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Estimation of Background Exposure to Toluene Using a Physiologically-Based Kinetic Model

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Abstract: Estimation of Background Exposure to Toluene Using a Physiologically-Based Kinetic Model: Crispin H. PIERCE, *et al.* Department of Environmental Health, University of Washington—Estimation of environmental exposure to toxicants has generally been limited to concentration measurements in air, water, and foods. Measurement of background levels of toxicants in biological tissues for this purpose has been limited by analytical detection. After developing a sensitive headspace GC-MS method, we conducted 33 controlled human exposures of 50 ppm $^1H_8$-toluene and 50 ppm $^2H_8$-toluene for 2 h, and measured concentrations in blood and breath for 100 h post-exposure. Blood and breath samples from a separate cohort of 9 men exposed to $^2H_8$-toluene only were also measured for background $^1H_8$-toluene levels. A physiologically-based kinetic (PBK) model, previously constructed and validated in an analysis of the $^2H_8$-toluene data, was used to predict the level of ambient $^1H_8$-toluene exposure that produced the observed breath levels. The model-derived estimate of mean background $^1H_8$-toluene exposure was 47 ± 44 ppb (mean ± s.d.), which is consistent with indoor air measurements from this and previous studies of 3–27 ppb and outdoor measurements of 2–43 ppb. According to the PBK model, background exposure was expected to produce an average blood concentration of 5.9 nmol/*l*, which was within a measured range of 3–16 nmol/*l*, and a corresponding alveolar air concentration of 310 nmol/m^3, within a range of 138–764 nmol/m^3. This work extends the use of physiologic modeling to back-predict environmental dose, and found that significant differences in inter-individual $^1H_8$-toluene background exposures exist. (*J Occup Health 1997; 39: 130–137*)

Key words: Toluene, Toxicokinetics, PBPK, Model, Isotope

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A major obstacle in defining the quantitative relationships between toxicant dose for individuals and biomarkers of exposure (such as concentrations of toxicants in blood or breath, or metabolites in urine) has been the variable contributions from background environmental exposure. There is overlap between the biological levels attributed to occupational or controlled exposure, and those resulting from background exposure. In the case of $^1H_8$-toluene, studies with controlled human exposures have assumed that blood concentrations of ≥100 nmol/*l* were well above background and solely due to administered $^1H_8$-toluene[1,2]. Occupational studies have attributed blood levels down to 12–110 nmol/*l* to workplace exposure alone[3–7]. However, average concentrations in blood from non-occupationally exposed groups have been measured to be 3–14 nmol/*l*, with a range of 0–206 nmol/*l*[8–13]. To distinguish the contributions of background and administered solvent, we conducted toxicokinetic studies using controlled exposures to both the native and a stable isotope-labeled toluene. Data were then analyzed within a physiologically-based kinetic (PBK) model to afford a more precise and adaptable method of background dose estimation for the native compound.

PBK models have been widely used in the prediction of biological levels of drugs and toxicants following known or estimated exposures. The flexible nature of these models allows for a variety of questions to be asked regarding the time-dependent relationships between xenobiotic exposure and concentrations in blood, breath, urine, or target tissue. Recently, Thomas *et al.*[14] used a Monte Carlo-based uncertainty analysis of PBK model parameters in a simulation study to estimate the fractions of workers expected to exceed Biological Exposure Index (BEI) values if exposed at current occupational guideline levels[15]. Leung[16] used a PBK model to predict 13 toxicant concentrations in breath, blood, and urine, given occupational exposure at current limits.

A more novel use of PBK models is the estimation of exposure resulting in the observed biological levels. This approach can be used to estimate absorbed dose, given

variations in occupational and environmental exposure concentrations and individual toxicokinetics. Georgopoulos *et al.*[17] used data previously collected on chloroform concentrations in exhaled breath to back-predict levels in air and water while subjects were showering or swimming[18]. We sought to use a PBK model to estimate the concentrations of $^1H_8$-toluene in ambient air that produced the measured background levels in blood and breath.

