

Toluene Tier 1 VCCEP Submission

Appendix C

PBPK Modeling for Toluene

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1.0 Description of Project

This project has several purposes including the review of existing physiologically-based pharmacokinetic (PBPK) models for toluene, the use of PBPK models to facilitate the interpretation of the human biomonitoring data for toluene and, finally, the estimation of human blood and milk concentrations that could correlate with measured or modeled exposure data for toluene.

2.0 Literature Review for Human Pharmacokinetics

2.1 Literature Review of Available PBPK Models

The assessment of information regarding human data on inhalation pharmacokinetics of toluene was performed using TOXLINE via National Library of Medicine, occupational health and biological monitoring literature as well as the contractor's knowledge of published work in this area.

Three lead researchers have been involved in developing human PBPK models for toluene, namely, Pierce, Jang and Tardif.

The models constructed by Pierce et al. (1996) are individual-specific but suffer from the parameter estimation methods. These authors estimated pulmonary metabolism rate and the blood flow rate to adipose tissues for individual subjects by model fitting. The basic biochemical parameters in the model – namely V_{\max} and K_m for hepatic metabolism, however, were derived from a previous University of Montreal study, Tardif et al. (1993). The modeling effort by Pierce et al. (1998) was identical to their own 1996 work, using fitted values of adipose blood flow rates and extrahepatic metabolism rates for individual subjects. The estimation of blood flow rates by fitting is not a preferred practice in PBPK modeling. Therefore, this model and parameter sets are of limited use in the present context.

The human models for toluene developed by Jang and Droz (1996) and Jang et al. (1999) were based on the metabolic constants determined by Purcell et al. (1990) in an animal study, as well as that of Tardif et al. (1993). The model structure and conceptual framework of these models were very similar to those developed by Tardif et al. (1993a, 1995), with the difference being that Jang and co-workers used very limited blood data for validation purposes (i.e., concentration determined in workers at 0.5 hr and 15 hr after toluene exposure) whereas Tardif et al. (1993a, 1995) used time-course data following more than one exposure concentration for validation purposes. As a result, we chose to use Tardif et al. (1995)'s toluene model in the present project. The Tardif models have been previously used by EPA scientists (Beningus et al. 1998) for conducting dosimetric analysis of behavioral effects of acute toluene exposure in rats and humans. The chemical-specific model parameters used in toluene PBPK model for humans are as follows:

Toluene - partition coefficients

Blood:air	15.6
Liver:air	83.6
Fat:air	1021.0
Richly perfused tissues:air	83.6
Poorly perfused tissues:air	27.7

Toluene - metabolism constants

Liver V_{\max} (mg/hr/kg)	4.8
Liver K_m (mg/L)	0.55

Table 2.1 presents a summary of the human pharmacokinetic studies, in which toluene blood concentrations were measured following inhalation exposures. These data are potentially useful for two purposes: (1) for validating the human PBPK models, and (2) to examine the relationship between blood concentration and exposure concentration in exposed individuals.

Table 2.1 Controlled human volunteer studies of Toluene BTX pharmacokinetics

Exposure Concentration	Exposure -Sampling Duration	Reference
50 ppm	2 hr	Pierce et al. (1998)
17 ppm	7 hr	Tardif et al. (1997)
1550 – 2500 $\mu\text{g}/\text{m}^3$	21 hr	Wallace et al. (1997)
21-66 ppm	7 h/d, 3 days	Lapare et al. (1993)
50 ppm	7 hr	Tardif et al. (1991)
95 ppm	4 hr	Tardif et al. (1991)
3.2 mmol/m^3	240 – 420 min	Wigaeus-Hjelm (1988)
3.25 mmol/m^3	240 – 420 min	Wallen (1986)
2.17 & 3.24 mmol/m^3	250 - 360 min	Wallen et al. (1985)
184 – 332 ppm	2 weeks	Konietzko et al. (1980)
50, 100, 125, 150 and 200 ppm	240 - 480 min	Veulemans & Masschelein (1978)
100 & 200 ppm	30 – 90 min	Astrand et al. (1972)

2.2 Reconstruction of Human PBPK models for Toluene

This section discusses the reconstruction of the human PBPK models for toluene (into Microsoft EXCEL® and Advanced Continuous Simulation Language (ACSL®)) and the successful reproduction of previously published simulations of toluene kinetics in humans.

