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USE OF A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL TO IDENTIFY EXPOSURES CONSISTENT WITH HUMAN BIOMONITORING DATA FOR CHLOROFORM

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Biomonitoring data provide evidence of human exposure to environmental chemicals by quantifying the chemical or its metabolite in a biological matrix. To better understand the correlation between biomonitoring data and environmental exposure, physiologically based pharmacokinetic (PBPK) modeling can be of use. The objective of this study was to use a combined PBPK model with an exposure model for showering to estimate the intake concentrations of chloroform based on measured blood and exhaled breath concentrations of chloroform. First, the predictive ability of the combined model was evaluated with three published studies describing exhaled breath and blood concentrations in people exposed to chloroform under controlled showering events. Following that, a plausible exposure regimen was defined combining inhalation, ingestion, and dermal exposures associated with residential use of water containing typical concentrations of chloroform to simulate blood and exhaled breath concentrations of chloroform. Simulation results showed that inhalation and dermal exposure could contribute substantially to total chloroform exposure. Next, sensitivity analysis and Monte Carlo analysis were performed to investigate the sources of variability in model output. The variability in exposure conditions (e.g., shower duration) was shown to contribute more than the variability in pharmacokinetics (e.g., body weight) to the predicted variability in blood and exhaled breath concentrations of chloroform. Lastly, the model was used in a reverse dosimetry approach to estimate distributions of exposure consistent with concentrations of chloroform measured in human blood and exhaled breath.

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official views of the Centers for Disease Control and Prevention.

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Biomonitoring has become a common approach to identify and quantify people's exposure to environmental and occupational chemicals. Public awareness of this approach rises since the Centers for Disease Control and Prevention (CDC) release, every 2 yr, results from their biomonitoring studies in the *National Report on Human Exposure to Environmental Chemicals* as an ongoing assessment of the U.S. population's exposure to environmental substances. Biomonitoring measures concentrations of chemicals and/or their metabolites in human specimens (e.g., blood, urine, hair, or breast milk) at a specific point in time. To place biomonitoring into the context of the "exposure → target tissue dose → adverse health effect" continuum, it needs to be integrated with the following information: (1) the nature of the exposures, including exposure sources, routes, duration, frequency, and intensity; (2) the timing of the biomonitoring data collection relative to key exposure events; and (3) the inherent (e.g., biological residence time) and behavioral (e.g., activity patterns) variation in a population. Such information can be obtained by various approaches, such as direct environmental monitoring, detailed activity diaries or questionnaires, exposure modeling, and physiologically based pharmacokinetic (PBPK) modeling. With proper use of these tools, biomonitoring data can be transformed to equivalent exposure concentrations or target tissue doses to assess their implications on toxicity and health risk.

The primary application of this study was to use a PBPK model to describe the nonlinear exposure–tissue dose (i.e., biomonitoring data) relationship for an environmental chemical. It was intended to demonstrate the implementation of PBPK modeling in a reverse dosimetry approach to estimate distributions of exposure consistent with biomonitoring data. At the same time, potentially critical data required to design an informative biomonitoring study would be identified. Specifically, a PBPK model (Corley et al., 2000) for chloroform (trichloromethane, $CHCl_3$) was exercised in conjunction with a mass transfer model (Weisel et al., 1999b), which describes the transfer of volatile organic chemicals (VOCs) from water to air during showering. The model was used to predict chloroform concentrations in blood and exhaled breath from multi-route exposure to chloroform in members of general public. A similar modeling exercise (i.e., PBPK models combined with exposure model) has been performed to estimate target tissue dose in human exposed to methyl *t*-butyl ether and tetrachloroethylene in showering and bathing (Rao & Brown, 1993; Rao & Ginsberg, 1997).

Human exposure to chloroform is widespread since chloroform is formed through reactions of chlorine with organic chemicals during the disinfection treatment of drinking water. Chloroform is a well-studied water disinfection by-product (DBP). Exposure at doses much higher than the environmental levels increases the incidence of liver and kidney tumors in rodents via a cytolethality-regenerative cellular proliferation mode of action (IPCS, 1994; ILSI, 1997; Butterworth & Bogdanffy, 1999). Mediated by cytochromes P-450 2E1, chloroform is mainly metabolized through an oxidative pathway that produces the toxic metabolites phosgene and hydrochloric acid (Pohl et al., 1977;

Constan et al., 1999). The metabolites were proposed to lead to cellular damage and subsequent cell death in liver and kidneys (Ilett et al., 1973; Smith et al., 1983). Following cytolethality, in most target tissues, compensatory cellular proliferation is triggered as part of the repair process. Although not being an exclusive cause for the onset of cancer, the increased cell proliferation is often associated in promotion and progression stages of tumor formation. Since chloroform toxicity and kinetics have been well characterized, the PBPK model can be used not only to evaluate biomonitoring data for the purpose of reconstructing environmental exposure as in the current study, but also to estimate human health risk associated with chloroform exposure in future research.

In this study, the predictive ability of the model was first evaluated with three published studies describing exhaled breath and blood concentrations in humans exposed to chloroform under controlled showering events (Jo et al., 1990; Backer et al., 2000; Levesque et al., 2002). A plausible exposure regimen was then defined combining inhalation, ingestion, and dermal exposures associated with residential use of water containing typical concentrations of chloroform to simulate blood and exhaled breath concentrations of chloroform. The model was exercised in conjunction with Monte Carlo analysis to manage variabilities regarding (1) exposure duration and intensity, (2) temporal profile of exposure events, (3) timing between sample collection and major exposure events, and (4) human pharmacokinetics. The objective of this study was to estimate distributions of exposure consistent with concentrations of chloroform measured in human blood and exhaled breath. This modeling approach will be applicable for evaluating biomonitoring data of other DBPs and VOCs to estimate either exposure or human health risk.

METHODS

Model Structure

Daily chloroform exposure comes from various sources, including (1) ingestion of tap water or food sources; (2) inhalation of chloroform volatilized from tap water (e.g., dishwashing or laundry) or from chlorine-containing cleaning agents; and (3) inhalation and dermal absorption while taking showers or baths. These routes of exposure were all incorporated, with assumptions for simplification, into a PBPK model for chloroform (Corley et al., 2000). The PBPK model was combined with a model (Weisel et al., 1999b) that describes the mass transfer of chloroform from tap water to ambient air during showering, an event that contributes significantly to inhalation exposure to VOCs like chloroform (Wilkes et al., 1992). The current study did not include bathing, which occurs less frequent compared to showering (U.S. EPA, 1996). The structures of both the PBPK model and the mass transfer model (key equations shown in Appendix) can be found in published literature (Corley et al., 1990, 2000; Weisel et al., 1999b). Parameter values (means and coefficients of

variance [CV]) from the original PBPK model (Corley et al., 1990, 2000) were reevaluated based on the latest studies (Brown et al., 1997) on human physiology (Table 1). Besides the change in parameter values, two additional modifications were made to the original PBPK model in the current study:

1. In the original PBPK model, fixed values were used for male and female body surface area (SA). In the current study, we set SA to be a function of body weight (BW): SA = 286 × BW (Phillips et al., 1993).
2. The blood flow to skin and the effective skin permeability coefficients in the original PBPK model were temperature dependent (Corley et al., 2000), but

TABLE 1. Parameters Used in the PBPK Model for Chloroform

Parameter	Mean	Standard deviation (SD)	Source
Tissue volume as percentage of body weight (assume unit density)[a]			
Fat	21.4	6.42	Brown et al., 1997
Liver	2.57	0.77	Brown et al., 1997
Kidney	0.44	0.13	Brown et al., 1997
Skin	5.1	1.53	Corley et al., 2000
Rapidly perfused tissue	5.39	1.62	Brown et al., 1997
Slowly perfused tissue	56.1	16.8	91%–other tissues
Flows			
Cardiac output (L/h/kg$^{0.75}$)	16.5	1.50	Clewell et al., 2000
Alveolar ventilation (L/h/kg$^{0.75}$)	24	3.8	Clewell et al., 2000
Blood flow to tissue as percentage of cardiac output[a]			
Fat	5	1.5	Brown et al., 1997
Liver	25	7.5	Brown et al., 1997
Kidney	19	5.7	Brown et al., 1997
Skin	8.6	2.6	Brown et al., 1997
Rapidly perfused tissue	25.4	7.62	100%–other tissues
Slowly perfused tissue	17	5.1	Brown et al., 1997
Partition coefficients for chloroform			
Blood/air	7.43	1.4	Delic et al., 2000
Fat/air	280	28	Delic et al., 2000
Liver/air	17	3.2	Delic et al., 2000
Kidney/air	11	2.2[b]	Corley et al., 1990
Skin/air	12	3.6[a]	Corley et al., 2000
Skin/water	3.85	1.16[a]	Corley et al., 2000
Rapidly perfused/air	17	3.2	Liver values
Slowly perfused/air	12	2.4	Delic et al., 2000
Metabolic constants[a]			
$V_{max}C$ (mg/h/kg$^{0.7}$)	15.7	4.7	Corley et al., 1990
K_m (mg/L)	0.448	0.134	Corley et al., 1990
Body surface area exposed (cm^2/kg)	286	—	Phillips et al., 1993
Effective skin permeability coefficients (cm/h)	0.05	0.015[a]	Corley et al., 2000

[a]Coefficient of variance (CV) set to 30% to calculate SD.
[b]Coefficient of variance (CV) set to 20% to calculate SD.

they were not described as a function of temperature. The values for these two parameters at 35°C from the original model were chosen as the mean values in the current study (Table 1). A CV of 30% was selected to include the values reported at 30°C and 40°C in the original model (Corley et al., 2000).