Methods

Chemicals

$^2H_8$-toluene (99.6 g-atom%) was obtained from Cambridge Isotope Laboratories (Andover, MA, USA). Toluene was distilled-in-glass grade (Burdick and Jackson, Muskegon, WI, USA).

Subjects

Twenty-six men ages 20 to 62 were recruited by advertisement on campus and given a self-administered questionnaire to screen for occupational solvent exposure. Five of these subjects participated in 2 or 3 replicate exposures, with at least 2 weeks between exposures, for a total of 33 experiments. These men were exposed to an equimolar mixture of $^1H_8$- and $^2H_8$-toluene. A separate group of nine men, ages 24 to 62, were exposed to $^2H_8$-toluene alone. Four of these subjects had two exposures each, for a total of 13 experiments. This group was used to test the ability of the model derived from the co-exposures to $^1H_8$- and $^2H_8$-toluene to back-predict ambient exposure levels of $^1H_8$-toluene. Smokers, those with chronic illness or on chronic medication, and those with occupational solvent exposure were excluded from the study. Individuals with anemia, acute respiratory infection, rhinitis or asthma were given medical evaluations before entering the study. This study was approved by the Institutional Review Board at the University of Washington.

Men participating in the combined exposures had a range in body weight of 67–129 kg, height of 1.65–1.98 m, and fraction of the body that was adipose tissue of 0.10–0.39 kg/kg, estimated by a skin fold method using Lange calipers[19]. Alveolar ventilation rates (4.5–9.7 *l*/min), estimated as 70% of total ventilation, and inhaled $^1H_8$-toluene concentrations (43–71 ppm) and $^2H_8$-toluene concentrations (45–68 ppm) were also measured[20]. Similarly, the group exposed to $^2H_8$-toluene alone had weights of 67–112 kg, heights of 1.64–1.90 m, adipose fractions of 0.13–0.36 kg/kg, and ventilation rates of 5.8–7.8 *l*/min. All subjects were Caucasian.

Exposures and sampling

Subjects inhaled via a gated mouthpiece either 100 ppm of an approximately equimolar mixture of $^1H_8$-toluene and $^2H_8$-toluene (first group) or 50 ppm of $^2H_8$-toluene (second group) for 2 h. The exposure system provided real time measurement of inhaled and exhaled concentrations of total $^1H_8$- and $^2H_8$-toluene, respiratory flow rate, and exhaled CO_2 concentration[20]. Inspired gas from each exposure was measured for exact $^1H_8$- and $^2H_8$-toluene concentrations[23].

One antecubital venous blood sample and one breath sample were taken prior to exposure for determination of pre-exposure $^1H_8$-toluene concentrations; 16 blood and breath samples were taken after the end of exposure over the following 4 d, at sampling intervals that varied from every 15 min immediately following exposure to every 12 h at times ≥24 h after exposure. In the group experimentally exposed only to $^2H_8$-toluene, twenty-two blood samples and 16 breath samples were collected for each exposure over a 100 h period, and analyzed for $^1H_8$-toluene concentration.

Blood samples were collected in 5 m*l* Vacutainer® tubes containing citrate. Exhaled breath samples were collected in 10 *l* (initial high-concentration samples) or 20 *l* (remaining samples) Tedlar® plastic bags pre-filled with dry nitrogen and kept at 37°C to prevent condensation.

Chemical analyses

Blood samples were analyzed in triplicate for $^1H_8$-toluene and $^2H_8$-toluene by headspace gas chromatography coupled with mass spectrometry detection in the selected ion mode[21]. Apparent low-level contamination through contact with Vacutainer® vials or catheters compromised the $^1H_8$-toluene concentrations in pre-exposure and late post-exposure blood samples from the combined $^1H_8$- and $^2H_8$-toluene mixture study. This source of $^1H_8$-toluene contamination was eliminated for the sampling of blood from the second cohort of subjects exposed only to $^2H_8$-toluene. The contents of breath sample bags and 500–600 *l* samples of ambient air in our laboratories were each drawn though a 2-section charcoal sampling tube using a calibrated personal sampling pump. The charcoal sections were then analyzed[22]. Alveolar $^1H_8$- and $^2H_8$-toluene concentrations were calculated from the exhaled breath concentrations by multiplying the levels in the collection bags by [baseline CO_2] / [bag CO_2], where the baseline CO_2 values were measured prior to exposure, or were assumed to be 5.26%.

