concentrations of serum dioxins increased with age. These increases are most likely the result of higher environmental dioxin levels in past expo- sure than in recent exposure, the number of years of past exposure, and slower elimination among older persons. The model can be used to predict the differences in serum dioxin concentrations by sex that may be due to differences in elimination between males and females. The elimination of TCDD in our recode model is dose-dependent because there is a dose-dependent sequestration of TCDD in the liver. Different approaches have been proposed to describe the dose-dependent induction of TCDD elimination because the biological bases of this process are poorly understood. These uncertainties compel consideration when apply- ing these pharmacokinetic models to human epidemiological studies.

4. Conclusions

Our laboratory is developing a toolkit, a library containing a series of models in a single sim- ulation language (Berkeley Madonna) to evaluate the toxicity of common environmental pol- lutants found at hazardous waste sites [15–18]. This paper demonstrates the application of the Aylward recoded model for TCDD. It can be used to delineate subgroups and populations at special risk, adequately predict data available from several studies in the literature, and predict exposures based on NHANES data. This model is a useful addition to our library, because TCDD is found at waste site, and risk assessors need such a tool to evaluate its toxicity.

We selected the Aylward model because it is a simple pharmacokinetic model that can be used as a prototype for other POPs apart from modelling the pharmacokinetic behavior of TCDD. The modelling applications presented in this paper clearly indicate that the assump- tion of simple first-order elimination kinetics is not valid for human dose estimations back-extrapolated over long periods and for elevated body burdens [7,8]. This recoded model can be used to evaluate its exposures under a variety of exposure scenarios. As is true for every pharmacokinetic model, it can be refined and improved. Furthermore, the model could be generalized for other DLCs using chemical-specific information. A more advanced series of models, the PBPK models are also being developed that, apart from the PK characteristics, consider and, when possible, incorporate anatomical and physiological features such as blood flows and distribution volume [55,56]. These models are increasingly being used in risk assessment as in the case of the reanalysis of dioxin toxicity by the US Environmental Protec- tion Agency (EPA) [57].

These kinds of models are designed and developed to help risk assessors evaluate chemi- cal threats. We believe increased application of such models and interaction between the developers and users will enhance awareness of the model advantages and limitations and, in turn, their acceptance in human health and environmental risk assessment. Computational tox- icology has the potential to contribute to future toxicological testing strategies and become an integral part of the risk assessment process [58–60]. Two major areas of computational toxi- cology exist: one that deals with model development and the other that addresses the shift to use alternative animal methods in response to the National Research Council (NRC) report, *Toxicity Testing in the 21st Century* [54]. Practitioners in the laboratory and in the field should be trained in these areas so that appropriate advances are made in data collection so that risk assessors keep pace with changing science and use the innovative information in rational decision making.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

A toxicokinetic model for predicting the tissue distribution of TCDD in humans was recoded on Berkeley Madonna software based on Aylward et al. [7, 8].

Method auto

Start time = 0; beginning of simulation stop time = 900; months

dtmin = 0.0002; minimum and initial step size dtmax = 0.1; maximum step size

tolerance = 1e-06; error tolerance for stiff solver dtout = 1; communication interval

;Dose

dose = 0.001; ng/d

added = 0.0;; additional dose

start_added = 0.0;; start of additional dosing stop_added = 0.0;; stop additional dosing

; PK parms

f_min = 0.01; minimum hepatic fraction f_max = 0.7; maximum hepatic fraction

ke_adult = 0.05; hepatic elimination rate constant per month ke_infant = 0.141; hepatic elimination in infants

K_half = 100; half maximal affinity for liver sequestration ka = 0.0025; adipose clearance factor

wa = 0.25; adipose fraction wh = 0.03; hepatic fraction

cb_init = 0.025; initial body concentration absorb = 0.97; absorption

;Breastfeeding

Breastfeed = 0; 0 = no, 1 = yes

; Body Weight parms p1 = 82.999

p2 = −3.869E-05 p3 = 1.5165E-08 p4 = 2.32

p5 = −0.0187

;Time

years = time/12

; Body weight eq

BW = p1*exp(p2*(time+1+p3))/(1+exp(p4+p5*(time+1)))

BW_old = IF (time>0) THEN p1*exp(p2*(time+p3))/(1+exp(p4+p5*time)) ELSE 7.427

; Intake eq - breast feeding from polynomial fit to data in Table 1 of Kerger et al 2007 intake = if (time<12 and Breastfeed = 1) then

