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TRANSLATIONAL RESEARCH TO DEVELOP A HUMAN PBPK MODELS TOOL KIT—VOLATILE ORGANIC COMPOUNDS (VOCS)

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Abstract

Toxicity and exposure evaluations remain the two of the key components of human health assessment. While improvement in exposure assessment relies on a better understanding of human behavior patterns, toxicity assessment still relies to a great extent on animal toxicity testing and human epidemiological studies. Recent advances in computer modeling of the dose-response relationship and distribution of xenobiotics in humans to important target tissues have advanced our abilities to assess toxicity. In particular, physiologically based pharmacokinetic (PBPK) models are among the tools than can enhance toxicity assessment accuracy. Many PBPK models are available to the health assessor, but most are so difficult to use that health assessors rarely use them. To encourage their use these models need to have transparent and user-friendly formats. To this end the Agency for Toxic Substances and Disease Registry (ATSDR) is using translational research to increase PBPK model accessibility, understandability, and use in the site-specific health assessment arena. The agency has initiated development of a human PBPK tool-kit for certain high priority pollutants. The tool kit comprises a series of suitable models. The models are recoded in a single computer simulation language and evaluated for use by health assessors. While not necessarily being state-of-the-art code for each chemical, the models will be sufficiently accurate to use for screening purposes. This article presents a generic, seven-compartment PBPK model for six priority volatile organic compounds (VOCs): benzene (BEN), carbon tetrachloride (CCl_4), dichloromethane (DCM), perchloroethylene (PCE), trichloroethylene (TCE), and vinyl chloride (VC). Limited comparisons of the generic and original model predictions to published kinetic data were conducted. A goodness of fit was determined by calculating the means of the sum of the squared differences (MSSDs) for simulation vs. experimental kinetic data using the

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generic and original models. Using simplified solvent exposure assumptions for oral ingestion and inhalation, steady-state blood concentrations of each solvent were simulated for exposures equivalent to the ATSDR Minimal Risk Levels (MRLs). The predicted blood levels were then compared to those reported in the National Health and Nutrition Examination Survey (NHANES). With the notable exception of BEN, simulations of combined oral and inhalation MRLs using our generic VOC model yielded blood concentrations well above those reported for the 95th percentile blood concentrations for the U.S. populations, suggesting no health concerns. When the PBPK tool kit is fully developed, risk assessors will have a readily accessible tool for evaluating human exposure to a variety of environmental pollutants.

Chemical risk assessments estimate public health consequences from exposure—specifically, exposure to environmental, occupational, or therapeutic chemicals. But chemical risk assessment remains a challenging area of public health and of environmental protection. Nevertheless, Congress has mandated that the Agency for Toxic Substances and Disease Registry (ATSDR) identify significant human exposure levels (SHELs), develop methods to evaluate such exposures, and design strategies to mitigate them.

Over the past two decades, developments in computational capabilities and advances in understanding molecular and cellular mechanisms of toxicity have helped to solve these challenges. These developments have produced new computational approaches, including physiologically based pharmacokinetic (PBPK) modeling. It integrates chemical absorption, distribution, metabolism, and excretion of a chemical or chemicals and converts external exposures into estimates of exposures in blood and tissues, including those that can be associated with known toxicities. PBPK models are designed and developed to support the chemical health assessment process by allowing prediction of internal dose at the blood/tissue/organ level—that is, the quantity of chemical in specific tissues of interest subsequent to exposure (Andersen 1994). The models' strength is in allowing the toxicologist and health assessor to perform interspecies comparisons of internal dose and extrapolation of internal dose for different routes of exposure, and to address uncertainty and variability in risk assessment (Bailer 1997). The models can be employed to calculate tissue levels resulting from complex exposures, allowing the assessor, for example, to effectively evaluate potential toxicity of environmental pollutants through multiple exposure pathways (i.e., assist in aggregate and cumulative risk assessments).

Although a promising methodology, PBPK models have not yet realized their full potential. The published literature contains many PBPK models (Clewell et al. 2005; Fisher et al. 1998; Reddy et al. 2005; Yokley et al. 2006) readily accessible to the health assessor. But the complexity of the multiple simulation languages used by the many different model developers limits acceptance and risk assessment applications of the models. Public health assessors who have limited experience with simulation software require substantial training to run the complex PBPK models. This limitation restricts field application of the models in public health practice. Even experienced PBPK modelers face problems when reconstructing published PBPK models for application due to the lack of key information or equations.

To better serve ATSDR's health assessors and state partners, ATSDR is developing a human PBPK model tool kit to assist with site related health assessment activities. The

kit comprises a series of published models coded in a common simulation language, Berkeley Madonna (Robson and Toscano 2007). Currently, the tool kit includes models at various stages of development for environmental contaminants including volatile organic compounds (VOCs), metals, and persistent organic pollutants. Previously we published work on recoding models for cadmium, mercury, and arsenic where we compared predictions of original and recoded model simulations. We generally obtained good agreement (Ruiz et al. 2010a). We also showed that the cadmium toxicokinetic model could be used to interpret biomonitoring data from the National Health and Nutrition Examination Survey (NHANES). Because cadmium has a long half-life and maintains a steady state in the body, it is particularly suited for comparison to the NHANES data set. In a second paper, we demonstrated the usefulness of this type of translational research activity by evaluating environmental exposures to the elements mercury and arsenic—elements that exhibit more complex pharmacokinetics because of the presence of multiple metabolites (Ruiz et al. 2010c).

ATSDR's goal is to develop a web linkage to a PBPK database where health assessors and other related health workers can easily access many different models for use in assessment activities. This collection will be referred to as the "ATSDR tool kit." This tool kit will assist researchers and risk assessors to assess potential chemical health effects. These models are not intended to be state-of-the-art models with metabolites or the latest version of a PBPK model. They should, however, be sufficiently vetted to allow health assessors to predict the consequences of complex exposures in terms of internal doses and their health implications. The models, including a basic training module, will be freely available on the Computational Toxicology and Methods Development Laboratory webpage upon the project's completion. Specifically, ATSDR staff will be provided initial training in the advantages and limitations of the models available in the human PBPK tool kit.

We present here progress toward the development of a generic PBPK model for six VOCs: benzene (BEN), carbon tetrachloride (CCl_4), dichloromethane (DCM), perchloroethylene (PCE), trichloroethylene (TCE), and vinyl chloride (VC). These VOCs are well-studied environmental contaminants predominately used as industrial solvents, degreasers, and refrigerants, or are industrial by-products. Potential toxicity associated with environmental exposures to these solvents is probably caused by short-lived or long-lived metabolites of the solvents. Some metabolites are common by-products of more than one solvent (Clewell et al. 2000; Dobrev et al. 2002; Fisher et al. 1998). The solvent model we have developed describe only the dosimetry of the parent chemical and are most useful for evaluating internal solvent exposure relative to environmental guidelines for solvent exposure. Communities in the vicinity of waste sites are potentially exposed to these contaminants by inhalation, ingestion, and/or dermal absorption. In this article dermal exposure was not evaluated as a route of exposure because dermal MRL values were not available for these VOCs.

Health concerns for solvents stem mostly from animal and human studies conducted at high levels of exposure relative to environmental exposures. Uncertainty factors are used to derive acceptable levels of environmental exposures. BEN causes acute myeloid leukemia. BEN affects tissues that form blood cells, marrow, and the immune system (ATSDR 2007). CCl_4 exposure can cause hepatotoxicity, hemorrhagic congestion, edema, and dyspepsia (ATSDR

2005). Exposure to DCM can result in central nervous system dysfunction, respiratory distress, and reproductive toxicity including infertility (ATSDR 2000). PCE exposure is associated with increased risk for kidney, bladder, and cervical cancer (ATSDR 1997a). Exposure to TCE can cause neurological toxicity and liver and kidney damage (ATSDR 1997b). VC exposure can lead to narcotic effects, Raynaud's phenomenon, acroosteolysis, hepatocellular alterations, and brain tumors (ATSDR 2006). Thus, as a group, these diverse VOCs are important environmental toxicants. Use or production regularly introduces these VOCs into the environment, where they may contaminate groundwater, surface water, drinking water, air, and soil at hazardous waste sites (HWS). Communities in the vicinity of waste sites are potentially exposed to these contaminants by inhalation, ingestion, and/or dermal absorption.