Physiologically-based model

A previously described semi-empirical PBK model[23] (Fig. 1) was implemented with SimuSolv® software (Dow Chemical Co., Midland, MI) which used subject-specific values of body weight, adipose tissue fraction, $^2H_8$-toluene blood/air partition coefficient, exposure concentration, and alveolar ventilation rate. Values of fractional tissue compartment volumes, fractional blood flows, tissue/blood partition coefficients, and hepatic metabolic constants $V_{max\text{-}h}$ and K_M were taken from literature sources (Table 1). A minimum number of tissue compartments (5) was used to represent toluene distribution in the body. As a small lipophilic molecule, toluene was expected to rapidly diffuse across tissue membranes. The exchange of toluene between arterial blood and tissue groups was therefore treated as being flow-limited. Cardiac output

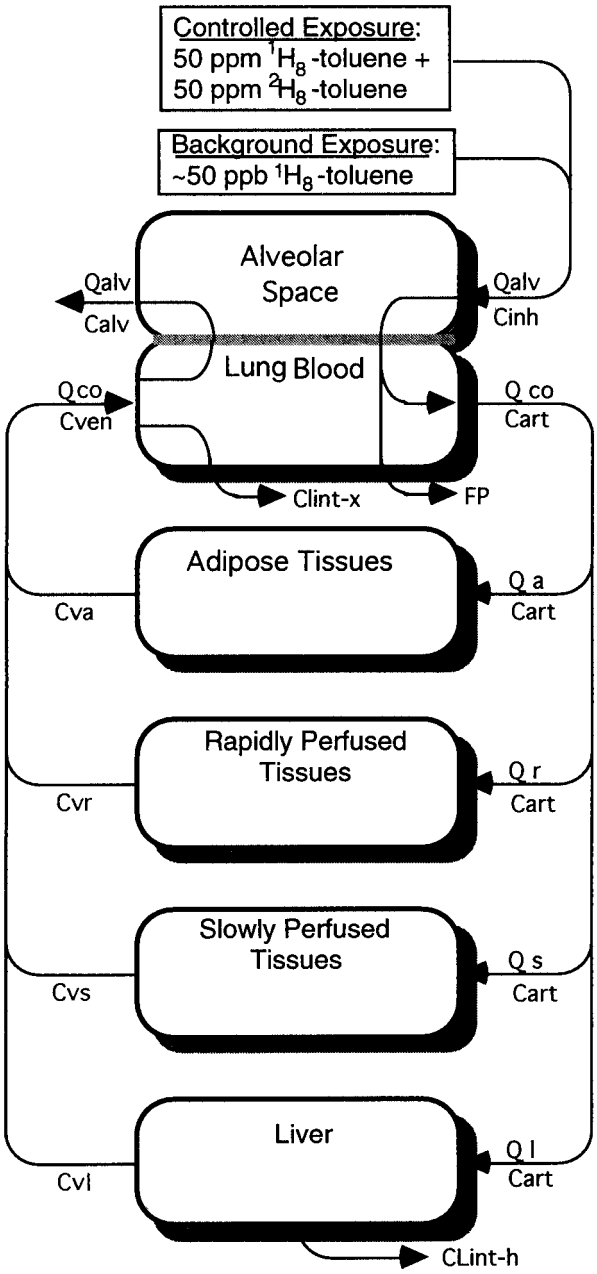

Fig. 1. Physiologically-based kinetic model for inhaled $^1H_8$- and $^2H_8$-toluene. Abbreviations and symbols. Q_{alv}, alveolar ventilation (*l* air/hr); C_{inh}, concentration in inhaled air (ppm); C_{alv}, concentration in alveolar air (ppm); FP, first-pass metabolism (μmol/hr); Q_{co}, cardiac output (*l* blood/hr); C_{art}, concentration in arterial blood (μmol/*l*); C_{ven}, concentration in venous blood (μmol/*l*); $CL_{int\text{-}x}$, intrinsic metabolic clearance in extrahepatic tissue, assumed to be the lung (*l*/hr); $CL_{int\text{-}h}$, intrinsic metabolic clearance in the liver (*l*/hr); Q_i, blood flow rate to tissue group i (*l*/hr); C_{vi}, concentration in blood leaving tissue group i (μmol/*l*).
Subscripts (i) for tissue groups or compartments: a, adipose tissues; r, rapidly perfused tissues; s, slowly perfused tissues; l, liver.

(CO), and therefore all tissue group blood flows, were scaled to (body weight)$^{0.74}$. While there is some evidence that CO and hepatic flow may be associated with lean body mass[29–31], the more clearly defined relationship with total body weight was employed[28,32–34].