Programming

The model was coded with the graphical simulation tool SIMULINK, which is part of the MATLAB technical computing product family (The MathWorks, Inc., Natick, MA). MATLAB m-file scripts describing exposure regimens were used to control the SIMULINK model for time-course and dose-response simulations. Other custom m-file scripts were used for sensitivity analysis and Monte Carlo analysis. All simulations were run on a computer equipped with dual 3.0-GHz Pentium processors and the Windows XP operating system. A copy of the source code in electronic form is available from the corresponding author.

Model Evaluation

The predictive ability of the combined PBPK model (Corley et al., 1990) and mass transfer model (Weisel et al., 1999b) was evaluated with three published studies providing exhaled breath or blood concentrations of chloroform measurements from volunteers taking showers under controlled conditions (Jo et al., 1990; Backer et al., 2000; Levesque et al., 2002). These three studies (Jo et al., 1990; Backer et al., 2000; Levesque et al., 2002) were selected because they contain the most complete descriptions of how the volunteers were exposed and when the exhaled breath or blood samples were collected. Such information allowed us to minimize the number of assumptions made about the exposure conditions. When predicting the chloroform concentrations in exhaled breath and blood, all parameters in the PBPK model (Corley et al., 1990) were set to their mean values (Table 1) except for body weight; blood flow rate to skin; and the effective skin permeability coefficient. The values for body weight were chosen to match those reported in the studies (Jo et al., 1990; Backer et al., 2000; Levesque et al., 2002), and the values for blood flow rate to skin and the effective skin permeability coefficient were determined based on the water temperature reported in each study (Jo et al., 1990; Backer et al., 2000; Levesque et al., 2002). A brief review of each study (Jo et al., 1990; Backer et al., 2000; Levesque et al., 2002) is presented in the following subsections.

Shower Studies From Jo et al. (1990) Jo et al. (1990) set up two experiments to quantify the relative chloroform dose from dermal and inhalation exposure to chlorinated tap water while individuals took 10-min showers (1) under typical conditions and (2) with no dermal contact with the shower water (i.e., inhalation exposure only). In both experiments, exhaled breath samples were taken prior to and 5 min after the shower. All major shower parameters

were controlled (e.g., water temperature was set to 40 ± 2°C) except for tap water concentration, which was measured immediately after each shower (5.3–35.9 μg/L).

Shower Studies From Levesque et al. (2002) Levesque et al. (2002) collected exhaled breath samples from 18 male volunteers before, immediately after, and 15 and 30 min after they took 10-min showers in their own homes. Concentrations of chloroform in the shower water, in household air before the shower, and in the subject's breathing zone during and after showers were measured. The preexposure chloroform concentration of 6.1 $\mu g/m^3$ measured in exhaled breath and an estimated ingestion amount of 1500 ml water per day were incorporated into the model.

Exposure Studies From Backer et al. (2000) Backer et al. (2000) examined 31 volunteers' exposure to trihalomethanes (THMs) through one of the following household activities: (1) showering for 10 min with tap water (n = 11); (2) immersing for 10 min in a bathtub filled with tap water (n = 10); or (3) drinking 1 L water during a 10-min time period (n = 10). The average chloroform concentrations in tap water measured in this study were 31.0 ± 3.54 μg/L, 31.8 ± 6.26 μg/L, and 20.4 ± 1.97 μg/L for showering, bathing, and drinking water, respectively. Blood samples were collected immediately before the exposure and 10 and 30 min (for showering and bathing) or 1 h (drinking) following the end of exposure. The model predicted the temporal profile of the blood concentrations after showering and drinking water to compare with the measured blood concentrations of chloroform (Backer et al., 2000).

Model Simulations for Realistic Exposure Scenarios

In this study, seven exposure-related parameters were identified to define a plausible exposure regimen aggregating inhalation, ingestion, and dermal absorption associated with residential use of water containing typical concentrations of chloroform. These exposure parameters were (1) chloroform concentrations in tap water; (2) background chloroform concentrations in ambient air from the use of hot water (excluding the exposure in showers) and cleaning agents in the household; (3) shower duration; (4) drinking water intake amount per day; (5) the mass transfer coefficient for the volatile emission of chloroform during showering; (6) shower water: flow rate; and (7) shower stall dimensions. Plausible distributions of these parameters, except for mass transfer coefficient and shower stall dimensions, were estimated based on summary statistics, such as percentile data, cited in various reports and surveys (Table 2) (Wallace, 1997; Mayer et al., 1999; U.S. EPA, 1996, 2000, 2001). It is noteworthy that the distributions of chloroform concentrations in tap water were taken from data collected in the 1980s (Table 3 in Wallace, 1997). Some of the chloroform concentrations reported in Wallace (1997) exceed the current U.S. EPA maximum contaminant level (MCL) for total trihalomethanes of 80 μg/L (U.S. EPA, 2001). More current distributions of chloroform concentration in tap water can be incorporated once data from a large-scale study, such as the one currently being performed by CDC, become available.

TABLE 2. Distributions of the Exposure Parameters Used in the Model

Percentile	1%	5%	10%	25%	50%	75%	90%	95%	99%
Water intake amount (ml/d)[a]	51	112	189	338	675	1132	1770	2175	3958
Chloroform in tap water (μg/L)[b]	—	—	—	8.6	50	64	76	83	105
Shower duration (min)[c]	3	5	5	10	15	20	30	35	60
Shower water flow rate (gpm)[d]	0.6	1.0	1.2	1.6	2.0	2.6	3.5	4.1	5.4
Chloroform in ambient air (μg/m^3)[e]	—	—	—	1.44	3.34	8.24	20.1	28.6	219

	Mean	CV or SD
Mass transfer coefficient (L/min)[f]	8.6	CV = 40%
Shower stall dimensions (m^3)	2.4	SD = 0.8

[a]From U.S. EPA. (2000); population-weighted distribution based on age groups 11–19 and 20+yr.

[b]From Wallace (1997), Table 3; weighted based on sample sizes for samples collected in Bayonne–Elizabeth, NJ, Los Angeles, CA, and Antioch–Pittsburg, CA (n = 785).

[c]From U.S. EPA. (1996).

[d]From Mayer et al. (1999).

[e]From Wallace (1997), Figure 13.

[f]From Little (1992). Assumed normally distributed; the mean was calculated as the average of 8 observed values, and CV was set to 40% so that all observed values were contained within the 95% bounds of the distribution.

[g]From Levesque et al. (2002). Assumed normally distributed; the mean and SD were obtained from 18 reported values.

TABLE 3. Lognormalized Sensitivity Coefficient (LSC) for Chloroform Concentrations in Blood and Exhaled Breath at 8:30 a.m.

	Chloroform in tap water = 8.6 μg/L		Chloroform in tap water = 50 μg/L	
Parameter	Blood	Exhaled breath	Blood	Exhaled breath
Shower duration	0.96	0.49	1.59	1.25
Chloroform in tap water	0.52	0.27	0.86	0.68
Shower stall volume	–0.38	–0.19	–0.63	–0.49
Chloroform in ambient air	0.47	0.73	0.14	0.32
Blood flow to liver	–0.73	–0.37	–0.76	–0.59
Cardiac output	–0.48	–0.28	–0.54	–0.35

Note. Chloroform concentrations in tap water used for analysis are the 25th and 50th percentiles from the distribution shown in Table 2.

It was assumed in the model that an individual resides in an indoor environment, in which the chloroform concentrations in tap water and in ambient air remain well mixed at constant values at all times within a 24-h

period. Although no direct data were found to support this assumption, the overlapping population-weighted frequency distributions of personal air concentrations measured at daytime and nighttime (Wallace, 1997) provided indirect evidence that chloroform concentration in ambient air does not vary much throughout the day. It was acknowledged that chloroform concentrations in tap water might vary from season to season (Wallace, 1997), but modeling chloroform formation and loss within the utility distribution system during different seasons was beyond the scope of the current study. In addition, the variance within a shorter period of time (i.e., 24 h) might not be as large as the seasonal variation. With the exposure regimens defined earlier, the model was exercised to simulate (1) the temporal profile of the blood and exhaled breath concentrations of chloroform over a 24-h period and (2) the dose-response (tap water concentration vs. blood concentration) relationship.

Time-Course Simulations The model was used to predict the temporal profile for a 24-h period to show how daily activities such as showering and drinking tap water affect the blood and exhaled breath concentrations of chloroform. In these time-course simulations, it was assumed that an individual takes a 15-min shower at 6:30 a.m. (shower water flow rate = 2 gal/min [gpm]; mass transfer coefficient = 8.6 L/min) and drinks water every 3 h between 6 a.m. and 9 p.m. every day. The amount of water ingested at each time was one-sixth of 675 ml/d, and the absorption of chloroform from the gastrointestinal (GI) tract over a 1.5-min period (drinking rate) was described as a first-order process with 100% bioavailability. The tap water concentration was set to 50 μg/L, and the ambient air concentration was set to 3.3 μg/m^3. Again, the current study did not consider the spatial or temporal fluctuations in water or air concentrations. The values of exposure parameters were the 50th percentiles from their respective distributions (Table 2) to reflect realistic exposure scenarios likely to be encountered by the members of general public.