0.352*(−0.00113*time^4 + 0.031516*time^3 −0.2861*time^;2 +0.7433*time+1.8951)/BW else if (time>start_added and time<stop_added) then

(dose+added)*30*absorb/BW

else dose*30*absorb/BW; ng/kg/mo absorbed

; Model

hfactor = f_min + ((f_max-f_min)*Cbody)/(K_half+Cbody)

hepatic_change = ke * Cbody * (f_min+((f_max-f_min)*Cbody)/(K_half+Cbody))
adipose_change = ka * Ca*wa

BW_change = (Cbody/BW)*(BW - BW_old) ke = if (time<12) then ke_infant else ke_adult
INIT Cbody = cb_init

d/dt(Cbody) = intake - hepatic_change - adipose_change - BW_change

Ch = (Cbody/wh) * (f_min + (((f_max - f_min)*Cbody)/(K_half+Cbody))) Ca = (Cbody/wa) * (1-(f_min+((f_max-f_min)*Cbody)/(K_half+Cbody)))

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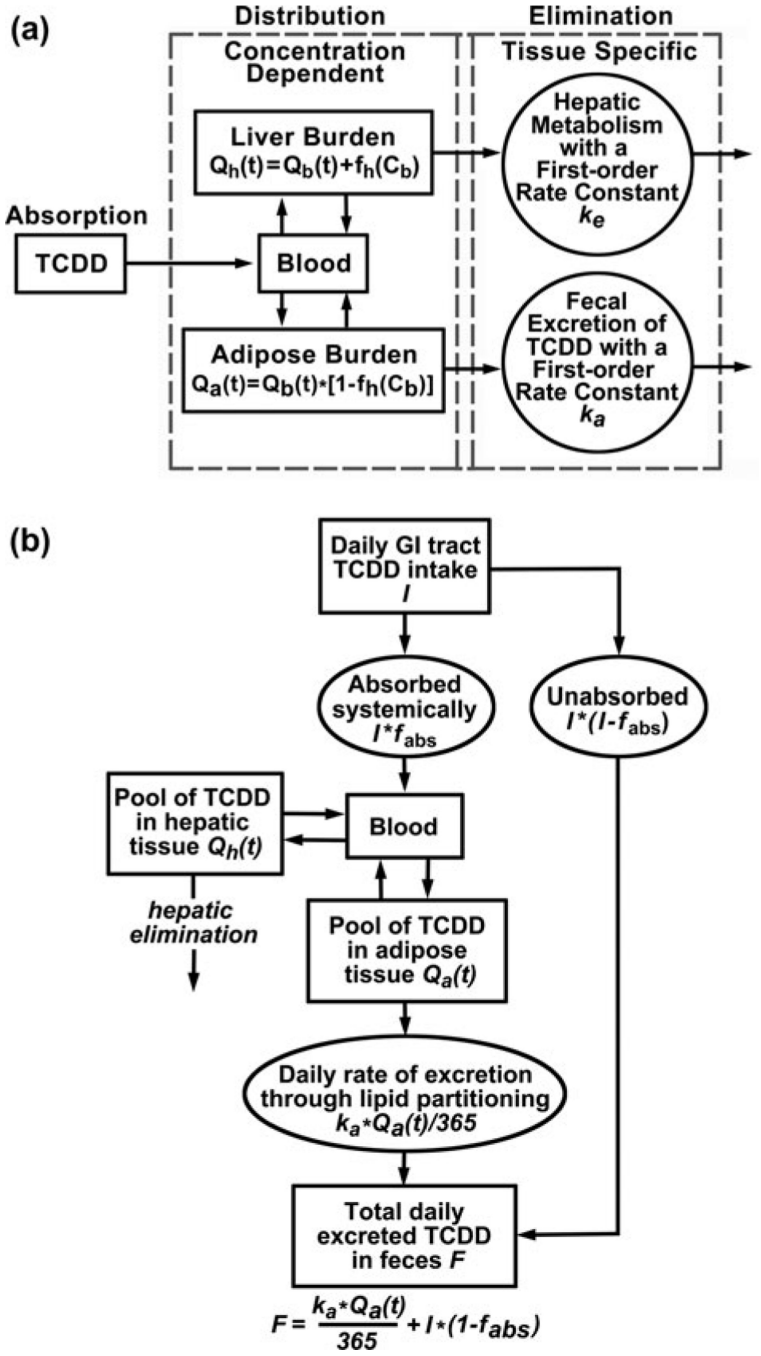

Figure 1.