METHODS

We first conducted a review of the literature to identify available human PBPK models for the six VOCs of interest. The PBPK models varied in their complexity. They contained different numbers of compartments (e.g., liver, kidney, and other organs), different metabolites, and were developed using different simulation languages, such as MatLab, Simusolve, and AcslX. Model selection was based in part on the number of data sets used to calibrate and evaluate the model, the model's maturity (number of predecessor models from which the model was derived), and the experience of the authors. We derived our generic VOC solvent model from the following sources: BEN (Yokley et al. 2006); CCl_4 (Thrall et al. 2000); DCM (David et al. 2006); PCE (Covington et al. 2007); TCE (Fisher et al.1998); and VC (Clewell et al. 2001). Only parent compound data sets and accompanying simulations were extracted from figures using *Grab It! XP2*, an Excel macro (Datatrend Software, Raleigh, NC). Original model simulations for metabolites and metabolite data were not included in this version of the solvent tool-kit development. However, including metabolites is a critical future improvement for use of the PBPK models in dose-response assessments, when toxicity is mediated by metabolite formation.

Model Structure and Physiological Parameters

We constructed a seven-compartment generic VOC model with blood, fat, skin, kidney, and liver, rapidly and slowly perfused tissue compartments, and a gas exchange compartment (Figure 1). We selected these compartments based on their use in previously published PBPK models for VOCs. Elimination and absorption were accounted for by incorporating a gas exchange and a skin compartment accounting for portal of entry and loss of the VOC from the body (not implemented in this article); the liver for metabolism, including first-pass metabolism after oral intake; the fat as a reservoir; the kidney as a possible target organ and potential excretory organ; and distribution to the remaining tissues was grouped based on rates of blood perfusion, to maintain mass balance. All compartments were described as well mixed and flow limited.

Human physiological parameters (Table 1) were taken from the literature (Brown et al. 1997; Clewell et al. 2000; 2005; Corley et al. 2000; Covington et al. 2007; Cowles et al. 1971; Fisher et al. 1998). Tissue volumes were scaled linearly with body weight and alveolar

ventilation (QPC, L/h/kg$^{0.75}$) and cardiac output (QCC, L/h/kg$^{0.75}$). The maximum rate of metabolism (VMaxC, L/h/kg$^{0.75}$) was allometrically adjusted to body weight.

This model code allowed simulation of three routes of exposure, either individually or simultaneously: inhalation, oral ingestion, and dermal absorption. However, comparison of the generic model predictions to data was only assessed against the published human data sets for inhalation. For exposure by oral ingestion, VOC absorption from drinking water was described as direct uptake into the liver compartment during 4 discrete drinking events spaced evenly throughout each 24-h day. For the dermal route of exposure, intake was calculated for the VOC dissolved in water. The transfer rate into and out of the skin was based on the concentration of the VOC in water, the permeability of the skin to a particular VOC (K_P), and the skin to water partition coefficient. Dermal exposure was turned off for simulations presented in this article. For each exposure route, a pulse (square-wave) function was used to simulate repeat dosing. Clearance of the VOC from the body occurred by metabolism and exhalation. All model simulations were conducted using Berkeley Madonna (Berkeley, CA). The model code is shown in the appendix; the Berkeley Madonna mmd files are available from ATSDR on request.

Biochemical Parameters

Table 2 shows chemical-specific model parameters (Brown et al. 1998; Clewell et al. 2001; 2005; Covington et al. 2007; David et al. 2006; Delic et al. 2000; Fisher et al. 1997; 1998; Poet et al. 2000; 2002; Reitz et al. 1996; Thomas et al. 1996; Thrall et al. 2000; Yokley et al. 2006). Skin:blood partition coefficients are reported for TCE (Poet et al. 2000) and PCE (Poet et al. 2002), while other skin:blood partition coefficient values for other solvents were set to the TCE value. To describe dermal uptake of other VOCs dissolved in water, we would need estimates of skin:water partition coefficients and Kp (permeability constant) values. We report these constant values for TCE in this article. Dermal exposure route is available in the model, but lack of chemical-specific parameters and human pharmacokinetic data for this route of exposure is a major challenge for many of the VOCs. Several approaches such as quantitative structure–activity relationship (QSAR) have been used to fill this data gap and could be employed with these models to estimate the dermal contribution to solvent exposure.

Model Comparison

Assessment of the applicability of our generic VOCs PBPK model was first performed by comparison of the published human kinetic data for each VOC and the corresponding published model predictions. To further insure the reliability of our generic VOC model, area under the concentration curve (AUC) for blood or exhaled breath was calculated for each VOC using both our generic VOC model and the original model. Predicted AUC values in blood or breath for each VOC were then compared with the data derived AUC values (using the trapezoidal rule) in blood or breath. For each VOC, the fit was expressed as a ratio (AUC_r) that equaled the AUC value for the published model or for our generic VOC model divided by the AUC value computed from the kinetic data. We recognize shortcomings in using data-derived AUC values, which may be either inflate or deflate the probable AUC values, depending on the quality of the data. Nevertheless, our interpretation of the AUC

ratios was that the closer the value was to 1, the better was the agreement between measured and model prediction.

For each kinetic time-course data set we also calculated the mean of the sum of the squared differences (MSSDs) between model prediction and observation. We computed MSSD by squaring the difference between a measured data point and the value of the simulation at the corresponding time. We summed these squares and then divided the sum by the number of data points. The MSSD was thus determined for both the published model and for our generic VOCs model. One interpretation is that the lower the MSSD value, the better the fit. However, the absolute values of the data can skew the results; thus, professional judgment is considered important in deciding the quality of the fits between model prediction and observation.

Model Applications

We used our VOCs PBPK model to simulate various Minimal Risk Levels (MRLs) exposures for each of the VOCs for which biomonitoring data on human blood levels were available from the National Health and Nutrition Examination Survey (NHANES) (Centers for Disease Control and Prevention [CDC] 2009). Simulations were run as a combination of continuous 24-h inhalation and oral ingestion exposures (equally spaced 4 times a day) at the MRLs for acute (14 d), intermediate (365 d), and chronic (>365 d) durations. Steady-state VOC concentrations in venous blood were then compared with NHANES data using these simplified assumptions about exposure frequency and duration. If the measured NHANES blood levels are below those estimated from the simulations, the exposures would be regarded as safe.

RESULTS

Benzene

Figure 2 contains comparative simulations of predicted exhaled breath concentrations following a 4-h, 10-ppm benzene inhalation exposure by both the original model (Yokley et al. 2006) and our generic PBPK VOC model. The results show that our generic PBPK VOC model adequately reproduces the predicted exhaled breath concentrations. The AUC ratio (AUC_r) for exhaled breath concentration of benzene was somewhat less for our generic VOC model (0.9) than for the Yokley model (1.6). The MSSD values were similar for both models (Table 3).

Carbon Tetrachloride

Figure 3 contains comparative simulations of predicted exhaled breath concentrations following a 3-h, 10-ppm CCl_4 inhalation exposure by the original model and by our generic VOC model. Thus, the original model (Thrall et al. 2000) appeared to fit the data somewhat better than did our generic VOC model. The AUC_r values for both models were above 1, with values of 1.9 for the original and 2.5 for our generic model, indicating overprediction of breath concentrations. Compared with the original model, the MSSD value (0.2344) was slightly higher for our generic VOC model (0.4515) (Table 3).

Dichloromethane

Comparative simulations of predicted arterial blood concentrations following a repeated, 1-h, 500-ppm DCM inhalation exposure by the original model and by our generic VOC model are shown in Figure 4. Both the original model (David et al. 2006) and our generic VOC model performed well. That said, each of the models described some aspects of the blood kinetic curve better than did the other. The AUC_r values were similar for both models, with values of 1.1 indicating good representation of the data by model predictions. Using MSSD values to compare model predictions, the original model (1.17) was lower than our generic VOC model (3.82) (Table 3).

Perchloroethylene

Figure 5 shows comparative simulations of predicted blood concentration following a 4-h, 72-ppm PCE inhalation by the original model and by our generic VOC model. These results show our generic model modestly under predicted arterial blood concentrations during most of the clearance phase. On the other hand, the original model (Covington et al. 2007) had an exceptional fit to this kinetic data set. AUC_r values were similar for both models, with values of 0.8 for the original model and 0.6 for our generic VOC model.