Dose-Response Simulations To generate dose-response relationships under conservative exposure scenarios, one predicted the chloroform concentrations in blood at 8:30 a.m. This time point was chosen to be shortly after the shower taken at 6:30 a.m. Note that the model could be used to predict the chloroform concentrations in blood at any other time points as well. Using the same exposure scenarios described in the previous subsection, three-dimensional (3-D) plots were generated to show dose-response simulations at different shower durations and amounts of water ingestion.

Sensitivity Analysis

A sensitivity analysis was performed to evaluate the relative importance of the model parameters for predicting chloroform concentrations in blood and exhaled breath. A lognormalized sensitivity coefficient (LSC) for each parameter was calculated to indicate the percent change in model output per unit change (±1%) in each parameter (Clewell et al., 1994; Evans et al.,

1994). If |LSC| (the absolute value of a LSC) is near or larger than 1, the specific parameter evaluated is considered to have significant model output sensitivity. In this study, two analyses were performed to investigate the following issues:

1. How does the sensitivity of parameters vary at different time points for a given exposure scenario?
2. How does the sensitivity of parameters vary at different chloroform concentrations in tap water at a fixed time point?

Sensitivity of Parameters at a Given Exposure Scenario In the first set of analyses, we evaluated the time-dependent sensitivity of predicted blood and exhaled breath concentrations of chloroform for all parameters and reported those with |LSC| values larger than 0.5. LSCs of these parameters were analyzed in a 24-h period to include activities such as showering and drinking tap water. The same assumptions were made, for an individual to take a shower at 6:30 a.m. and to drink water every 3 h between 6 a.m. and 9 p.m. All parameters in the PBPK model were set to their individual mean values (Table 1), and all exposure parameter values were set to the 50th percentiles or means from their respective distributions (Table 2).

Sensitivity of Parameters at a Fixed Time Point In the second set of analyses, the same exposure scenario already described was used to examine the sensitivity of parameters on the blood and exhaled breath concentrations of chloroform at 8:30 a.m. The analyses were performed at two given chloroform concentrations in tap water (the 25th and 50th percentiles in Table 2) as examples. As in the first analysis, only parameters with |LSC| values larger than 0.5 were reported.

Monte Carlo analysis

Monte Carlo analysis can be used to evaluate the propagation of variability through a model and results in an estimate of the variance in model output (U.S. EPA, 1997). This estimation is achieved by randomly sampling model parameters from defined distributions and running the model for large number of iterations. A Monte Carlo implementation of a PBPK model can be viewed as conducting in silico studies in a large number of humans with diverse physiology. In this study, the Monte Carlo implementation of the model has the capability to simulate the distributions of chloroform concentrations in blood and exhaled breath at any specific time point. This capability is lacking from a large-scale biomonitoring study. For example, it is impractical and expensive to take a blood sample every hour from the same individual to evaluate how chloroform concentrations in blood vary throughout the day.

Among the pharmacokinetic (PK) parameters, the distributions of cardiac output, alveolar ventilation rate, partition coefficients, and metabolic parameters were assumed be lognormal, while tissue volume, tissue blood flow, and

effective skin permeability coefficient were assumed to have normal distributions (Table 1) (Corley et al., 1990, 2000; Brown et al., 1997; Clewell et al., 2000; Delic et al., 2000). All distributions were truncated at 1.96SD above and below the mean (95% of the distribution) to exclude physiologically implausible values. The distribution of body weight, from age 12 yr and up for both genders, was obtained from National Health and Nutrition Examination Survey (NHANES) (CDC, 1996). To be consistent, the body weight distribution was also truncated at the 2.5th and 97.5th percentiles to include only 95% of the distribution. The same truncating principle was applied to exposure parameters. One exception was the distribution of shower stall dimensions, truncated at mean ± 1SD, since the size of commercially available stalls were fairly consistent.

In our analysis, the chloroform concentrations in ambient air (C_{air}) was assumed to be either (1) independent of chloroform concentrations in tap water (C_{water}) or (2) linearly related to chloroform concentrations in tap water (C_{air} in ppm $= 0.0179 \times C_{water}$ in mg/L). This relationship was obtained from linear regression ($R^2 = .24$) of personal air versus drinking-water concentrations from the TEAM Study (Table 14 in Wallace, 1997). The first assumption was made considering chloroform concentrations in ambient air was more a function of factors other than chloroform concentration in water. These factors included water usage behaviors, air circulation, household dimensions, etc.

Two sets of Monte Carlo analyses were conducted, to mimic the following cases:

1. A controlled laboratory setting in which all individuals shower at 6:30 a.m. and drink tap water every 3 h between 6 a.m. and 9 p.m. All blood and exhaled breath samples are collected at a specific time point.
2. A real-life situation in which individuals shower and drink at different time points. Blood and exhaled breath samples are collected at various time points.

Controlled Laboratory Setting In this setting, two time points were chosen, 8:30 a.m. and 2 p.m., at which blood and exhaled breath samples were collected to investigate the impact of the timing of sample collection for VOCs like chloroform. The first time point (8:30 a.m.) represents a sample collection time closer to a main exposure event (shower at 6:30 a.m.) at which relatively higher chloroform concentration in the body is expected. In contrast, the second time point (2 p.m.) represents a collection time at which the chloroform concentration is expected to be close to the baseline concentration. The baseline concentration defined here is a result of exposure to chloroform in ambient air. Given the values of exposure parameters being the 50th percentiles shown in Table 2 and shower duration being 30 min, blood concentration at 8:30 a.m. is approximately 6.8% of the peak concentration (at the end of shower), while blood concentration at 2:00 p.m. is approximately 0.95% of the peak. At each of these two time points, the distributions of blood and

exhaled breath concentrations of chloroform were obtained from 10,000 iterations.

Real-Life Situation In this setting, along with other parameters in the model, the time of blood and exhaled breath samples collection and starting time of showering and drinking water were varied and the model was run for 10,000 iterations. Varying these time variables made this set of Monte Carlo analysis even closer to reality compared to the preceding analysis. A uniform distribution was assumed for the time of blood and exhaled breath samples collection between 8 a.m. and 8 p.m. The distribution of the starting time of showering was obtained from relative percentage data in a published report (Mayer et al., 1999). For drinking water, we assumed a water-drinking frequency of 6 times/d and the intervals between incidents were normally distributed with a mean of 3 h and SD of 0.9 h (CV = 30%). Same as other distributions, the distribution of the interval between each drinking-water incident was truncated at mean ± 1.96SD. The first drinking-water incident was obtained by sampling the interval twice from time zero (12:00 a.m.). For example, if the first interval was 3.2 h and the second interval was 2.9 h, the first drinking-water incident in this example would occur at h 6.1 (= 3.2 + 2.9; 6:06 a.m.). Each subsequently sampled interval was added to the previous time of drinking to get the time for the next drinking water event. This sampling process was repeated until six drinking-water events were achieved. Several features were added into the model to prevent unrealistic situations: (1) taking blood or breath samples in the shower or while drinking water; (2) drinking water while showering; and (3) taking blood or breath samples within 30 min after the end of shower (time to get dressed and get to the sample collection site).

Statistical Analysis

Statistical analysis was performed to examine the correlation between exposure (i.e., chloroform concentrations in tap water and ambient air and shower duration) and outcome (i.e., chloroform concentrations in blood or exhaled breath). From the Monte Carlo analyses, 10,000 pairs of exposure parameters and their corresponding chloroform concentrations in blood or exhaled breath were obtained. A Pearson correlation coefficient was computed from these 10,000 pairs to determine whether, in a gross sense, there is a relationship between exposure and outcome.

Reverse Dosimetry Predictions

The reverse dosimetry approach (Figure 1) demonstrated a simple approach to reconstruct the exposures that could have produced the measured biomonitoring data. Here the Monte Carlo analysis was first performed with timing of sampling and exposure events varied with other model parameters, because the variation in these time variables was inevitable in large-scale biomonitoring studies. A reference chloroform concentration in water (= 1 μg/L) was then used to predict the distribution of chloroform concentrations in blood (pg/ml). These output distributions were then inverted to obtain a distribution

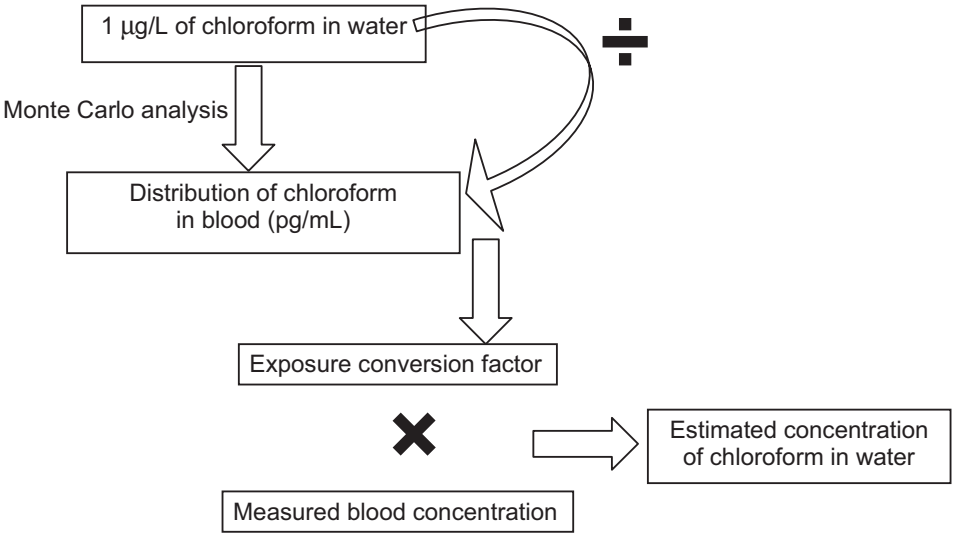

FIGURE 1. Schematic description of the reverse dosimetry approach.

of an "exposure conversion factor" (ECF) in (µg/L in water)/(pg/ml in blood). The distribution of the ECF can be multiplied by any observed chloroform concentrations in blood to estimate a distribution of chloroform concentrations in water to which the individual might have been exposed. Note that the distribution predicted by the reverse dosimetry approach is based on measurements obtained at a specific time point, with the variability between timing of sample and exposure events taken into consideration.