Fractional blood flow to adipose tissue ($Q_{a/co}$) and maximal rate of extrahepatic metabolism ($V_{max\text{-}x}$) were fitted to each of the $^1H_8$- and $^2H_8$-toluene data sets because these values are difficult to measure and may vary widely between individuals[23]. Based upon previous measurements and estimates of $Q_{a/co}$[24,35–38], this model parameter was expected to vary within the bounds of 0.04–0.17. A search range for values of $V_{max\text{-}x}$ was defined using the observation by Wheeler *et al.*[39] that human lung microsomes contain 10.5% of the liver activity of P450 2E1. Thummel *et al.*[40] found about a 7-fold range of P450 2E1 content (49–372 pmol/nmol protein) in 12 human liver samples examined *in vitro*. We therefore expected maximal extrahepatic rate of metabolism to range from 0–70% of that in the liver. Values of K_M and V_{max} in the liver were assumed to be identical for $^1H_8$- and $^2H_8$-toluene, based upon the relative insensitivity of modeled blood concentrations to these parameters because of flow rate-limited clearance in the liver[23].

Estimation of background exposure

To estimate the contribution of background exposure to the resulting $^1H_8$-toluene concentration in exhaled alveolar breath, the model included a pre-exposure period to background $^1H_8$-toluene for 130 hours, approximately 4 terminal-phase half-lives[2,23,41]. The concentration of $^1H_8$-toluene ($C_{ambient}$), during this period and following the controlled exposure was optimized in an unrestricted range, starting with a nominal value of 50 ppb. Assuming a constant level of ambient exposure is admittedly a simplification, since both indoor and outdoor solvent concentrations commonly vary by a factor of 2 or 3 over several days[42]. This is nonetheless the approach frequently used in risk assessment[43].

$C_{ambient}$ was determined in two steps. The model was first independently fitted to each set of the $^1H_8$-toluene breath or $^2H_8$-toluene blood and breath concentrations over the time period reflecting the controlled 50 ppm exposures. This was accomplished by optimizing $V_{max\text{-}x}$ and $Q_{a/co}$ and using individually measured values for body weight, fraction of adipose tissue, alveolar ventilation rate, exposure concentration, and blood/air partition coefficient. Next, the model was optimized to best describe all $^1H_8$- or $^2H_8$-toluene data, including the pre-exposure and terminal samples, by varying $C_{ambient}$.