Trichloroethylene

Figure 6 shows the original model's and our generic VOC model's comparative simulations of predicted arterial blood concentration following a 4-hour, 50-ppm TCE inhalation exposure. These results show our generic VOC model simulation of TCE inhalation exposure in male humans compared favorably with the original model (Fisher et al. 1998). For both models, the AUC_r values were 0.8; the MSSD values were similar and low: 0.0089 for the original model and 0.0095 for our generic VOC model (Table 3).

Vinyl Chloride

Figure 7 shows comparative simulations of predicted exhaled breath concentrations following a 0.25-h, 2.5-ppm VC inhalation exposure to the original model and to our generic VOC model. These results show that both the original model (Clewell et al. 2001) and our generic VOC model adequately predicted blood concentrations during exposure and for several minutes postexposure. Both models showed somewhat slower systemic clearance than the data suggest. The AUC_r values were 1.2 for the original model and 1.1 for our generic VOC model. MSSD values were low for both the models at 0.183 for the original model and 0.187 for our generic VOC model (Table 3).

Minimal Risk Level (MRL) Simulations

The Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) provides a representative sample of the civilian, noninstitutionalized U.S. population.[1] NHANES uses a stratified, multistage, probability-cluster design to gather questionnaire data about demographics, health-related behaviors, and physical exam measurements, as well as medical, nutritional, and environmental testing

[1]Find information about NHANES at http://www.cdc.gov/nchs/nhanes.htm.

on blood and urine specimens. As reported in the *Fourth National Report on Human Exposure to Environmental Chemicals*, the CDC Environmental Health Laboratory conducts biomonitoring for about 28 VOCs (CDC 2009). Blood levels in this report provide a geometric mean and a range of percentile of each VOC. To be protective of public health, the health practitioner would like for the vast majority of individuals (95% or greater) be exposed to VOCs below the ATSDR MRL level. So in this study, the 95th percentile blood concentrations of each of the six VOCs were used to compare to the blood levels modeled at MRL exposure levels. The generic VOC PBPK model was used to estimate the blood concentrations for the available MRL values of each of the specific VOCs (http://www.atsdr.cdc.gov/mrls/mrllist.asp). A safe outcome would be for the modeled blood concentrations at the MRL to be greater than the observed blood concentrations from NHANES.

Simultaneous simulation of oral and inhalational exposure to the chronic duration MRL concentrations of BEN resulted in a steady-state blood concentration of 0.04 ng/mL. These values are below the 0.26 ng/ml reported in NHANES population biomonitoring 95th upper confidence interval (Table 4). Simultaneous simulation of steady-state blood concentrations for oral and inhalational exposures to intermediate duration MRL concentrations of CCl_4 yielded a value of 0.40 ng/mL—well above blood detection limits. In NHANES population biomonitoring, the CCl_4 levels were reported as below the detection limit, at the 95th upper confidence interval (Table 4). Simulation of steady-state blood concentrations for simultaneous oral and inhalational exposures for acute and chronic duration MRL concentrations of DCM gave results well above the limits of detection for blood. Like CCl_4, the NHANES biomonitoring data for DCM were reported as below the detection limit. Simulation of simultaneous oral and inhalational exposures to acute-duration MRL concentrations of PCE (0.05 mg/kg/d and 0.2 ppm) and TCE (0.2 mg/kg/d and 2 ppm) resulted in blood-concentration values well above those reported in NHANES (Table 4). In general, we observed that the NHANES-reported VOC blood concentrations were several orders of magnitude below acceptable levels (MRL equivalents) except in the case of BEN. This outcome indicates possible concern for benzene exposure in the general population and warrants further analysis, such as accounting for metabolites, simulating more realistic exposure frequency and duration profiles, and considering varying body weight and other physiological parameters that may affect predicted blood levels of BEN.

DISCUSSION

Our generic seven-compartment PBPK VOCs model performed quite well for these six solvents in comparison to the limited data sets used and the original model prediction. We showed with these case studies how a generic solvent PBPK model can be evaluated against the original model predictions. Changing the number of compartments has been shown to have little effect on solvent predictions in blood, liver or fat for TCE (Keys et al. 2003). Thus, changing the number of compartments in a PBPK model to describe the kinetics for similar solvents appears feasible. More rigorous evaluation of generic model predictions should be undertaken with other data sets published with the original models, in addition to refining the exposure profiles to these solvents. Further improvements would include accounting for metabolite production in the solvent models. Even with these existing

limitations the generic solvent model has utility for screening purposes, as was shown by comparing model-predicted steady-state blood levels using MRL dose rates with NHANES data. Professional judgment would need to be used to determine whether exposures are adequately characterized in the models and whether the resulting simulations can be used for decision making.

For VOCs with physicochemical properties different from those used in these case studies, our generic VOC model may require further evaluation and modification. Our generic VOC model is applicable to lipophilic and volatile solvents and should be useful for other VOCs with similar physical-chemical properties. However, polar VOCs with increased water solubility, such as acetone, would require special considerations. We are now collecting and organizing chemical-specific data for VOCs found at hazardous waste sites or identified through environmental and biomonitoring programs. For VOCs lacking key parameters needed to simulate their kinetics, we will adopt an integrated QSAR-PBPK approach to augment their experimental database (Peyret and Krishnan 2011; Kamgang et al. 2008).

CONCLUSIONS

Health assessors are increasingly interested in using PBPK models to better estimate the risk arising from exposure at contaminated sites. Easy accessibility to such models will further refine public health assessments of communities exposed to chemicals and will help evaluate the health concerns those chemicals pose. Biomonitoring (such as use of the NHANES data set) can put MRL data simulation in perspective. Our generic VOC PBPK model can be used as a screening tool to interpret biomonitoring data, in predicting steady-state blood concentrations. Limitations of the methodology are comparable to other uncertainties the risk assessment process faces; for example, assessors currently use several default values when performing overall risk assessments. Thus limitations notwithstanding, our generic VOC PBPK model can provide useful information for the protection of public health.

Enhanced application, transparency, and ease of use of these computational techniques (PBPK models) will assist future research in several ways. For example, PBPK models are designed to predict the internal tissue concentration of a chemical following exposure by any one or more routes. This information can then be used in PBPK-driven targeted research to determine the appropriate dose for in vitro test systems. Hypothetically, the reverse could also be true. That is, if we know the in vitro concentration that causes adverse effect(s) at a cellular level, we could use PBPK models to extrapolate to in vivo tissue level and ultimately to a human-allowable external dose. This process is called reverse dosimetry (Clewell et al. 2008; Tan et al. 2006; Tan et al. 2007). Determinations of human external exposures to VOCs based on measured blood levels are extremely difficult because the latter only represent the concentration at the sample time while they are a product of complex exposures from multiple routes and multiple sources (Bogen and McKone 1988; Clewell et al. 2008; McKone 1993; Redding et al. 2008; Sohn et al. 2004). Combining in vitro pharmacokinetics and pharmacodynamics information can produce a concentration that could be used for risk assessment (Blaauboer 2003; Clewell et al. 2008; Forsby and Blaauboer 2007). Once identified. the in vivo exposure corresponding to the in vitro concentration can be estimated through in vitro-in vivo extrapolation (Blaauboer 2010; De

Buck and Mackie 2007). This is achieved through developing appropriate dose metrics, incorporating mode of action and other chemical-specific information to predict in vivo dose-response curves from in vitro data (Blaauboer 2010; Clewell et al 2008; Louisse et al. 2010). Thus, PBPK models can serve two purposes in future research endeavors: predict target organ concentrations of chemicals, and integrate such information to predict the whole animal exposures.