(a,b) Schematic of the CADM structure. GI = gastrointestinal. Reproduced from Aylward et al., 2005. *Risk Analysis* 25 (4), 945–956 and Aylward et al., 2005. *Journal of Exposure Analysis and Environmental Epidemiology* 15, 51–65.

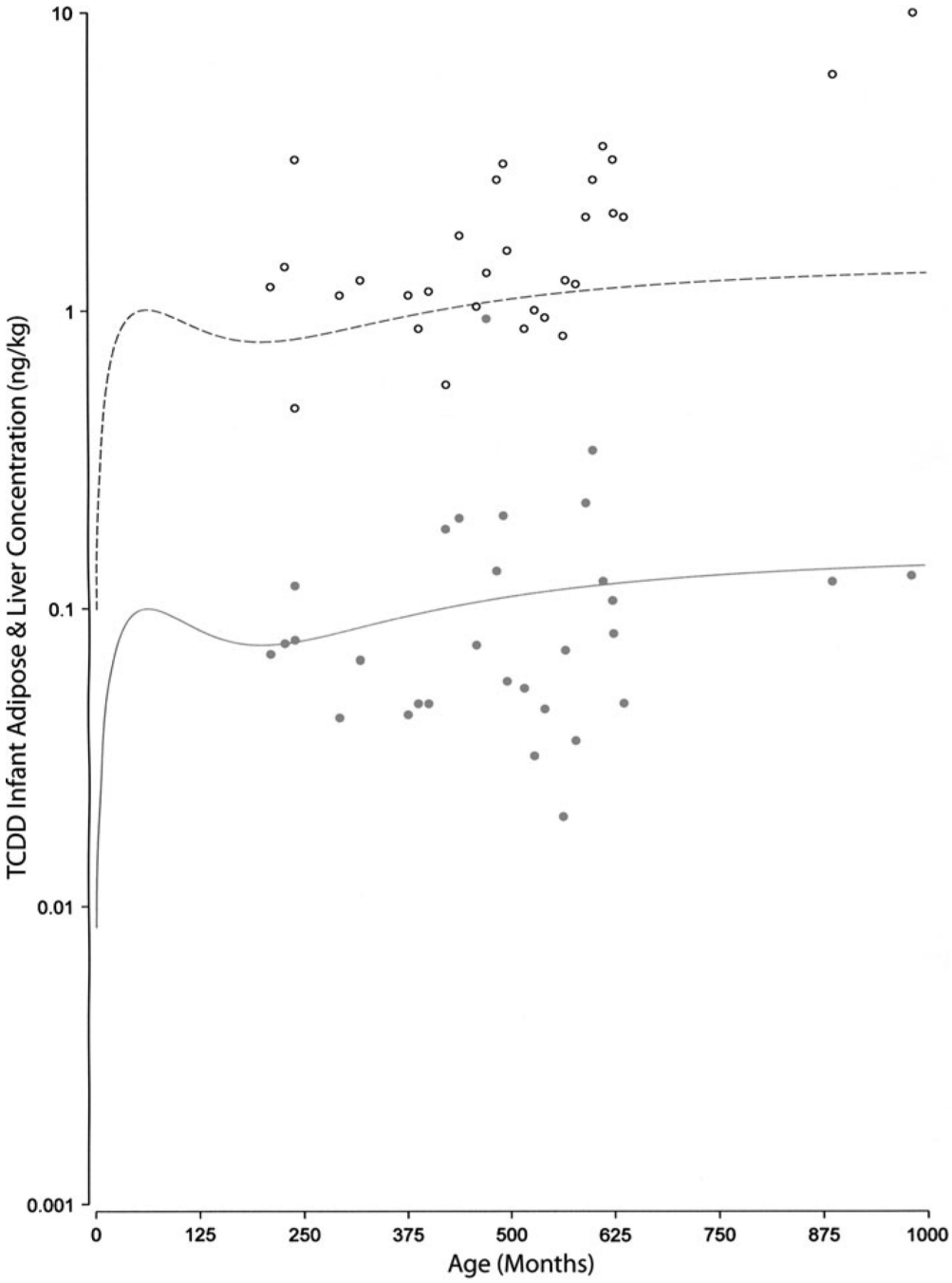

Figure 2.