RESULTS

Model Evaluation

Shower Studies From Jo et al. (1990) The model predictions agreed with the observation from Jo et al. (1990) that inhalation exposure and dermal exposure during showering both contribute to the elevated chloroform concentrations in exhaled breath (Figure 2). Jo et al. (1990) compared the breath samples from the normal shower study and the inhalation-only study and concluded that skin absorption during showers was roughly equivalent to the inhalation exposure of chloroform. Our simulation results, which agreed well with the observed data, suggested the same.

Shower Studies From Levesque et al. (2002) Under the shower conditions reported by Levesque et al. (2002), the model-predicted chloroform concentrations in exhaled breath agreed well with the exhaled breath data collected 15 and 30 min after the end of the shower. Assuming the initial data

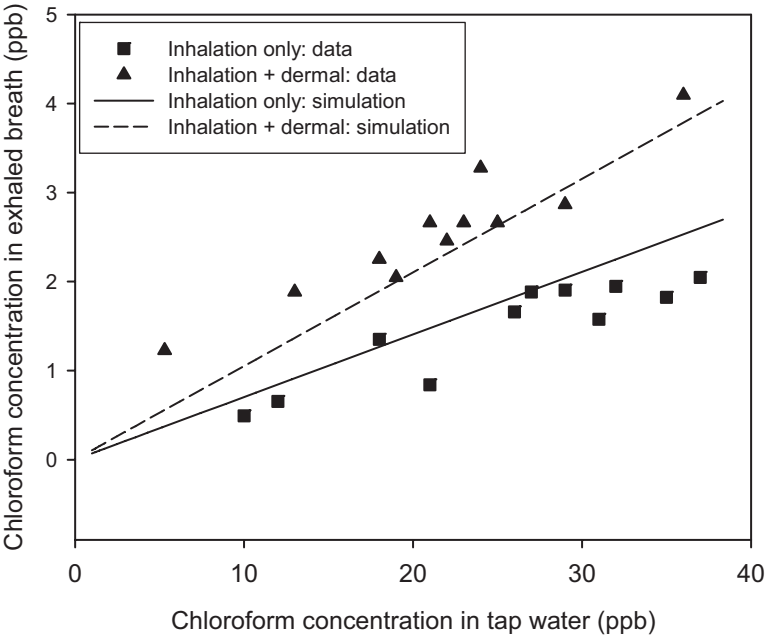

FIGURE 2. Simulations (lines) of chloroform concentrations in exhaled breath after shower and comparison with data (symbols) from Jo et al. (1990) at various chloroform concentration in tap water. The data were collected 5 min after the subjects were in 10-min normal showers (dermal and inhalation exposure) or 10-min showers wearing rubber clothes and boots (inhalation-only exposure).

were collected immediately after the end of the shower, the model overpredicted the chloroform concentrations in exhaled breath (Figure 3). However, if assuming a 2-min time gap between end of showering and sample collection (e.g., time to dry off and putting on clothes), the model would predict the chloroform concentration in exhaled breath to be 39.1 μg/m^3, which was very close to the mean of the observed data.

Exposure Studies From Backer et al. (2000) Model predictions for chloroform concentrations in blood agree well with experimental data measured by Backer et al. (2000) following 10-min showers and drinking of 1 L tap water (Figure 4). The chloroform concentrations in blood measured before the exposure were used as the baseline concentrations in the model. Backer et al. (2000) reported that ventilation fans were on in the bathrooms at the time of the shower study, but did not report the actual ventilation rate. Thus, a standard ventilation rate of 50 cfm (ft^3/min) recommended by the Home Ventilating Institute (http://www.hvi.org) was used. It is noteworthy that even without adding air ventilation into the model, the predicted chloroform concentrations in blood would still fall within the range of the experimental data (<90th percentile). Another important observation is that drinking 1 L water increased

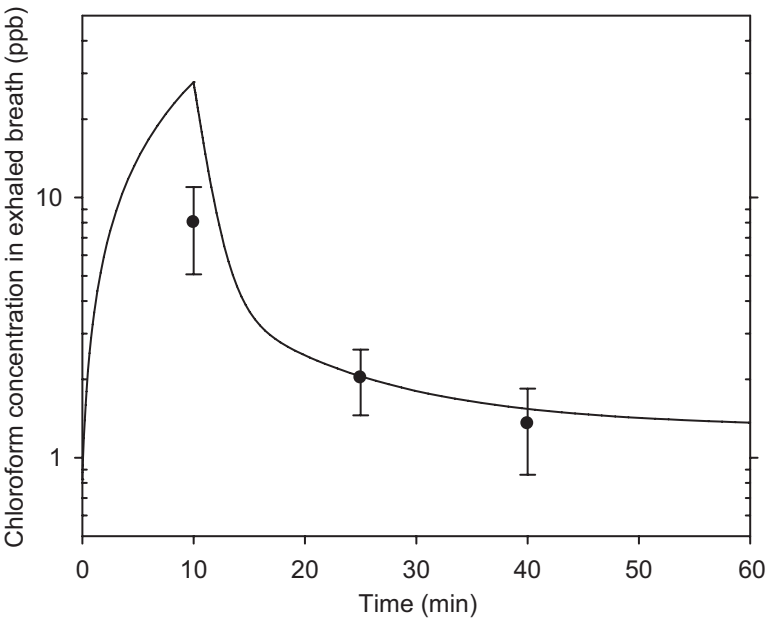

FIGURE 3. Temporal profile of chloroform concentrations in exhaled breath following a 10-min shower. Simulation (line) of the mean chloroform concentration (ppm) in exhaled breath and its comparison with data (means [symbols] ± 95% confidence intervals [error bars]) from Levesque et al. (2002).

chloroform concentration in blood by less than 10% of the increase resulting from showering for 10 min. The model simulations were able to capture this discrepancy in blood concentrations of chloroform resulting from different routes of exposure. In summary, the combined PBPK model and mass transfer model appeared to have reliable predictive ability for chloroform concentrations in blood and exhaled breath.

Model Simulations for Realistic Exposure Scenarios

Time-Course Simulations The model predicted increasing chloroform concentrations in blood during the shower and after water ingestion, followed by rapid elimination of chloroform from the blood via metabolism and exhalation (Figure 5A). Under the exposure scenarios defined, the model predicted much larger peak chloroform concentrations following the showering event than following drinking-water events. This prediction suggested that dermal and inhalation exposures to chloroform during showers account for the majority of the total chloroform exposure, which was consistent with other reports (Wilkes et al., 1996; Backer et al., 2000).

As seen with the simulations in blood, chloroform concentrations in exhaled breath increased rapidly during the shower and after water ingestion, followed by rapid elimination (Figure 5B). Compared to water drinking,

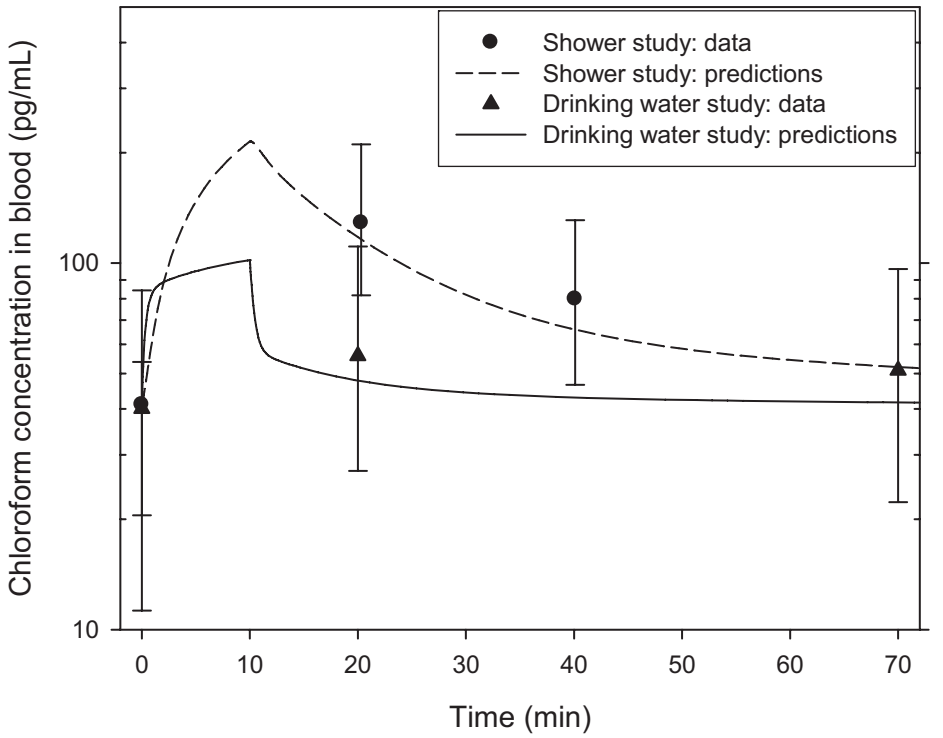

FIGURE 4. Temporal profile of chloroform concentration in blood following 10-min showers and drinking of 1 L tap water. Lines represent model simulations. Symbols are the median of experimental data, while the lower and upper bounds of the error bars represent the 5th and 95th percentiles, respectively (Backer et al., 2000).