ATSDR's CompTox laboratory has used and pursued the development of computational tools (El-Masri et al. 2002; Mumtaz et al. 1995; Ruiz et al. 2010a; 2010b; 2010c). Federal agencies such as the ATSDR, U.S. Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Institute for Occupational Safety and Health (NIOSH), Consumer Product Safety Commission (CPSC), and others need to accelerate the use of PBPK models in risk assessment. Translational research such as presented in this article is necessary to make models accessible to health assessors in easy-to-use formats. The idea of converting published models into a series of models in a common simulation language will increase the agency's PBPK capabilities and will help assist health risk assessment at waste sites based on internal dose rather than on concentrations in the environmental media. These efforts also help in future studies to link models of various chemical components of a mixture based on the mechanism of potential interactions (Dennison et al. 2005; Haddad et al. 2000; Krishnan et al. 2002; Price and Krishnan 2011).

This work is also in line with the current thinking of the National Academy of Science (NAS) that encourages systems approach to toxicity testing (NAS 2008). In *Toxicity Testing in the 21st Century: A Vision and a Strategy*, NAS recommends the use of a complex array of animal/human in vitro bioassays to identify toxicity pathways and the concentrations causing excessive pathway perturbations. In the near future, through integrating physiological and anatomical considerations, PBPK models that are mathematical representations of the animal or human body can help integrate this mechanistic data to extrapolate holistically from these in vitro data to whole animals.

To optimize the use of PBPK models, publishing alone is not enough. The models have to be made available and accessible to various users. Publishing and archiving the model code in a common programming language will go a long way toward achieving increased application and promoting transparency about the model's characteristics, limitations, and advantages.

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APPENDIX

A PBPK model for predicting the tissue distribution and elimination of TCE following exposure in humans was recoded on Berkeley Madonna software based on Fisher et al. (1998).

```
 METHOD RK4
 STARTTIME = 0
 STOPTIME=24
 DT = 1e-4
 dtout=.01

{Physiological Parameters}
BW=70.0                 ;Body Weight- kg
QPC=24                  ;Alveolar ventilation rate- L/H
QCC=16.5                ;Cardiac Output- L/H
VFC=.214                ;Fraction fat tissue- kg/kg BW
VLC=.026                ;Fraction liver tissue- kg/kg BW
VBloodC=.079            ;Fraction venous blood- kg/kg BW
VRC=.09                 ;Fraction rapidly perfused tissue- kg/kg BW
VSC=.82                 ;Fraction slowly perfused tissue- kg/kg BW
VSkC=.051               ;Fraction skin tissue- kg/kg BW
VKC=.044                ;Fraction kidney tissue- kg/kg BW
QFC=.052                ;Fractional blood flow to fat- (L/H)/QC
QLC=.24                 ;Fractional blood flow to liver- (L/H)/QC
QRC=0.7                 ;Fractional blood flow to rapidly perfused- (L/H)/QC
QSC=.30                 ;Fract bld flow to slowly perf-(L/H)/QC
QKC=.197                ;Fractional blood flow to kidney- (L/H)/QC
QSkC=.05                ;Fractional blood flow to skin
SA=19975                ;surface area, body-head-cm^2

{Chemical-Specific Parameters for TCE, will change for each chemical}
PB=11.2                 ;Blood/air partition coefficient
PL=4.9                  ;Liver/blood paritition coefficient
PF=63.9                 ;Fat/blood partition coefficient
PR=4.9                  ;Rapidly perf/blood partition coefficient
PS=1.4                  ;Slowly perfused/blood partition coefficient
PK=1.08                 ;Kidney/blood partition coefficient
PSk=1.45                ;Skin/blood partition coefficient
MW=131.4                ;Molecular Weight TCE, g/mole
Vmaxc=4                 ;Max velocity of metabolism- mg/h/kg
Km=1.8                  ;Michaelis Menten- mg/L

{Calculated Parameters}
VS=VSC*BW-VF-VSk        ;Volume slowly perfused tissue- L
VF=VFC*BW               ;Volume fat tissue- L
VK=VKC*BW               ;Volume kidney- L
VL=VLC*BW               ;Volume liver- L
VBlood=VBloodC*BW       ;Volume venous blood- L
VSk=VSkC*BW             ;Volume skin- L
VR=VRC*BW-VL-VK         ;Volume rapidly perfused tisse- L
QC=QCC*BW**.75          ;Cardiac output- L/hr
QP=QPC*BW**.75          ;Alveolar ventilation- L/hr
QF=QFC*QC               ;Blood flow to fat- L/h
QL=QLC*QC               ;Blood flow to liver- L/h
QR=QRC*QC-QL-QK         ;Blood flow to rapidly perfused tissue- L/h
QS=QSC*QC-QF-QSk        ;Blood flow to slowly perfused tissue- L/h
QK=QKC*QC               ;Blood flow to kidney- L/h
QSk=QSkC*QC             ;Blood flow to skin- L/h
VMAX=Vmaxc*BW**.75      ;max metabolism, mg/hr
```

```
{Mass Balance for blood flows and volumes tissues}
Qtot=QS+QR+QSk+QL+QK+QF                    ;sum of blood flows to compartments
Vtot=vs+vr+vk+vf+vsk+vl                    ;sum of tissue volumes
Qbal=Qtot-QC                               ;check on blood
Vbal=BW-Vtot                               ;check on volume

{Exposure Parameters}
CONC=0                                     ;Inhaled concentration- ppm, default set=0
inhale_time=5                              ;Length for inhalation exposure- h
inhale_interval=100000                     ;Period for repeated inh exposures, Set to large value for no
                                             repeat dosing
CIX=CONC*MW/24450                          ;Inhaled concentration- mg/L

;Oral
pdose=0                                    ;oral dose mg/kg/day, default=0
dose_per_drink=(pdose*BW)/number_drink     ;oral dose mg per drink equally divides for each drink
doser=dose_per_drink/drink_time            ;drink rate/hr
drink_interval=6                           ;24/drink_interval= number of drinks
daily_drink_interval=IF drink_interval>24 THEN   ;sets max daily_drink_interval at 24 for single drink
  24 ELSE drink_interval
number_drink=24/daily_drink_interval       ;number of drinks per day
drink_time=.25                             ;length of time drinking water/hr

;Dermal
Kp=.015                                    ;Skin permeability constant- cm/hr, Poet et al., 2000
Cliq=0                                     ;concentration of TCE in water- mg/L, default=0
PSkliq=53                                  ;Skin/water partition coefficient, Poet et al., 2000
skin_time=0                                ;Length for Dermal Exp - hr SET =to 0 when no dermal exposure
skin_interval=100000                       ;Period for repeated derm exposures Set to large value for default
                                             no repeat dosing

{Exposure Routes}

;Dosing Schedule
;INHALATION
CI=CIX*AIR                                 ;Turning on multiday exposure
AIR=IF MOD(TIME,inhale_interval)>          ;repeated square wave function
  =inhale_time THEN 0 ELSE 1
;ORAL repeated exposure
ORALH20=IF MOD(TIME,drink_interval)>       ;repeated exposure to TCE by oral exposure
  =drink_time THEN 0 ELSE 1
;DERMAL exposure in water
SKINH20=IF MOD(TIME,skin_interval)>        ;repeated exposure of skin to TCE in water
  =skin_time THEN 0 ELSE 1

{Model Equations}
;Chemical in Blood
CA=(QC*CV+QP*CI)/(QC+(QP/PB))              ;Arterial- mg/L
AVBlood'=(QF*CVF+QL*CVL+QS*CVS+QR*CVR+     ;rate of change in venous blood amount- mg/h
  QK*CVK+QSk*CVSk)-(QC*CV)
init AVBlood=0                             ;initial amount in venous blood
CV=AVBlood/VBlood                          ;venous concentration
;Exhaled Chemical
CX=CA/PB                                   ; Alveolar concentration- mg/L
CXppm=(.7*CX+.3*CI)*24450/MW               ;Exhaled breath concentration
AX'=QP*CX                                  ;Amount exhaled
init AX=0                                  ;initial amount in exhaled breath
AINH'=QP*CI                                ;Amount inhaled
init AINH=0                                ;initial amount inhaled
;Chemical in Rapidly perfused tissue compartment
AR'=QR*(CA-CVR)                            ;rate of change in viscera amount- mg/h
init AR=0                                  ;initial amount in viscera- mg
```

```
CR=AR/VR                                    ;viscera concentration- mg/L
CVR=CR/PR                                   ;concentration in visceral capillary blood- mg/L

;Chemical in Slowly perfused tissue compartment
AS'=QS*(CA-CVS)                             ;rate of change in slowly perfused amount- mg/h
init AS=0                                   ;initial amount in slowly perfused tissue- mg
CS=AS/VS                                    ;slowly perfused tissue concentration- mg/L
CVS=CS/PS                                   ;concentration in SP tissue capillary blood- mg/L

;Chemical in Fat compartment
AF'=QF*(CA-CVF)                             ;rate of change in fat amount- mg/h
init AF=0                                   ;initial amount in fat- mg
CF=AF/VF                                    ;fat concentration - mg/L
CVF=CF/PF                                   ;concentration in fat capillary blood- mg/L

;Chemical in Liver compartment
AL'=QL*(CA-CVL)-RAM+Roral                   ;rate of change in liver amount with oral exposure- mg/h
init AL=0                                   ;initial amount in liver -mg
CL=AL/VL                                    ;liver concentration- mg/L
CVL=CL/PL                                   ;concentration in liver capillary blood- mg/L

;Oral ingestion into the Liver
Roral=doser*ORALH20                         ;repeated oral intake- mg/hr
AORAL'=Roral                                ;amount ingested-mg
init AORAL=0                                ;initial amount
;Chemical in Kidney compartment
AK'=QK*(CA-CVK)                             ;rate of change in the kidney amount-mg/h
init AK=0                                   ;initial amount in kidney- mg/h
CK=AK/VK                                    ;kidney concentration- mg/h
CVK=CK/PK                                   ;concentration in kidney capillary blood- mg/h

;Chemical in Skin compartment
ASk'=QSk*(CA-CVSk)+RASkin                   ;rate of change in skin amount- mg/h
init ASk=0                                  ;initial amount in skin- mg/h
CSk=ASk/VSk                                 ;skin concentration- mg/h
CVSk=CSk/PSk                                ;concentration in skin capillary blood- mg/h

;Chemical across skin
RASkin=(Kp*SA/1000)*(Cliq-                  ;rate of transfer of chemical across skin (flux)-mg/hr with repeated
  CSk/PSkliq)*SKINH20                         exposure
ASkin'=RASkin                               ;amount of chemical transferred-mg
init ASkin=0                                ;initial amount in skin-mg
ASkinOut'=(Kp*SA/1000)*(CSk/PSkliq)*SKINH20 ;rate of loss through skin (mg/hr)
init ASkinOut=0;                            ;total amount lost through skin (mg)

;Chemical metabolism
RAM=Vmax*CVL/(Km+CVL)                       ;rate of metabolism- mg/h
AM'=RAM                                     ;amount metabolized- mg
init AM=0                                   ;initial amount metabolized- mg

;Mass Balance for inhalation, Check InhDose=Mass
InhDOSE'=QP*(CI-CX)                         ;net absorption- mg/h
init InhDOSE=0                              ;initial net absorption- mg
Mass=AF+AR+AS+AL+AM+AK+ASk+AVBlood          ;in tissues+metabolized-mg+AVBlood

;Mass Balance for oral intake, Check Oralwater=MASSWATER
Oralwater=Aoral
drink_day=dose_per_drink*number_drink       ;mg ingest each day
MASSWATER=AF+AR+AS+AL+AM+ASk+AK+            ;in tissues+metabolized-mg+AVBlood+amount exhaled
  AX+AVBlood

;Mass Balance for dermal intake, Check Dermalwater=MASSWater
Dermalwater=ASkin
```