Concentration of TCDD in liver (grey circles) and adipose tissue (black circles) as a function of time. The lines show model results of 0.003 ng/day. The dashed line is for adipose tissue concentration and the solid line is for liver tissue concentration (ng/kg).

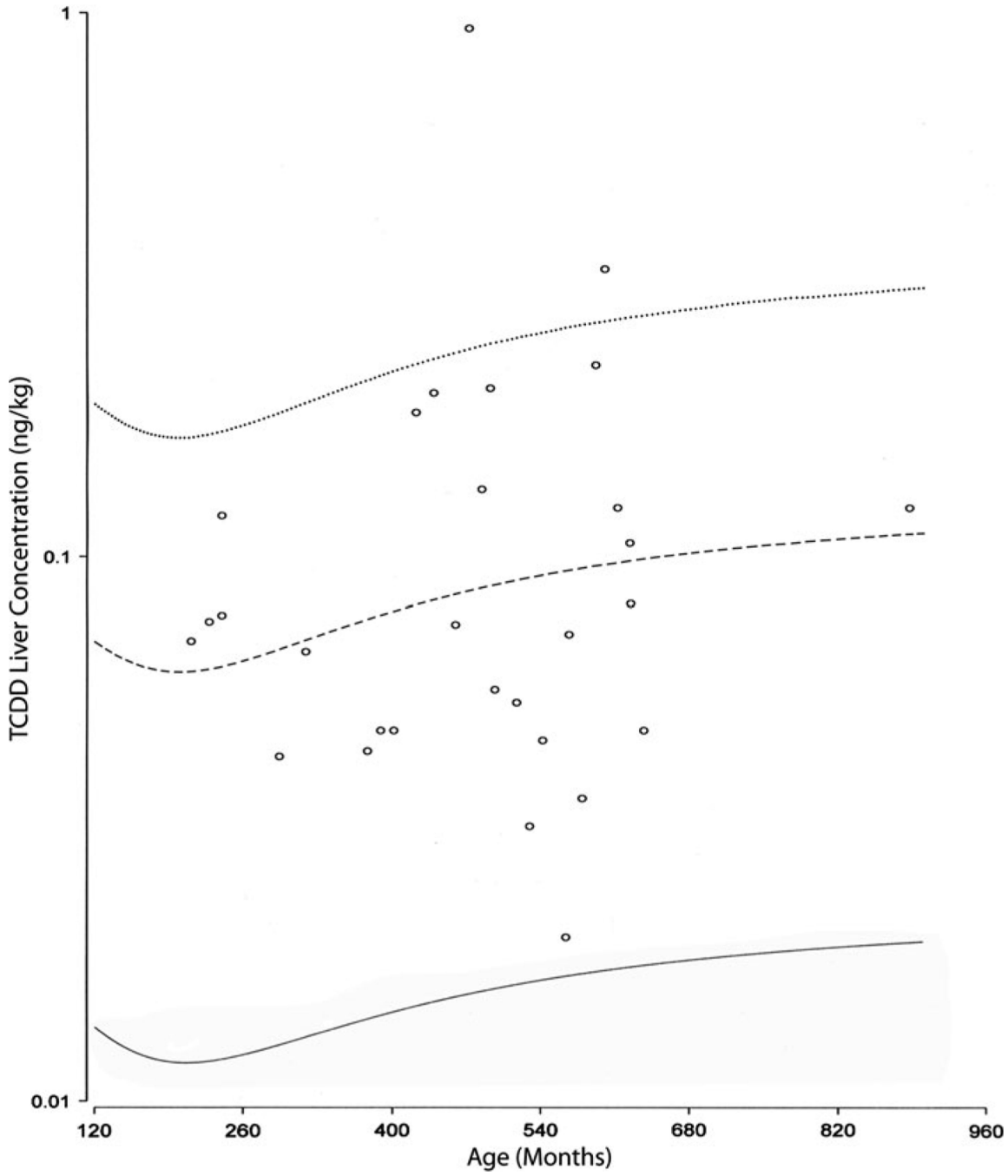

Figure 3.

Modelled and measured liver concentrations from background exposures to TCDD. The lines represent model results from exposure to 0.0005 (10th percentile, solid line), 0.0025 (median, dashed line), and 0.006 ng TCDD/d (90th percentile, dotted line).