showering had a much larger exhaled breath:blood ratio, because the exhaled breath from an individual during and after a shower contained chloroform from the dead space. In other words, part of the chloroform in exhaled breath was inhaled but did not partake in gas exchange for absorption. These time-course simulations suggested that correlating the exposure concentration with biomonitoring samples collected at a specific time point is a great challenge, especially with chemicals of relatively short half-lives.

Dose-Response Simulations With the chloroform concentration in tap water being varied from 0 to 80 μg/L (MCL for total trihalomethanes; U.S. EPA, 2001), three-dimensional plots were generated to show dose-response simulations at various shower durations and amount of water ingestion (Figure 6). Under the assumption of drinking water at 6 a.m. and showering at 6:30 a.m., model-predicted chloroform concentrations in blood at 8:30 a.m. increased linearly with the increasing concentrations in tap water (Figure 6A). On the other hand, chloroform concentrations in blood increased nonlinearly, at a

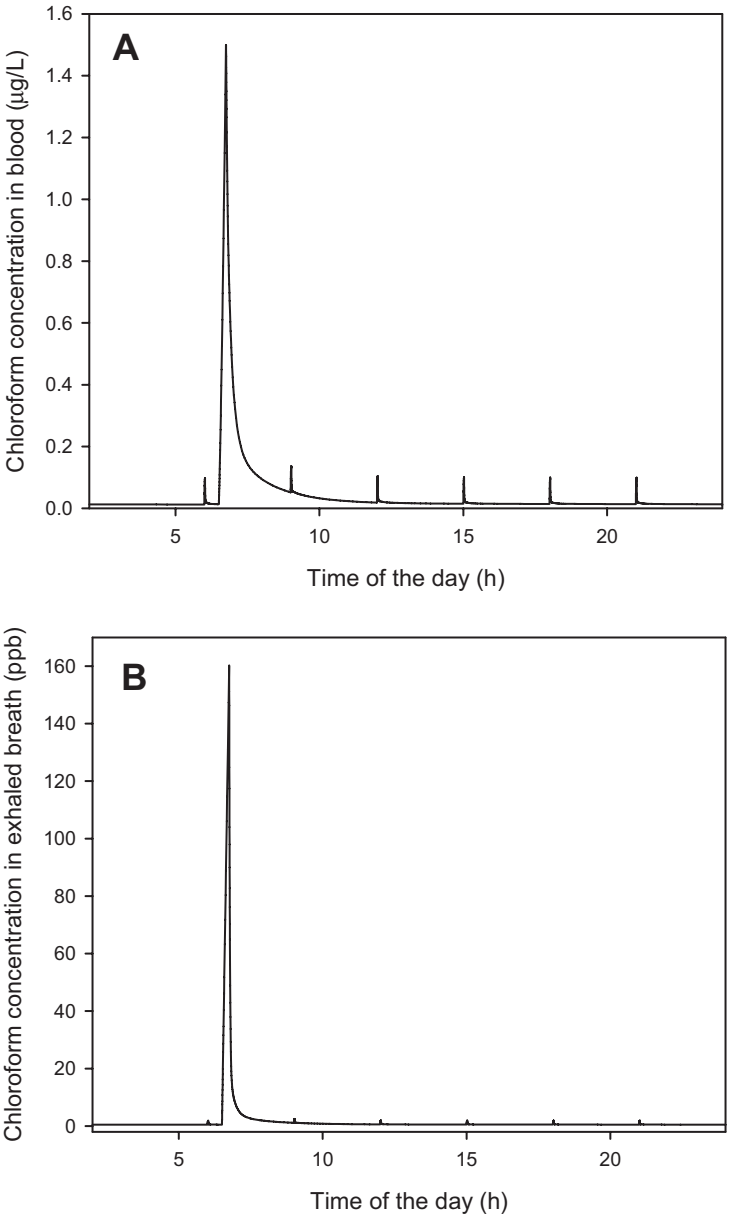

FIGURE 5. Time-course simulations for chloroform concentrations in (A) blood and (B) exhaled breath. For model simulations, the elevations in chloroform concentrations from the background were caused by dermal and inhalation exposures to chloroform during a 15-min shower (6:30 a.m.), and by oral exposure from drinking tap water (675 ml/d) at 6 a.m., 9 a.m., noon, 3 p.m., 6 p.m., and 9 p.m. Chloroform concentrations in the tap water and ambient air were assumed to be 50 μg/L and 3.3 $\mu g/m^3$, respectively.

given chloroform concentration in water, with increasing shower duration (Figure 6A). This nonlinear relationship between shower duration and chloroform concentrations in blood is a result of the chloroform vapor buildup in the shower stall as the shower duration lengthens. In contrast to shower duration, increasing the amount of water intake did not produce significant increases in chloroform concentrations in blood (Figure 6B). This is caused, in part, by the first-pass metabolism of chloroform from oral exposure; a significant amount of chloroform in drinking water was metabolized in the liver before being distributed to the rest of the body. Although chloroform concentrations in blood are still elevated with the increasing concentrations of chloroform concentrations in water (Figures 6B), the elevations were mostly produced by events other than drinking tap water, such as showering.

Sensitivity Analysis

Sensitivity of Parameters at a Given Exposure Scenario The results of the sensitivity analyses showed that only a few parameters had relatively large impacts on blood or exhaled breath concentrations of chloroform. Here data only showed the time-dependent sensitivity for parameters with |LSC| values larger than 0.5 (Figure 7). These parameters were shower duration, chloroform concentrations in tap water and ambient air, shower stall volume, cardiac output, and blood flow rate to the liver. Data showed the LSCs of these parameters over a 24-h period to reflect exposure events such as showering. Immediately after the shower at 6:30 a.m., the impacts of shower duration, tap-water chloroform concentration, and shower stall volume on predicted chloroform concentrations in blood and exhaled breath concentrations surged (Figure 7). Outside of the showering period, chloroform concentration in ambient air had the greatest sensitivity.

Sensitivity of Parameters at a Fixed Time Point Sensitivity analysis at 8:30 a.m., shortly after showering at 6:30 a.m., was also performed and showed those parameters with |LSC| value greater than 0.5 (Table 3). Shower duration was the only parameter that had an LSC value larger than 1. The largest impact on chloroform concentrations in blood was for shower duration, tap-water chloroform concentration, and blood flow to liver (Table 3), while the largest impact on chloroform concentrations in exhaled breath was for shower duration and ambient chloroform concentration. The magnitudes of LSC for shower duration increased with rising tap-water concentrations, while the magnitudes of LSC for chloroform concentrations in ambient air decreased with increasing tap-water concentrations. Consistent with other model simulations, blood and exhaled breath concentrations of chloroform were not sensitive to changes in water ingestion amounts.

Monte Carlo Analysis

Controlled Laboratory Settings In the first analysis, the distributions of chloroform concentrations in blood and exhaled breath were assessed at 8:30 a.m. and 2 p.m. (Table 4). The model-predicted chloroform concentrations in blood were compared with the data measured by the Third National Health