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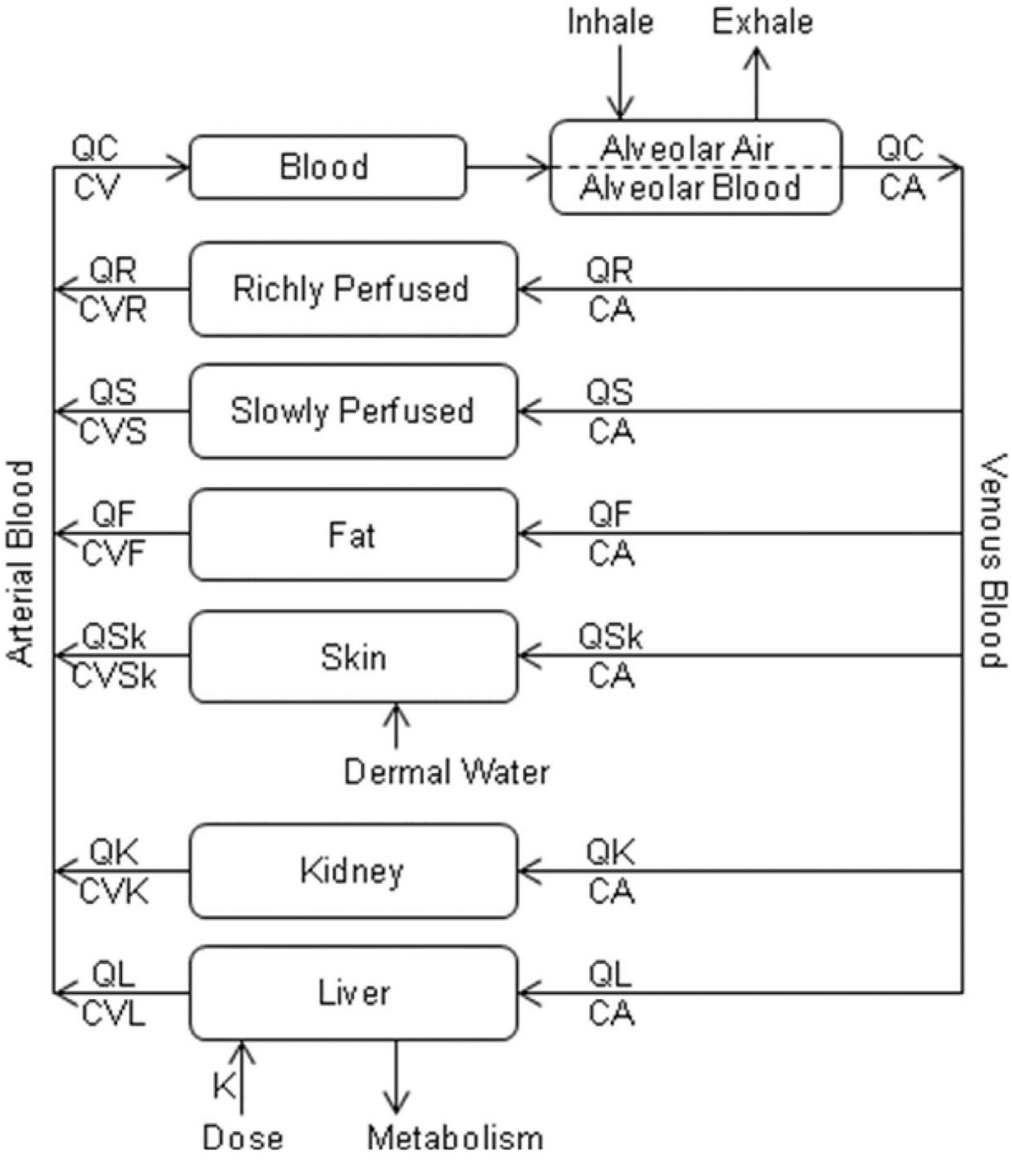

FIGURE 1.

Schematic of generic PBPK model that depicts various compartments, the blood flow pattern, and interconnect ability of the various tissues in the body.