To fit the model to the blood and breath concentrations reflecting the controlled exposure, two conflicting concerns were addressed: the post-exposure time interval over which the model was fit had to be long enough to adequately characterize all phases of $^1H_8$- and $^2H_8$-toluene disposition but short enough to minimize the effect of background exposure on fitting the terminal phase. To this end, we

Table 1. Values of parameters used in the physiologic model

Physiologic parameter	Tissue group			
	Slowly-perfused	Rapidly-perfused	Liver	Adipose
Volume (V, *l*)	0.95 BW-$V_{adipose}$[a]	0.05 BW-V_{liver}[a]	0.023 BW[a]	0.10–0.39 BW (measured)
Blood Flow (Q, *l*/hr)	0.24 Q_{co}-$Q_{adipose}$[b]	0.76 Q_{co}-Q_{liver}[b]	0.27 Q_{co}[a]	0.06–0.18 Q_{co} (fitted to data)
K_p	1.54[c]	4.64[c]	4.64[c]	55.9[d]
K_m (μmol/l)	—	—	5.97[b]	—
V_{max} (μmol/hr)	—	—	52.1 $BW^{0.7}$ [b, e, f]	—

Note: BW=body weight (kg) and Q_{co}=cardiac output (*l*/hr)=12.92 $BW^{0.74}$, based on similar scaling of cardiac output and alveolar ventilation rate[24] and measurements of ventilation rate in our subjects. K_p=blood/air partition coefficient. [a]From[25]. [b]From[24]. [c]From[26]. [d]From[27]. [e]Scaling of body weight from[28]. [f]Maximal extrahepatic rate of metabolism was varied to fit the data within a range of 0–70% of $V_{max\text{-}h}$.

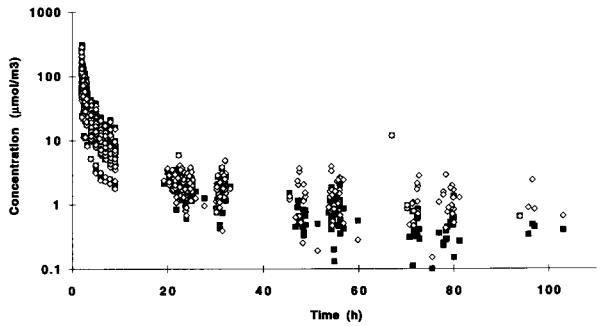

Fig. 2. Measured concentrations of $^1H_8$-toluene (◇) and $^2H_8$-toluene (■) in alveolar breath from 33 exposures of 50 ppm each for 2 h.

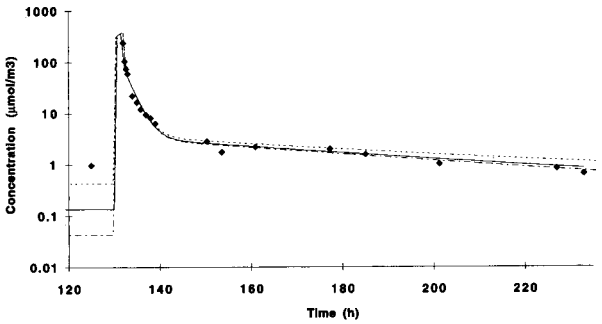

Fig. 3. Typical model fit to breath concentrations of $^1H_8$-toluene (◆) with model predictions of 5 ppb (—·—), 16 ppb (—, optimized value for this exposure), and 50 ppb (---) ambient exposure in addition to the controlled 50 ppm exposure. For modeling purposes, the concentration due to ambient exposure was allowed to "build up" over the period 0–130 h, and controlled exposure occurred during 130–132 h. The pre-exposure sample is plotted at 125 h.

visually examined the data *en masse* from all subjects exposed to $^1H_8$- and $^2H_8$-toluene to determine when the breath concentrations of the two compounds diverged. Figure 2 indicates that after 40 h, $^2H_8$-toluene concentrations decreased more rapidly than $^1H_8$-toluene levels, which were ostensibly supplemented by background exposure. In addition, we also repeatedly varied $C_{ambient}$ around an anticipated value of 50 ppb (Fig. 3) to observe the magnitude of background contribution to measured $^1H_8$-toluene breath levels. The model simulations in Fig. 3 suggested that a nominal 50 ppb background level of exposure was expected to result in a breath concentration of about 0.5 μmol/m^3, similar to the measured values at time >40 h (Fig. 2). We therefore considered breath concentrations in the 2–40 h period to be due to the controlled exposure only, and optimized $V_{max\text{-}x}$ and $Q_{a/co}$ to fit these data.