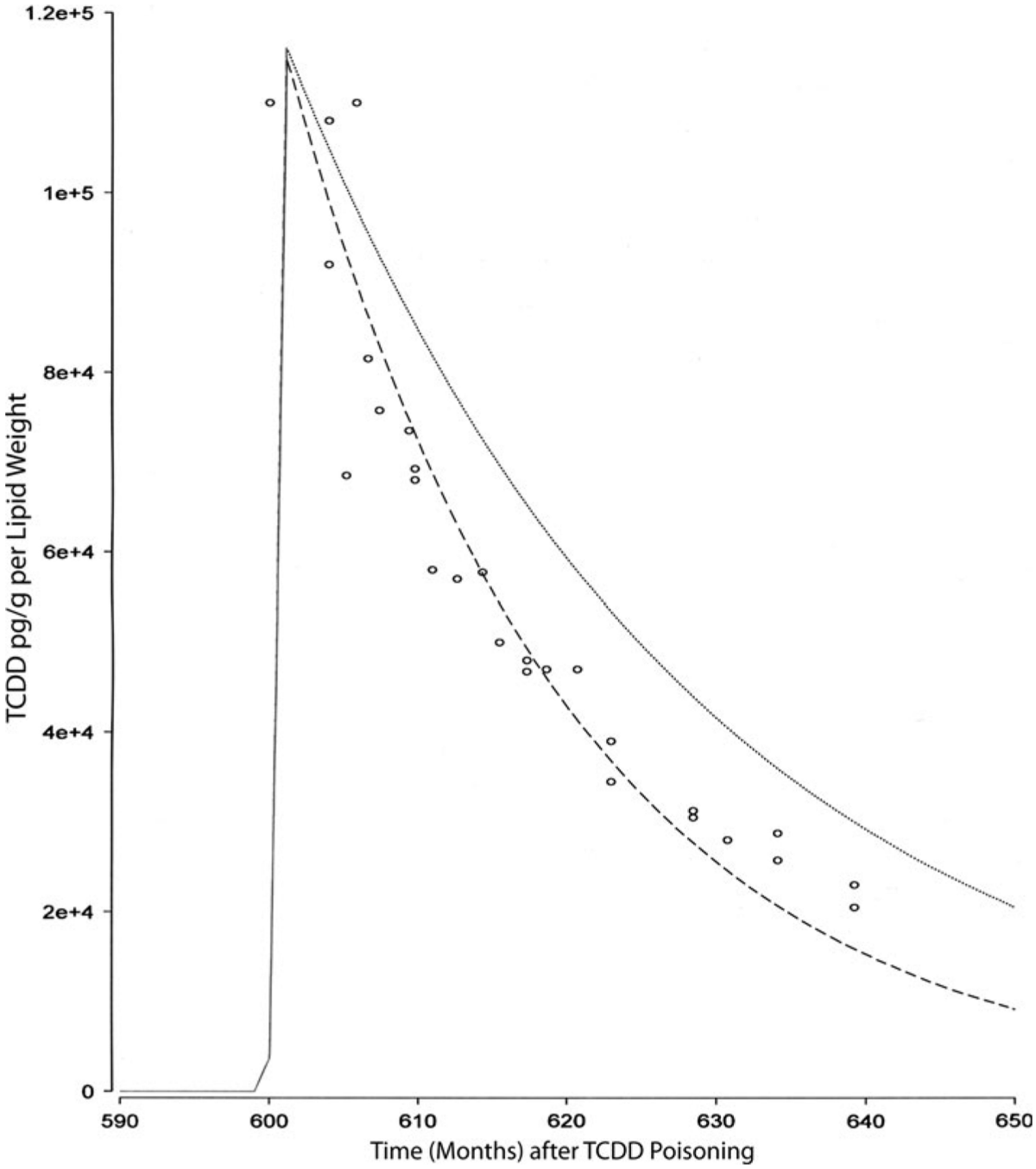

Figure 4.

After mathematical optimization of the hepatic elimination rate (k_e = 0.074 per month), the model simulation predicts the TCDD lipid-normalized concentration (dashed line). The solid line represents the expected decay curve for persons not at risk of TCDD exposure.