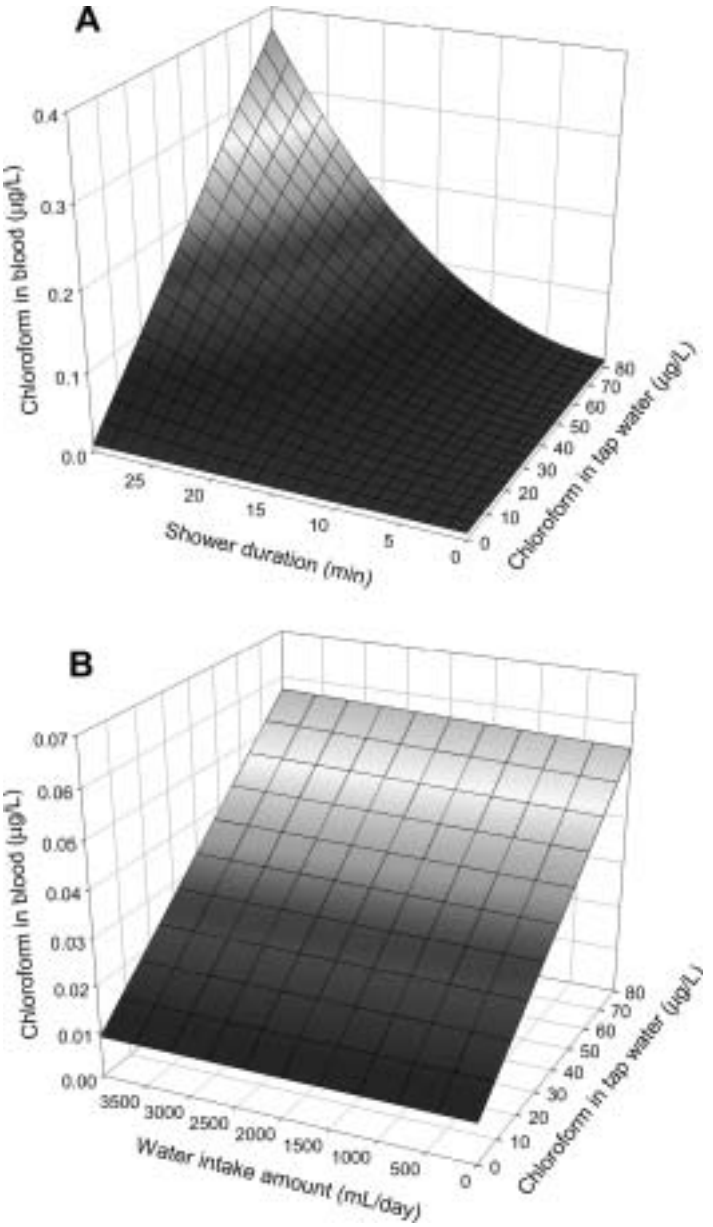

FIGURE 6. Dose-response relationships between chloroform concentrations in tap water and in blood at (A) various shower durations and (B) water intake amounts. Chloroform concentrations in blood shown on *z* axis are the model predictions at 8:30 a.m. The individual was assumed to start the shower at 6:30 a.m. (for 15 min in B), which results in dermal and inhalation exposures to chloroform during the shower. The individual was also exposed to chloroform from drinking tap water (675 ml/d in A) at 6 a.m., 9 a.m., noon, 3 p.m., 6 p.m., and 9 p.m.

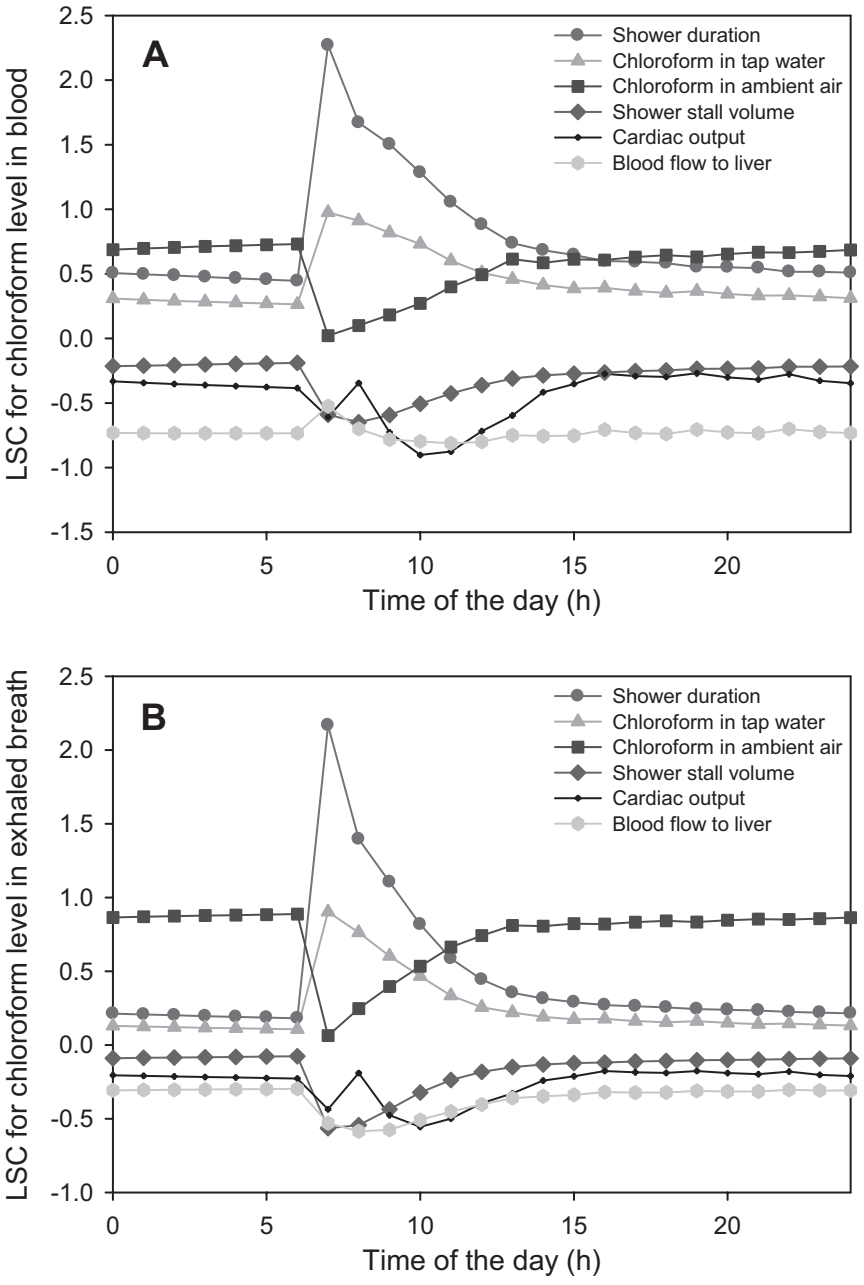

FIGURE 7. Lognormalized sensitivity coefficients (LSCs) for parameters with $|LSC| > 0.5$. The model output was chloroform concentrations (A) in blood and (B) in exhaled breath. It was assumed that an individual takes a 15-min shower at 6:30 a.m. and drinks water every 3 h between 6 a.m. and 9 p.m. (6 times/d).

TABLE 4. Predicted Percentiles of the Distribution of Chloroform Concentrations in Blood (pg/ml) and Exhaled Breath (ppb) at Fixed Sampling Time, 8:30 a.m. and 2 p.m.

	Percentile						
	5%	10%	25%	50%	75%	90%	95%
Measured distributions of chloroform concentrations in blood (pg/ml)							
NHANES III data	—	—	—	23	41	77	127
Predicted distributions of chloroform concentrations in blood (pg/ml)							
Assume chloroform concentrations in ambient air independent of chloroform concentrations in water							
Sampled at 8:30 a.m.	7.2	11	22	51	106	206	306
Sampled at 2 p.m.	3.1	4.7	8.7	17	34	60	77
Assume chloroform concentrations in ambient air (ppm) = 0.0179 × chloroform concentrations in water (mg/L)							
Sampled at 8:30 a.m.	2.4	4.1	15	42	93	180	276
Sampled at 2 p.m.	0.9	1.5	4.6	16	24	35	46
Predicted distributions of chloroform concentrations in exhaled breath (ppb)							
Assume chloroform concentrations in ambient air independent of chloroform concentrations in water							
Sampled at 8:30 a.m.	0.22	0.32	0.63	1.31	2.59	4.45	6.53
Sampled at 2 p.m.	0.11	0.161	0.31	0.62	1.25	2.50	3.29
Assume chloroform concentrations in ambient air (ppm) = 0.0179 × chloroform concentrations in water (mg/L)							
Sampled at 8:30 a.m.	0.07	0.11	0.36	1.08	1.98	3.44	4.96
Sampled at 2 p.m.	0.04	0.06	0.17	0.64	0.88	1.11	1.28

Note. It was assumed that an individual takes a 15-min shower at 6:30 a.m. and drinks water every 3 h between 6 a.m. and 9 p.m. (6 times per day). Percentiles of the distribution of chloroform concentrations in blood measured by the NHANES III (summarized by Wallace, 1997) are also shown for comparison with the predictions.

and Nutrition Examination Survey (NHANES III; Table 4). NHANES III data fell in the range predicted by the model at the two hypothetical sampling time points (conservative predictions at 8:30 a.m. and background levels at 2 p.m.). The difference in model predictions between these two time points suggested that timing of sample collection is an important factor when evaluating biomonitoring data for chloroform.