In the next step, $C_{ambient}$ was optimized to each $^1H_8$- or $^2H_8$-toluene data set using the full time course of the experiment (pre-exposure to 80–175 h). The optimized $C_{ambient}$ levels for each form of toluene were then compared using paired t tests. We hypothesized that the optimized $C_{ambient}$ values for the $^2H_8$-toluene data would not be different from zero and that the values for the $^1H_8$-toluene data would be similar to reported ambient concentrations (3–43 ppb). To test this, the values of $C_{ambient}$ for $^1H_8$- and $^2H_8$-toluene were compared to zero using a two-sided t-test. To examine the model's ability to accurately simulate $^1H_8$-toluene blood and breath levels, the predicted background concentrations were compared to the measured concentrations in the group of subjects not exposed to $^1H_8$-toluene. To probe for inter-individual differences, the grouped multiple blood or breath concentrations from each of these 9 subjects were compared using analysis of variance. A significance level of $p<0.05$ for all tests was chosen.

Model goodness-of-fit

The model was fitted to the breath ($^1H_8$-toluene) or blood

Table 2. Concentrations of $^1H_8$-toluene in blood of non-occupationally exposed subjects

Population	Blood concentration (nmol/*l*, mean ± s.d. [range])	Reference
US (n=114)	3.26 [1.30–19.6][a]	8)
US (n=604)	5.6 [1.2–16][a]	9)
Hospital staff (n=58)	9.02 ± 9.49 [0.25–54.5]	10)
Workers (n=59)	10.4 ± 40.2 [0–206]	11)
Workers (n=269)	12.0 [98%ile=77.2]	12)
Administrative officers (n=19)	12.1 ± 6.78	13)
Traffic officers (n=20)	12.2 ± 5.83	13)
Chemical workers (n=28)	13.5 ± 14.8 [0.543–56.4]	10)
US urban (n=9)	16 ± 9 [2.7–106]	This study

Table note: [a]Range is 5–95 percentiles.

and breath ($^2H_8$-toluene) data from each exposure by varying $V_{max\text{-}x}$ and $Q_{a/co}$ or $C_{ambient}$ to maximize the log likelihood function (LLF)[44]:

$$LLF = \frac{1}{2}\left[n(\log(2\pi) + 1) + n\log\left[\frac{1}{n}\sum_{i=1}^{n}\frac{(z_i - f_i)^2}{f_i^{\gamma}}\right] + \gamma\sum_{i=1}^{n}\log f_i\right]$$

where:

n = the number of measurements at each time point
z_i = the measured value of the i^{th} data point
f_i = the predicted value of the i^{th} data point
γ = the heteroscedasticity (weighting) parameter, which was optimized over the range 0–2

The model goodness-of-fit to each of the 33 sets of data was measured by the fraction of variation in the data that was explained by the model. Similar to the calculation of the coefficient of multiple determination (r^2), this value was computed using the following equation[44]:

$$r^2 = 1 - \frac{\text{model error}}{\text{total error}} = 1 - \frac{\sum_{i=1}^{n}\frac{(z_i - f_i)^2}{f_i^{\gamma}}}{\sum_{i=1}^{n}\frac{(z_i - \bar{z})^2}{f_i^{\gamma}}},$$

where $$\bar{z} = \frac{\sum_{i=1}^{n}\frac{z_i}{f_i^{\gamma/2}}}{\sum_{i=1}^{n} f_i^{1/(\gamma/2)}}$$