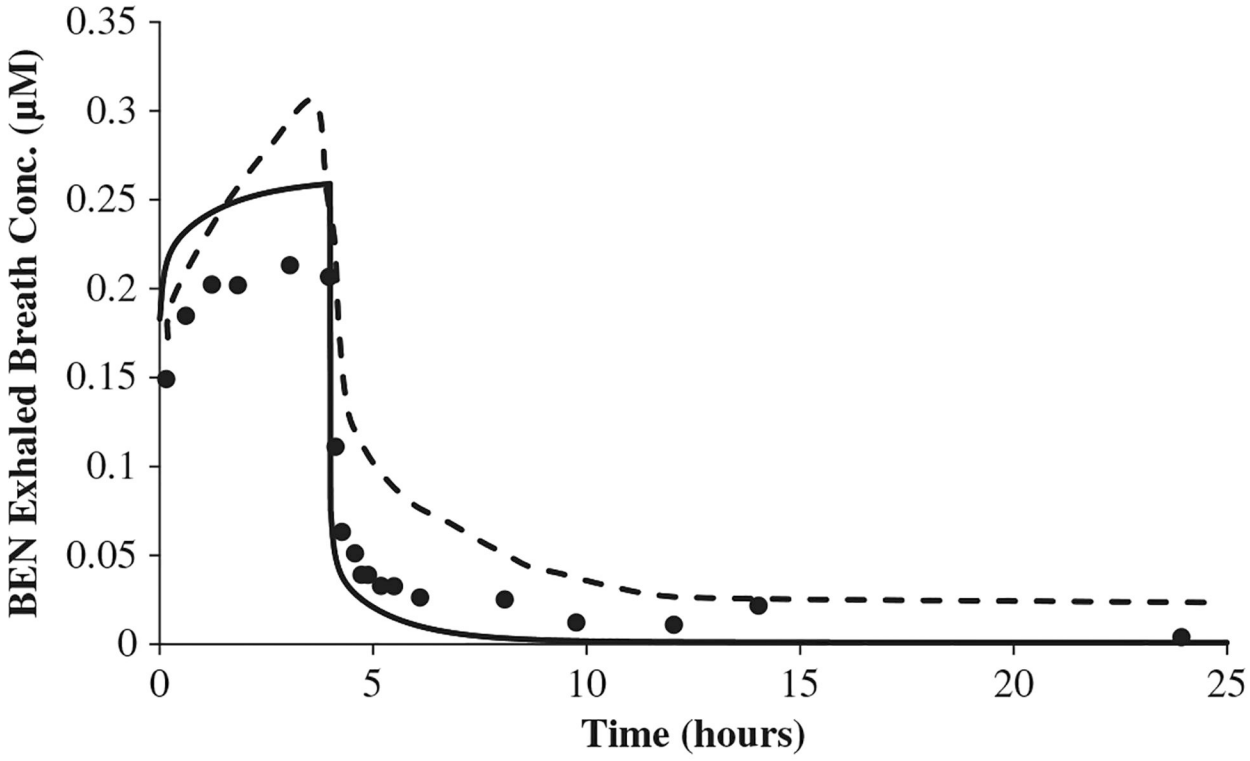

FIGURE 2.

Benzene. Exhaled breath concentrations (•) measured over time, following a 4-h, 10-ppm benzene (BEN) inhalation exposure (Yokley et al. 2006). The original PBPK simulation (- - -) and the generic VOCs model simulation (—) are also shown.

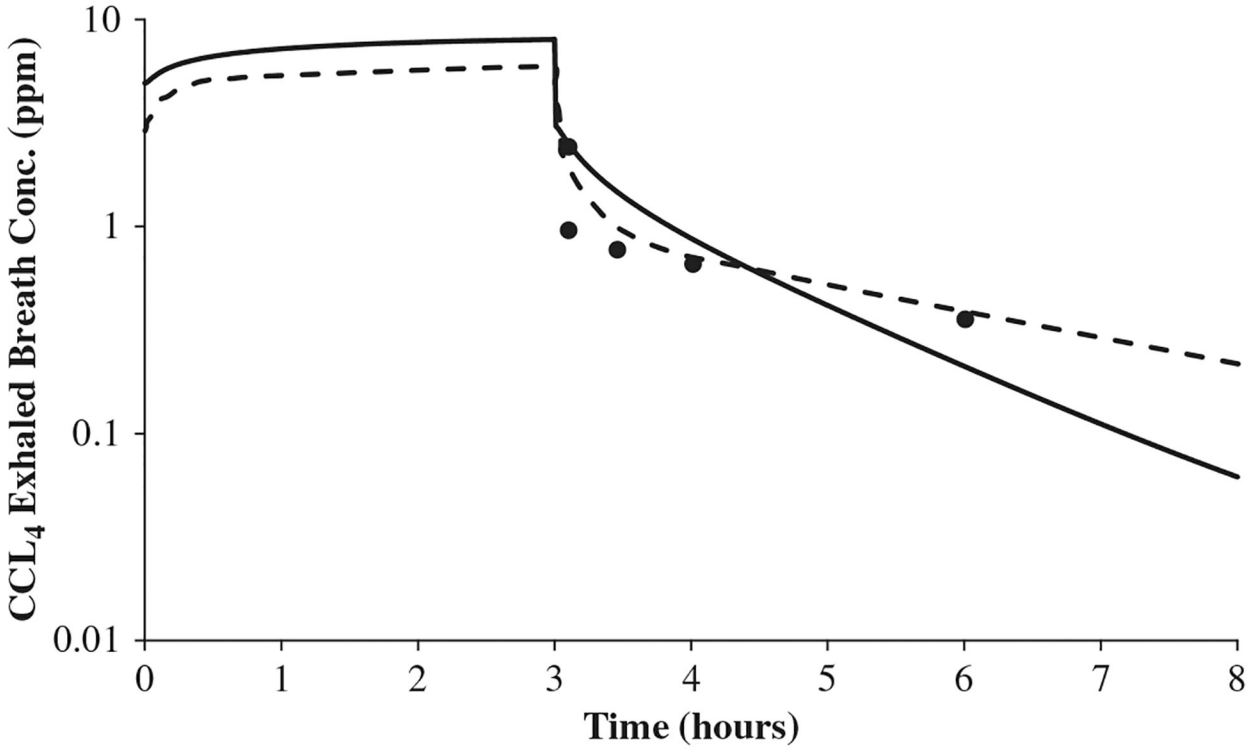

FIGURE 3.

Carbon tetrachloride. Exhaled breath concentration (•) measured over time, following 3-h, 10-ppm carbon tetrachloride (CCl_4) inhalation exposure (Thrall et al. 2006). The original simulation (- - -) and our generic VOCs model simulation (—) are also shown.

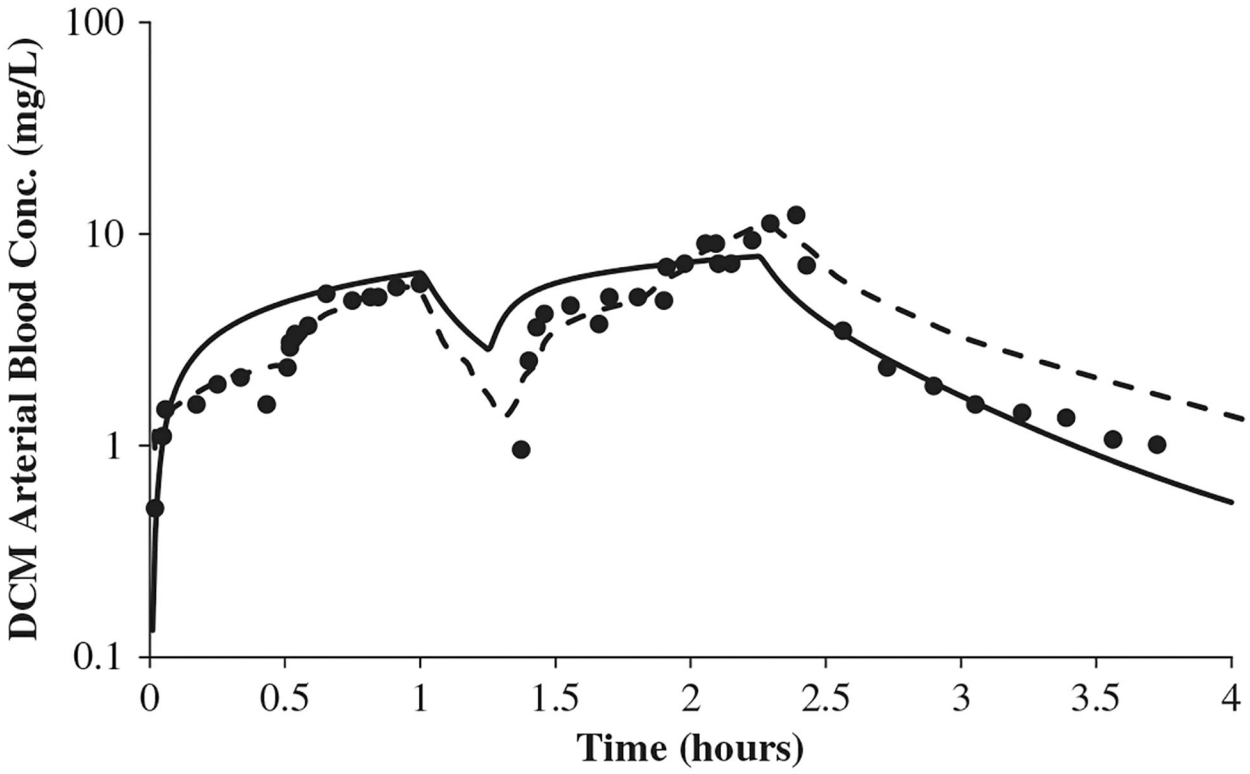

FIGURE 4.