The correlation coefficients between exposure parameters and outcome were also calculated (Table 5). In the case where chloroform concentrations in water and ambient air were independently sampled, chloroform concentrations in blood and exhaled breath were more strongly correlated with chloroform concentrations in water and shower duration at the 8:30 a.m. sampling time than at the 2 p.m. sampling time. Conversely, the correlation with ambient air concentrations was stronger at 2 p.m. than at 8:30 a.m. These results suggested that at 8:30 a.m., chloroform concentrations in the body were the results of inhalation and dermal exposure from the shower taken at 6:30 a.m. By 2 p.m., chloroform in the body from the exposure to the early morning shower has long been metabolized and eliminated; instead, exposure to

TABLE 5. Correlation Coefficients Between Exposure Parameters (i.e., Chloroform Concentrations in Water and in Ambient Air and Shower Duration) and Outcome (i.e., Chloroform Concentrations in Blood and Exhaled Breath)

	Water	Shower duration	Ambient air
Correlations with chloroform concentrations in blood			
Assume chloroform concentrations in ambient air independent of chloroform concentrations in water			
Sampled at 8:30 a.m.	0.366	0.596	0.330
Sampled at 2 p.m.	0.120	0.178	0.929
Assume chloroform concentrations in ambient air (ppm) = 0.0179 × chloroform concentrations in water (mg/L)			
Sampled at 8:30 a.m.	0.429	0.631	—
Sampled at 2 p.m.	0.693	0.466	—
Correlations with chloroform concentrations in exhaled breath			
Assume chloroform concentrations in ambient air independent of chloroform concentrations in water			
Sampled at 8:30 a.m.	0.281	0.453	0.700
Sampled at 2 p.m.	0.035	0.062	0.991
Assume chloroform concentrations in ambient air (ppm) = 0.0179 × chloroform concentrations in water (mg/L)			
Sampled at 8:30 a.m.	0.511	0.600	—
Sampled at 2 p.m.	0.893	0.293	—

Note. All correlation coefficients shown in the table are significantly different from zero ($p < 0.05$).

chloroform in ambient air now has a greater impact on the chloroform concentrations in blood and exhaled breath at 2 p.m.

In the case where chloroform concentrations in ambient air were a linear function of water concentrations, correlations between exposure (water concentration and shower duration) and chloroform concentrations in blood and exhaled breath were stronger than those assuming background air concentrations were independent of water concentrations (Table 5). The shower duration had greater correlation with the outcome at 8:30 a.m. than at 2 p.m.

Real-Life Situations In this analysis, the distributions of chloroform concentrations in blood and exhaled breath were predicted, with timing of sample collection and exposure event varied with other model parameters. The predicted distribution of chloroform concentrations in blood agreed well with the measured distributions from NHANES III (Table 6). In particular, the median of the NHANES III data (23 pg/ml chloroform in blood) was included in the range bounded by the 25th and 75th percentiles of model predictions, whether chloroform concentrations in air was assumed to be independent or linearly correlated with chloroform concentrations in water.

Again, the correlation coefficients between exposure and outcome were calculated (Table 7). In the case where chloroform concentrations in water and ambient air were independently sampled, chloroform concentrations in blood and exhaled breath were most strongly correlated with chloroform concentrations in ambient air, even though shower duration and water

TABLE 6. Predicted Percentiles of the Distribution of Chloroform Concentrations in Blood (pg/ml) and Exhaled Breath (ppb) With Timing of Sample Collection and Exposure Events Varied

	Percentile						
	5%	10%	25%	50%	75%	90%	95%
Measured distributions of chloroform concentrations in blood (pg/ml)							
NHANES III data	—	—	—	23	41	77	127
Predicted distributions of chloroform concentrations in blood (pg/ml)							
Assume chloroform concentrations in ambient air independent of chloroform concentrations in water							
Blood (pg/ml)	3.3	4.8	9.3	19	42	79	135
Assume chloroform concentrations in ambient air (ppm) = 0.0179 × chloroform concentrations in water (mg/L)							
Blood (pg/ml)	1.1	1.7	5.9	17	28	54	95
Predicted distributions of chloroform concentrations in exhaled breath (ppb)							
Assume chloroform concentrations in ambient air independent of chloroform concentrations in water							
Breath (ppb)	0.12	0.17	0.32	0.69	1.49	2.82	3.80
Assume chloroform concentrations in ambient air (ppm) = 0.0179 × chloroform concentrations in water (mg/L)							
Breath (ppb)	0.04	0.07	0.20	0.68	0.95	1.37	2.02

Note. Percentiles of the distribution of chloroform concentrations in blood measured by the NHANES III (summarized by Wallace, 1997) are also shown for comparison with the predictions.

TABLE 7. Correlation Coefficients Between Exposures (i.e., Chloroform Concentrations in Water and in Ambient Air, Shower Duration) and Outcome (i.e., Chloroform Concentrations in Blood and Exhaled Breath)

	Water	Shower duration	Ambient air	Interval[a]
Model predictions with independent chloroform concentrations in water and in ambient air				
Blood	0.196	0.229	0.604	–0.248
Breath	0.110	0.125	0.911	–0.131
Model predictions with correlation between chloroform concentrations in water and in ambient air				
Blood	0.302	0.260	—	–0.279
Breath	0.464	0.237	—	–0.260

Note. All correlation coefficients shown in the table are significantly different from zero ($p < 0.05$).
[a]Time interval between the end of shower and sampling time.

concentration of chloroform still played important roles. In addition, with increasing time interval between the end of shower and sampling time, the model-predicted chloroform concentrations in blood and exhaled breath decreased (Table 7). In the case where chloroform concentrations in tap water and ambient air were linearly correlated, chloroform concentrations in the body were mainly determined by chloroform concentration in tap water, shower duration, and the interval between the end of shower and sampling time (Table 7).

REVERSE DOSIMETRY PREDICTIONS

For the reverse dosimetry predictions, the case in which chloroform concentrations in ambient air was linearly correlated with concentrations in tap water was selected. This case was selected because it resulted in a higher degree of correlation between chloroform concentrations in water and blood (Table 5). By setting the chloroform concentration in water to a reference value of 1 μg/L, Monte Carlo simulations provided a distribution of chloroform concentrations in blood, which was inverted to obtain the distribution of ECFs (Table 8). To obtain the approximate distribution of chloroform concentrations in water associated with a measured chloroform concentration in blood, one can multiply the known blood concentration by the distribution of ECFs. Taking the observed values from the NHANES III study, for example, the median blood concentration (23 pg/ml) is likely to be associated with 61 μg/L chloroform in tap water (23 pg/ml × median of ECF), with a 5th percentile of 12 μg/L and a 95th percentile of 104 μg/L. The applicability of this reverse dosimetry approach can be validated once data with corresponding chloroform concentrations in tap water and in blood become available.

DISCUSSION

Exposure assessment is a key aspect in studying potential health effects that may result from environmental toxicants. Exposure can be estimated based on indirect measures (e.g., centralized monitoring of community air or water) and then interpreted as the individually exposed concentration based on questionnaires or activity diaries. For some environmental toxicants, direct measurement of the individuals is sometimes possible. For example, personal air monitoring can evaluate chloroform exposure by the inhalation route. Although this method documents potential exposure, it does not provide information about the concentrations of environmental toxicant that actually enter the body. The concentrations of environmental toxicants that actually enter the body can be assessed using biomonitoring. Biomonitoring offers the advantage of verifying actual uptake of the environmental toxicant from all

TABLE 8. Distribution of Exposure Conversion Factor (ECF)

	Percentile						
	5%	10%	25%	50%	75%	90%	95%
ECF (μg/L in water per pg/ml in blood)	4.52	4.11	3.42	2.65	1.73	0.877	0.506

Note. This distribution ECF can be multiplied by any observed chloroform concentrations in blood to estimate a distribution of chloroform concentrations in water to which the individual might have been exposed.

possible sources at the point in time when the sample is collected. Biomonitoring data combined with PBPK models, which can relate exposure to the biologically effective dose delivered to the target tissue, can be effective tools in better characterizing exposure and estimating human health risk.

There has been considerable progress over the years in developing PBPK models for toxic chemicals by integrating animal toxicological studies and mitigating extrapolation issues (from low to high dose and from animal to human). PBPK models have been primarily used in a prognostic manner to predict chemical concentrations at target tissues with a given dose. Previous studies utilized PBPK models to predict chloroform concentrations in blood or exhaled breath resulting from typical daily human exposure (Blancato & Chiu, 1993; Chinery & Gleason, 1993; Levesque et al., 2002). Although using the same model from Corley et al. (1990, 2000), these studies did not account for the interindividual variability in human pharmacokinetics, exposure concentrations, and temporal profiles of human activities related to relevant exposure pathways. By incorporating these variabilities in the Monte Carlo analysis, the current study was able to characterize the distributions of chloroform concentrations in blood and exhaled breath in a population.

Besides applying PBPK models in a prognostic manner as described earlier, PBPK models have also been utilized in a diagnostic mode to reconstruct exposures using biomonitoring data (Georgopoulos et al., 1994; Roy et al., 1996a). For example, one study compared the measured chloroform concentrations in exhaled breath with the PBPK model-predicted concentrations while varying chloroform concentrations in ambient air and water until the statistically optimized agreement was obtained. The estimated concentrations in ambient air and water were within a factor of two of the measured concentrations (Georgopoulos et al., 1994; Roy et al., 1996a). Such an approach directly estimates multiroute exposure concentrations from the biomonitoring data. One major limitation of this approach, however, is that the number of parameters (e.g., exposure concentrations in different media) that can be varied has to be less than the number of data points being optimized. Rather than this optimization approach, Monte Carlo analysis was used to perform reverse dosimetry predictions after utilizing the PBPK model in a prognostic manner to predict the distribution of chloroform concentrations in tissues at a given exposure concentration. A similar technique was used in a study that estimated the distribution of methylmercury (MeHg) concentrations in the hair of pregnant women, and subsequently inverted the output distribution to generate a distribution of MeHg ingestion rates (Clewell et al., 1999).