Results

Optimized model parameters

The optimized values of $V_{max\text{-}x}$ were 6.7 ± 4.3 (range 2.3 × 10^{-4} — 14) μmol/h-kg for $^1H_8$-toluene, and 9.6 ± 5.4 (0.34–26) μmol/h-kg for $^2H_8$-toluene, all within the expected physiologic bounds (0–70% of $V_{max\text{-}h}$, or 0–36 μmol/kg-h)[39,40]. The fit values of $Q_{a/co}$ were 0.09 ± 0.03 (range, 0.015–0.15) for $^1H_8$-toluene, and 0.08 ± 0.03 (range, 0.03–0.14) for $^2H_8$-toluene. Two of these 66 values were below the expected physiologic range of 0.04–0.17[24,35–38]; for one of these two subjects only limited data (1 breath, 2 blood samples) were available in the terminal phase, where adipose blood flow is most influential. The model was able to explain 94 ± 2.7% (range, 85–98%) of the $^1H_8$-toluene data variability, and 90 ± 6.5% (range, 68–98%) of the $^2H_8$-toluene data variability in the 33 exposure sets.

Estimation of background exposure

The subject-specific optimized values of $C_{ambient}$ for $^1H_8$- and $^2H_8$-toluene were significantly different ($p<0.05$). The mean value for $^2H_8$-toluene was — 9 ± 40 ppb, (range — 140–90 ppb), not significantly different from zero, and for $^1H_8$-toluene was 47 ± 44 ppb (range — 90–135 ppb), significantly greater than zero. The $^1H_8$-toluene concentration in the laboratory, measured after the completion of all exposures, was 3.7 ppb; the values measured in 12 locations within our suite of laboratories was 2.2 ± 1.9 ppb (range 0.65–6.4 ppb). A depiction of the modeled contribution of background exposure to alveolar breath concentration is presented in Fig. 3.

Comparison of predicted and measured background blood and breath levels

Based on the average predicted background level of 47 ppb in our $^1H_8$- and $^2H_8$-toluene exposure group, the predicted blood concentration was 5.9 nmol/*l*. Using the relationship between an occupational exposure limit of 100 ppm and an end-of-shift biological indicator of exposure of 1 mg/*l* in blood[45], a background exposure of 47 ppb would be expected to produce a blood concentration of about 5.1 nmol/*l*. The average measured concentration of $^1H_8$-toluene in blood from the non-exposed cohort group of 9 men was 16 ± 9 nmol/*l* (range 2.7–106), with inter-individual differences ($p<0.01$), which was slightly higher than a range of 3–14 nmol/*l* measured in previous studies (Table 2).

Based upon the average predicted background level of 47 ppb in our controlled-exposure group, the average $^{1}H_{8}$-toluene breath concentration was expected to be 310 nmol/m^3. This compares reasonably well with a nominal value of 380 nmol/m^3 obtained by scaling the ACGIH BEI end-of-shift breath level of 20 ppm indicative of a 100 ppm exposure[46] to a 47 ppb background exposure. The average measured concentration in breath of the cohort group exposed only to $^{2}H_{8}$-toluene was 138 ± 187, nmol/m^3, with 4 measurements (assumed to be 5 nmol/m^3) below the lower quantitation limit of 10 nmol/m^3. This level is lower than values of 334 ± 225 nmol/m^3 found in 39 hospital staff and 764 ± 598 nmol/m^3 found in 28 chemical workers, both groups described as non occupationally-exposed to $^{1}H_{8}$-toluene, by Brugnone *et al.*[10]. Our measured background values were about three orders of magnitude lower than alveolar concentrations measured in $^{1}H_{8}$-toluene-exposed workers[47,48].

Discussion

The mean optimized background concentration, 47 ppb, is about 3-fold higher than measured ambient concentrations (Table 3). This result may reflect personal activities and microenvironment exposure, such as car and mover refueling, woodworking and staining, home garage hobbies, and passive cigarette smoke exposure. Additional contributors may be other pathways of exposure (e.g. ingestion in foodstuffs), and/or low-level contamination during breath sampling and analysis. Inter-individual exposure variability is reflected in the approximately 200-fold range in background blood concentrations (Table 2), and in the large spread in optimized $C_{ambient}$ values among the study subjects (−90–135 ppb). The standard deviation of the estimated background concentration of 47 ppb $^{1}H_{8}$-toluene is considerable (44 ppb), and limits the extent to which generalized estimates can be made. The finding of inter-individual differences in the blood concentrations amongst the 9 men (2.7–106 nmol/*l*) not exposed to $^{1}H_{8}$-toluene also suggests different levels of exposure.