Dichloromethane. Arterial blood concentration (•) measured over time, following repeated 1-h, 500-ppm dichloromethane (DCM) inhalation exposures (David et al. 2006). The original simulation (- - -) and our generic VOCs model simulation (—) are also shown.

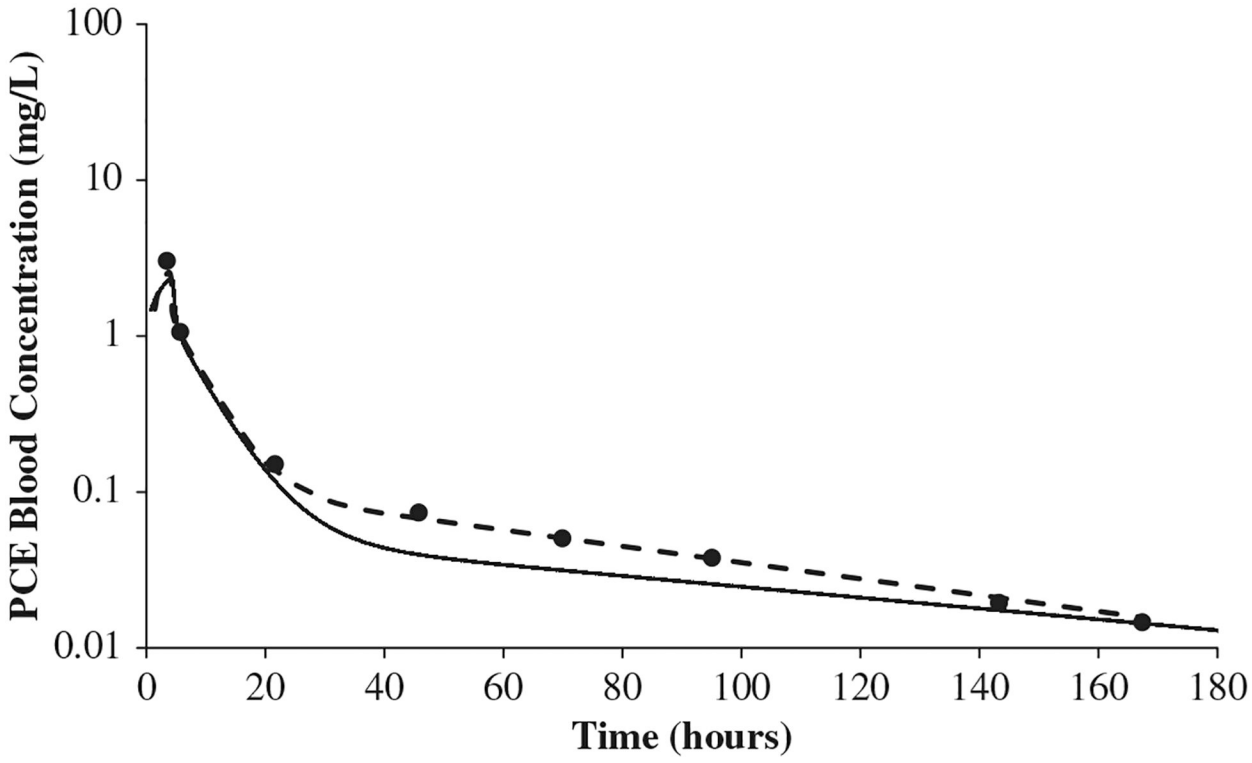

FIGURE 5.

Perchloroethylene. Blood concentrations (•) measured over time, following 4-h, 72-ppm perchloroethylene (PCE) inhalation (Covington et al. 2007). The original simulation (- - -) and our model simulation (—) are also shown.

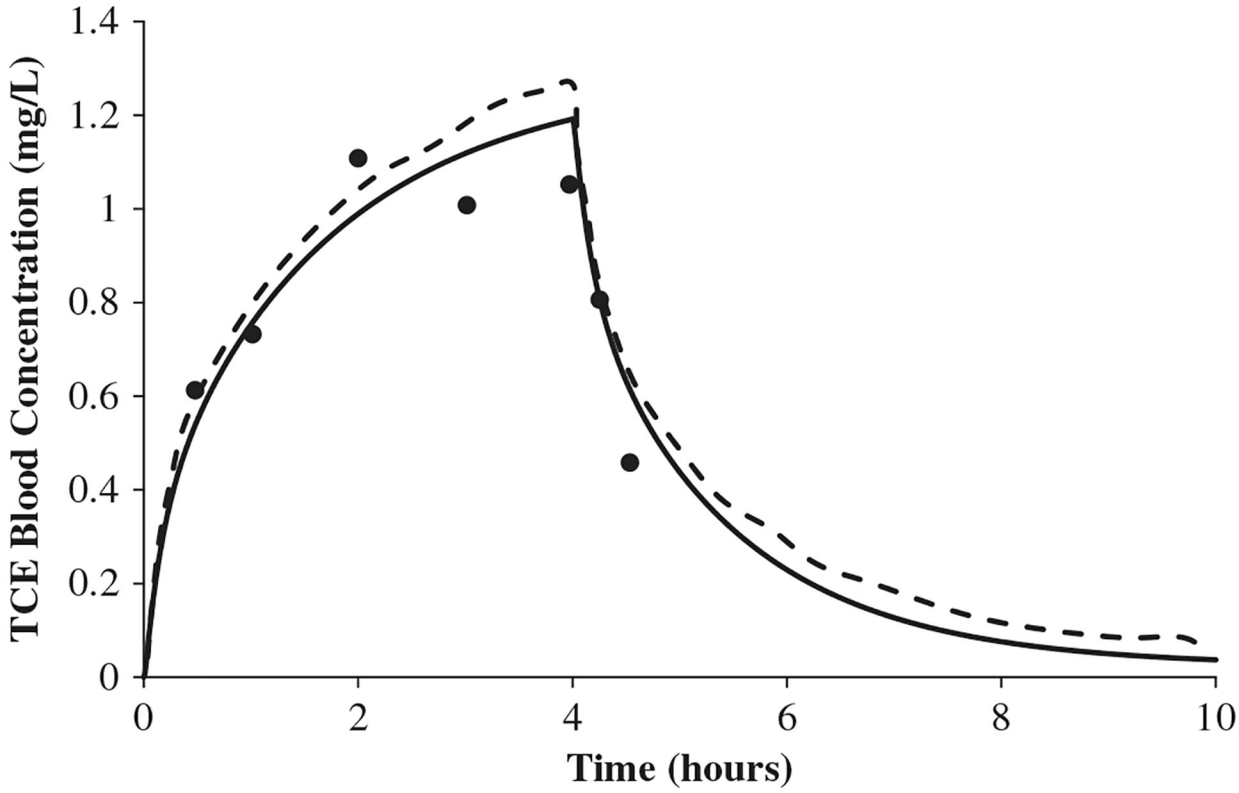

FIGURE 6.

Trichloroethylene. Blood concentrations (•) measured over time, following 4-h, 50-ppm trichloroethylene (TCE) inhalation exposure (Fisher et al. 1998). The original simulation (- - -) and our generic VOCs model simulation (—) are also shown.