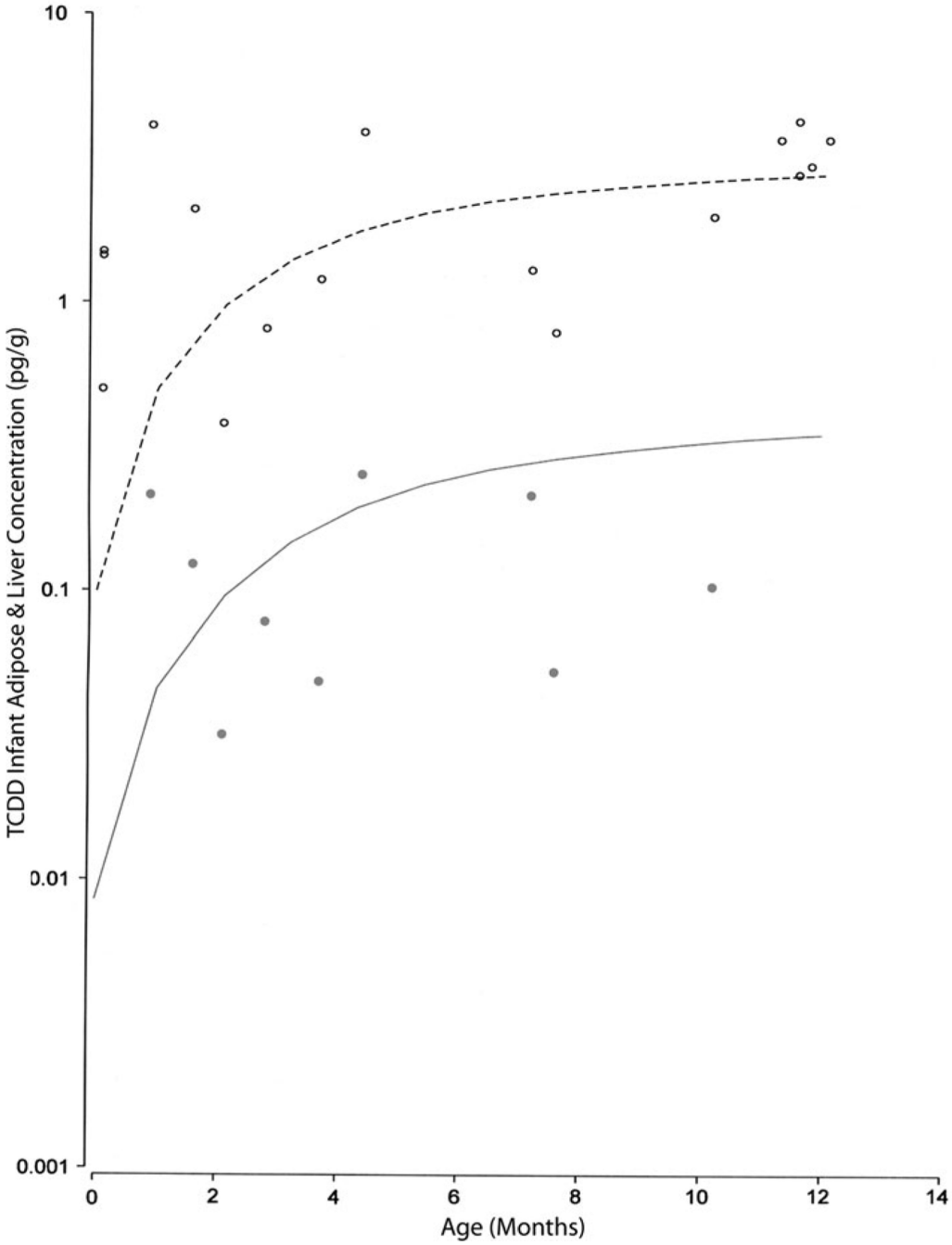

Figure 5.
Concentrations of dioxin in breastfed infants. The lines show model results of liver (dashed line) and adipose (solid line) data.