The use of the combined $^{1}H_{8}$-/$^{2}H_{8}$-toluene exposure identified the late post-exposure period of >40 h where background $^{1}H_{8}$-toluene levels contributed to measured breath concentrations (Fig. 2). Previously measured background breath levels of 334 and 764 nmol/m^3 [10] from ambient exposure would clearly have biased interpretation of this washout curve following controlled $^{1}H_{8}$-toluene exposure.

Most physiologic models, including the one used in this

Table 3. Airborne environmental concentrations of $^{1}H_{8}$-toluene

Sampling area	Air concentration (ppb mean ± s.d. [range])	Reference
Indoor		
Train compartment during commute (8 trips)	3.28	49)
Indoor cannister samplers (8 homes)	3.7 ± 2.1	50)
Our laboratory	3.7	This study
Chemical plant infirmary	11.3 ± 11.7 [2.66–57.0]	10)
Indoor personal samplers (3 subjects)—"Nonstagnant" air	14.1–20.8	43)
Hospital infirmary	15.3 ± 11.8 [1.86–51.4]	10)
Kitchens	16.0 [9.05–27.7]	51)
Indoor rooms	16.5 [4.53–30.9]	51)
Indoor personal samplers (3 subjects)—"Stagnant" air	18.4–23.6	43)
Indoor personal samplers (19 subjects)	23.7 [12.5–43.1]	13)
Car dashboard during commute (8 trips)	26.6	49)
Outdoor		
Outdoor cannister samplers (8 homes)	1.5 ± 1.0	50)
Outdoor personal samplers (3 homes)—"Nonstagnant" air	2.08–4.37	43)
Local urban setting	2.22	52)
Urban setting #1 (3 sites)	2.31 ± 0.62 [1.85–3.01]	52)
Urban setting #2 (3 sites)	2.60 ± 0.76 [1.83–3.36]	52)
Urban setting #3 (3 sites)	2.64 ± 0.76 [1.77–3.00]	52)
Urban setting	2.93	53)
Outdoor personal samplers (3 homes)—"Stagnant" air	9.05–12.4	43)
Outdoors next to dwellings	9.32 [4.26–16.0]	51)
Traffic intersection	39.1 [5.33–110]	51)
Traffic warden personal samplers (20 locations)	43.1 [17.6–83.4]	13)

study, assume instantaneous equilibrium between blood leaving the lungs and alveolar breath. Use of this assumption for $^1H_8$-toluene is supported by the comparison of *in vitro* blood/air partition coefficient values of 18.3 ± 1.42[27]; with reported *in vivo* values of 21.2 ± 11.5[23], a range of 20.0–27.4[48], 5.7 and 8.6[47], and 17.6 and 27.0[10]. While the predicted ratio of background blood to breath was within this range, 19 (5.9/0.31), the measured ratio of concentrations in our non-exposed cohort, 116 (16/0.138) was much larger. This observation, coupled with the relatively high blood level compared to previous measurements (Table 2) suggested a positive bias in our measurement of background blood concentrations.

The predicted alveolar air/ambient air ratio of 0.16 (310 nmol/m^3 ÷ 47 ppb) is less than one, as expected for a toxicant that is absorbed principally through inhalation and for which blood clearance is dominated by hepatic metabolism. Wallace *et al.*[50] found breath/personal air ratios of 0.07–0.20 for benzene, *m* + *p*-xylene, *o*-xylene, ethylbenzene, and styrene.

Physiologically-based models have been used to develop exposure standards for parent toxicant[54] and biological indicators of exposure[14,16]. This investigation extended the application of PBK modeling to estimate ambient exposures by using toxicant concentrations in breath. Future applications could include testing the efficacy of exposure control interventions and occupational dose estimation using serial post-exposure biological samples.

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