Besides PBPK models, linear compartmental models were also used to relate concentrations of VOCs in exhaled breath to exposure (Wallace et al., 1993). These linear models are easy to construct since chemical distribution in the body is described with one to three compartments. These models are also easy to use because analytical solutions are often obtainable for special cases (e.g., when exposure concentration is zero, constantly high, or linearly increasing). Linear models could be of use when the chemical-specific (i.e., metabolism)

and kinetic parameters are not well characterized in humans. However, they lack the capability to describe a physiological system with large tissue-to-tissue concentration variations. Other limitations of such classical compartmental models are the inability to (1) estimate target tissue concentrations, (2) conduct route-to-route extrapolation, and (3) perform intraspecies extrapolation for human risk estimates.

One question addressed when designing the current study was how much detail should be included in the model. This question was investigated in two regards: (1) the complexity of the PBPK model structure, and (2) the description of human exposure to chloroform from various sources and routes. In the first regard, a PBPK model (Corley et al., 2000) was chosen that has a simpler description of the skin compartment than other chloroform models (Chinery & Gleason, 1993; Roy et al., 1996b). The other models used more than one compartment to represent different layers of the skin (e.g., stratum corneum and viable epidermis). The additional complexity of the skin compartment might be more realistic biologically, but weighed against that is the corresponding increase in the number of model parameters and their uncertainty. Therefore, the PBPK model (Corley et al., 2000) with the simplest description of the skin compartment was first evaluated against the controlled shower studies (Jo et al., 1990; Backer et al., 2000; Levesque et al., 2002), and the predicted results showed the model to be adequate without added complexity.

In the second regard, a comprehensive exposure regimen needed to aggregate all major contributing factors. Such factors include spatial and temporal profiles of chloroform in water, chloroform in ambient air, human activities, and water consumption patterns. The spatial and temporal profile of VOCs present in household air has been evaluated with compartment models in several studies (McKone, 1987; Weisel et al., 1999a; Wilkes, 1999; Kim et al., 2004). These models divided the entire household into three or more compartments (e.g., shower/bath stall or bathroom). In each compartment, the temporal profile of VOCs was estimated by solving mass balance equations coupled with descriptions of human activity patterns. Patterns considered to have an impact on exposure included duration and frequency of water device usage, the flow rate and/or volume of use of water when operating water devices, water usage/consumption rate, and occupancy in each compartment. There are even models that estimate the mass transfer of VOCs while operating residential dishwashers and washing machines (Shepherd et al., 1996; Howard & Corsi, 1998; Howard-Reed et al., 1999). This study focused mainly on major exposure events (i.e., showering and drinking water) and merged all other contributing factors (e.g., dishwashing, laundry, use of bleach) into one parameter: chloroform concentrations in ambient air. It was also assumed that chloroform concentrations in ambient air do not vary spatially or temporally in a well-mixed household environment while evaluating the correlation between chloroform concentrations in ambient air and in tap water at two extreme conditions: (1) chloroform concentrations in ambient air is independent of chloroform

concentrations in tap water (zero correlation), and (2) chloroform concentrations in ambient air is correlated with chloroform concentrations in tap water.

The current study focuses on using PBPK modeling to estimate exposure consistent with biomonitoring data. Although not the purpose of the current study, PBPK modeling can also be used to link biomonitoring data to target tissue dose in risk assessment. PBPK models are known for their abilities to integrate toxicological and mechanistic data from animal studies and to extrapolate pharmacokinetics from high dose to low dose and from animals to humans. In addition, PBPK models can be combined with pharmacodynamic (PD) models to describe the tissue dose–adverse health effects relationship. For example, the carcinogenic risk of chloroform resulting from exposure when showering and swimming was estimated using a PBPK/PD model that predicts concentrations of chloroform metabolites bound to hepatic and renal tissue (Levesque et al., 2000, 2002). The PBPK/PD model used by Levesque et al., however, did not describe regenerative cellular proliferation and thus cannot be used for multiple-exposure scenarios (Reitz et al., 1990). Alternatively, a PBPK/PD model in which the rate of chloroform metabolism was connected with cytolethality to predict regenerative cellular proliferation may be used for risk assessment (Tan et al., 2003).

From our analysis, showering results in much higher chloroform concentrations in blood than does water drinking. The conclusion is consistent with that suggested by the experimental studies (Backer et al., 2000). This result alone, however, does not tell us anything about chloroform metabolism or possible adverse health effects. Note that it is chloroform metabolites, not the parent compound, that induce cytolethality in target tissues. Chloroform concentration in blood is higher after showering than after water–drinking exposure. However, it is possible that more chloroform is metabolized (first–pass) after water–drinking exposure and may exert more toxicity compared to showering exposure. Only by integrating biomonitoring and PBPK/PD modeling techniques into both exposure and risk assessments can one obtain a more scientific basis for regulatory decisions made to protect the public health.

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APPENDIX

In the mass transfer model developed by Weisel et al. (1999b), chloroform is assumed to transfer from a plug flow stream of water to a completely mixed volume of air in shower stalls (Figure A1). The air entering the shower stall has chloroform concentration C_A and flow rate Q_A. Chloroform concentrations of water entering and leaving the shower stall are $C_{W,\,in}$ and $C_{W,\,out}$, respectively, with constant water flow rate Q_W. As the water passes through the air in y-direction, chloroform is evaporated from water to air. The concentrations of chloroform in the plug flow of water (C_W) can be described as:

$$\frac{dC_W}{dy} = \frac{K_{OL}(C_W - C_A/H)P}{Q_W} \tag{A1}$$

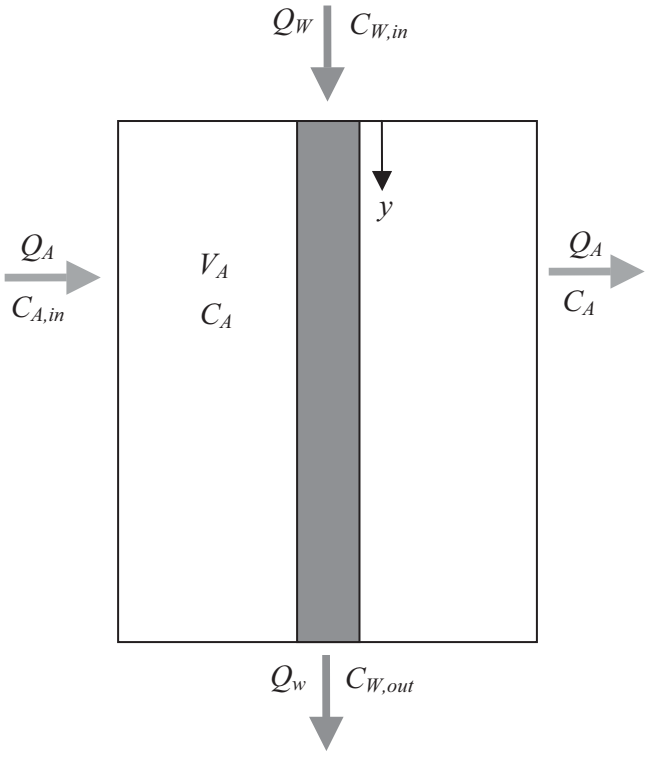

FIGURE A1. Hypothetic shower system for the mass transfer of chloroform from a plug flow of water to a completely mixed volume of air. Q_A, air flow rate; Q_W, water flow rate; V_A, air volume in shower stall; $C_{A,\,in}$, chloroform concentration in the air entering the system; C_A, chloroform concentration in the air of shower stall; $C_{W,\,in}$, chloroform concentration in the water entering the system; $C_{W,\,out}$, chloroform concentration in the water leaving the system.

where K_{OL} is the mass transfer coefficient and P is the perimeter of the water stream (Weisel et al. 1999b). H is the Henry's law constant for chloroform, which describes the phase equilibrium between air and a dilute aqueous solution of dissolved chloroform. The Henry's law constant is a function of temperature (Weisel et al. 1999b). For chloroform, the temperature dependency of H is:

$$H = 0.12\left(\frac{293}{T}\right)10^{1930\cdot\left(\frac{1}{293}-\frac{1}{T}\right)} \tag{A2}$$

where T is the absolute temperature. If we assume C_A to be a constant during the residence time of the water passing through the compartment (pseudo steady state), Eq. (A1) can be integrated (Weisel et al., 1999b) to:

$$C_{W,out} = C_{W,in}\exp\left(-\frac{K_{OL}A}{Q_W}\right)+\left(\frac{C_A}{H}\right)\left[1-\exp\left(-\frac{K_{OL}A}{Q_W}\right)\right] \tag{A3}$$

where A is the active interfacial area through which the mass transfer takes place (P multiplied by the length of the water stream). The rate of change for chloroform concentration in shower air is then expressed as:

$$\left(\frac{dC_A}{dt}\right)V_A = Q_W(C_{W,in}-C_{W,out})-Q_A(C_A-C_{A,in}) \tag{A4}$$

Equations (A3) and (A4) were solved simultaneously in our modeling program. The volumetric mass transfer coefficient $K_{OL}A$ was reported by Weisel et al. (1999a, 1999b) based on different shower systems. The variation of $K_{OL}A$ from different shower systems might be caused by the difference in the design of shower heads (Weisel et al., 1999a, 1999b). In summary, the rate of the volatile emission of chloroform is determined by the water temperature, the concentrations of chloroform in water and air, the flow rates of the showering water and air circulation in the shower stall, and the design of the shower head.