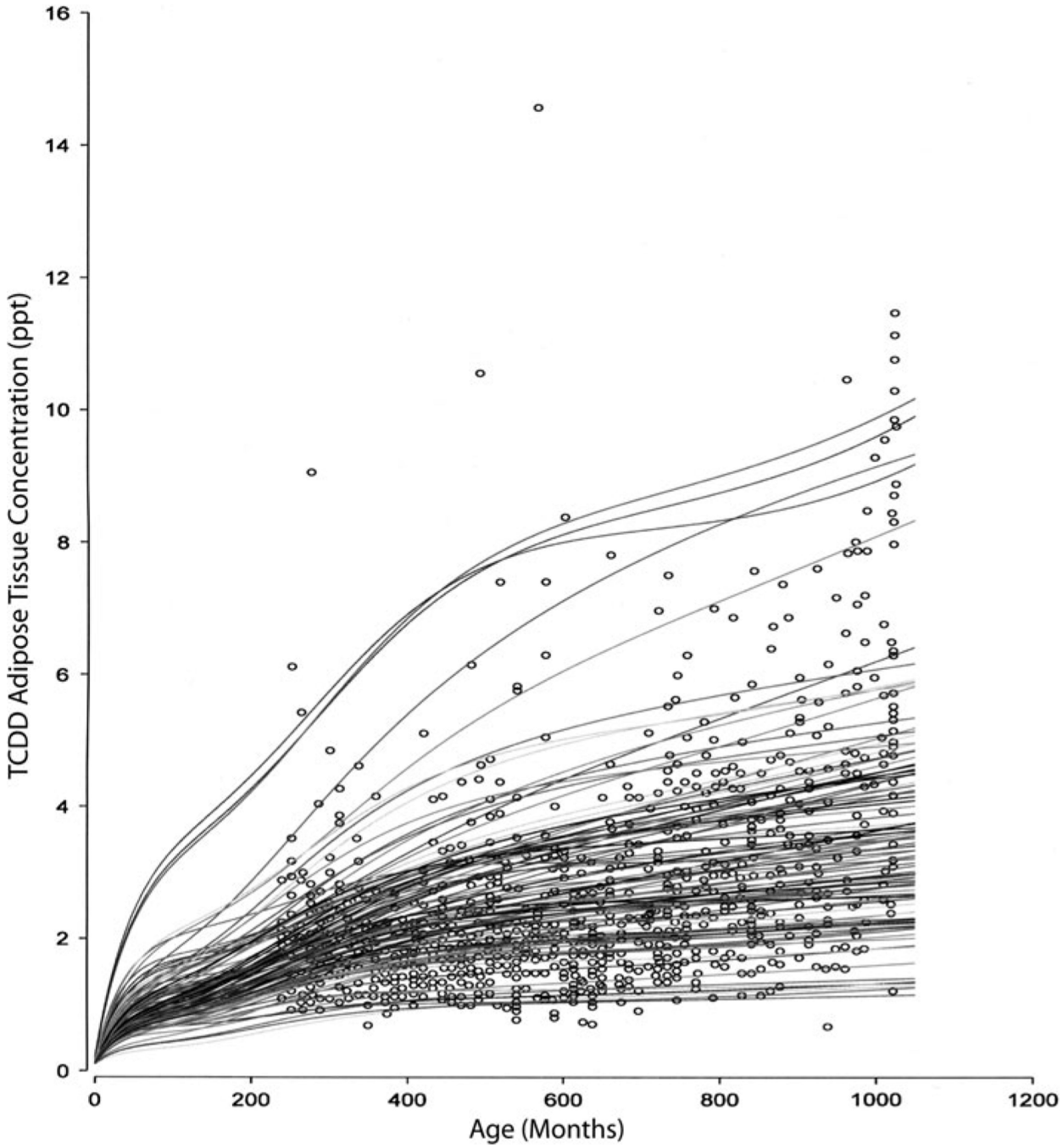

Figure 6.

Estimated serum TCDD concentrations in sampled individuals in NHANES 2001–2002 (dots, see text for basis of TCDD concentration estimation) and lines representing the lifetime concentration versus time profiles for selected model simulations based on a range of average lifetime TCDD exposure levels (0.0001–0.0014 ng/kg-day) and variation of other model parameters in the Monte Carlo exercise.

Table 1.

Model parameters, definitions and values.

Model parameter	Description, units	Value
$f_{h\,min}$	Minimum proportion of body burden distributed to liver, unitless	0.01
$f_{h\,max}$	Maximum proportion of body burden distributed to liver, unitless	0.7
K	Body concentration for half-maximum increase in liver distribution proportion, ng/kg	100
k_a	Rate constant for elimination based on partitioning from circulating lipids into large intestine, per year	0.0025
k_e	Rate constant for hepatic elimination, per year (adult)	0.05
k_e	Rate constant for hepatic elimination, per year (infant)	0.141
w_a	Fraction body weight adipose/lipid tissue	0.25
w_h	Fraction body weight liver	0.03

Source: Carrier et al. [9,10].