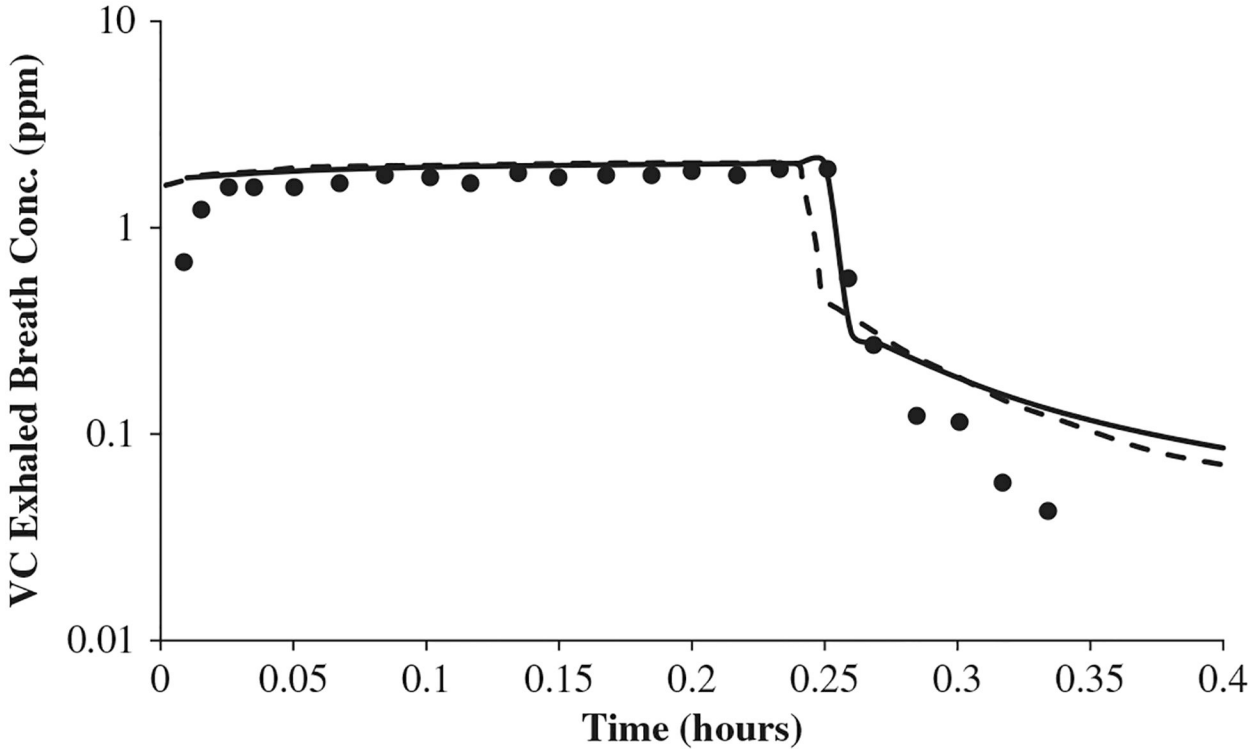

FIGURE 7.

Vinyl chloride. Exhaled breath concentration (•) measured over time, following 0.25-h, 2.5-ppm VC inhalation exposure (Clewell et al. 2001). The original simulation (- - -) and our generic VOCs model simulation (—) are also shown.

TABLE 1.

Physiological Parameters Values Used in the Generic VOCs PBPK Model

Parameter	Abbreviation	Value[a]
Body weight (kg)	BW	70[b]
Alveolar ventilation rate (L/h/kg$^{0.75}$)	QPC	24[c]
Cardiac output (L/h/kg$^{0.75}$)	QCC	16.5[d]
Blood flows (fraction of cardiac output)		
Fat	QFC	0.052[d]
Liver	QLC	0.24[e]
Kidney	QKC	0.197[f]
Skin	QSkC	0.05[g]
Rapidly perfused[f]	QRC	0.7
Slowly perfused[f]	QSC	0.3
Tissue volumes (fraction of body weight)		
Blood	VBloodC	0.079
Fat	VFC	0.214[d]
Liver	VLC	0.026[d]
Kidney	VKC	0.0044
Skin	VSkC	0.051[g]
Rapidly perfused	VRC	0.09
Slowly perfused	VSC	0.82
Body surface area excluding head (cm^2)	SA	19,975[g]

[a] Parameter values taken from Brown et al. (1997) unless otherwise noted.

[b] ICRP Reference Man.

[c] Covington et al. (2007).

[d] Clewell et al. (2000; 2005).

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[e] Fisher, Mahle & Abbas (1998).

[f] Cowles et al. (1971).

[g] Corley et al. (2000).

TABLE 2.

Chemical-Specific Model Parameters Used in the Generic VOCs PBPK Model

Parameter	Symbol	TCE	PCE	DCM	VC	BEN	CCl_4
Partition coefficients							
Blood:air	PB	11.2	10.3	9.7	1.16	7.79	2.64
Fat:blood	PF	63.9	125.2	12.4	20.7	21.11	135.98
Liver:blood	PL	4.9	5.28	1.46	1.45	1.41	5.38
Kidney:blood	PK	1.08	5.06	5.38	1.45	1.92	5.38
Rapidly perfused:blood	PR	4.9	5.06	1.46	1.45	1.41	5.38
Slowly perfused:blood	PS	1.4	6.11	0.82	0.83	1.93	1.73
Skin:blood	PSk	1.45	3.578	1.45	1.45	1.45	1.45
Skin:water	PSkLiq	53					
Metabolic constants							
Maximum rate of metabolism[a]	VMaxC	4	1.36	9.42	3.97	0.574	0.526
Michaelis constant[b]	Km	1.8	4.66	0.433	0.04	0.35	0.25
Skin permeability[c]	Kp	0.015					

Note. Dermal exposure was turned off. Skin:blood partition coefficient values for TCE and PCE were measured, while other solvents were set to the TCE value. TCE, trichloroethylene; PCE, perchloroethylene; DCM, dichloromethane; VC, vinyl chloride; BEN, benzene; CCl_4, carbon tetrachloride.

[a] $mg/h/kg^{0.75}$.

[b] mg/L.

[c] cm/h.

TABLE 3.

Model Validation

Metric	BEN	CCl_4	DCM	PCE	TCE	VC
Generic model AUC/Data AUC	0.9	2.5	1.1	0.6	0.8	1.2
Original model AUC/Data AUC	1.6	1.9	1.1	0.8	0.8	1.1
Generic model MSSD	0.0008[a]	0.4515[b]	3.8214[c]	0.0805[c]	0.0095[c]	0.1875[b]
Original model MSSD	0.0009[a]	0.2344[b]	1.1722[c]	0.0164[c]	0.0089[c]	0.1831[b]

Note. BEN, benzene; CCl_4, carbon tetrachloride; DCM, dichloromethane; PCE, perchloroethylene; TCE, trichloroethylene; VC, vinyl chloride.

[a] *μM*.

[b] ppm.

[c] mg/L.

TABLE 4.

Simulated Blood Concentration of Each Solvent, Assuming Simultaneous Inhalation (24 h/d) and Oral Ingestion (4 Drinking Bouts per Day) Is Compared to the Measured Blood Concentration of Solvent Reported by NHANES 2003–2004

	BEN$^+$	**CCl_4^+**	**DCM$^+$**		**PCE$^+$**	**TCE$^+$**	**VC$^+$**
MRL *	0.003/0.0005	0.03/0.007	0.6/0.2	0.3/0.06	0.2/0.05	2/0.2	None
Exposure duration	Chronic	Intermediate	Acute	Chronic	Acute	Acute	–
NHANES **	Blood concentration (ng/ml)						
	0.260 (0.210–0.320)	<LOD	<LOD		0.140 (0.091–0.300)	<LOD	ND **
Limit of detection (LOD)	0.024	0.005	0.07		0.048	0.012	ND
PBPK model	Blood concentration (ng/ml)						
Predicted peak	0.04	0.40	18.12	6.70	10.76	111.65	–

Note. The simulated solvent exposure is set to the Minimal Risk Level (MRL) for inhalation of the solvent in air and ingestion of the solvent in water. Ben$^+$, benzene; CCl_4^+, carbon tetrachloride; DCM$^+$, dichloromethane; PCE$^+$, perchloroethylene, TCE$^+$, trichloroethylene; VC$^+$, vinyl chloride.

*Inhalation concentration (ppm)/oral ingestion rate (mg/kg-d).

**NHANES 2003–2004. 95th percentiles of blood concentration (in ng/ml) for U.S. population. ND, not done.