The PBPK model used in this study describes the organism as a set of tissue compartments interconnected by systemic circulation and a gas-exchange lung (Figure 2.1). The compartments refer to liver, slowly perfused tissues, richly perfused tissues and adipose tissue (fat). The rate of change in the amount of toluene in each non-metabolizing tissue compartment is described as follows (Note: all abbreviations are defined in the legend for Figure 3.2):

$$V_t \frac{dC_t}{dt} = Q_t(C_a - C_{vt}) \quad (1)$$

The rate of change in toluene concentration in liver is described as follows:

$$V_l \frac{dC_l}{dt} = [Q_l(C_a - C_{vl})] - \frac{dA_{met}}{dt} - \frac{dA_{bm}}{dt} \quad (2)$$

In lay terms, the above equation signifies:

Rate of change in the amount of the chemical in the tissue = (blood flow x arteriovenous concentration difference) – rate of loss due to metabolism

The rate of the amount metabolized was described as a saturable process as follows:

$$\frac{dA_{met}}{dt} = \frac{V_{max} C_{vt}}{K_m + C_{vt}} \quad (3)$$

In the toluene PBPK model, the mixed venous blood concentration has been calculated as follows:

$$C_v = \frac{\sum_t^n Q_t C_{vt}}{Q_c} \quad (4)$$

The above equation represents the steady-state solution of the mass-balance differential equation for venous blood:

$$\left[V_b(dC_b/dt) = \sum_t^n Q_t C_{vt} - C_v Q_c \right] \quad (5)$$

The arterial blood concentration of toluene is computed with the following equation:

$$C_a = \frac{Q_p C_{inh} + Q_c C_v}{Q_c + \left(\frac{Q_p}{P_b}\right)} \quad (6)$$

The toluene PBPK model is comprised of the above equations, which are interconnected as shown in Figure 2.2.

FIGURE 2.1: Conceptual representation of the PBPK model for toluene.

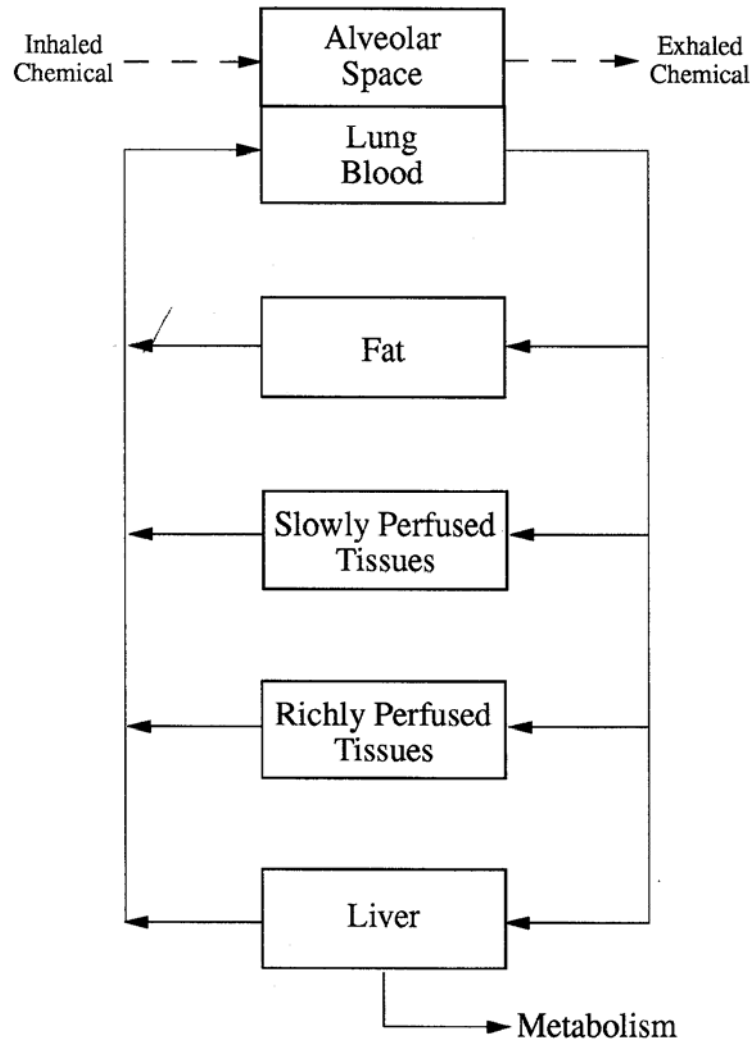
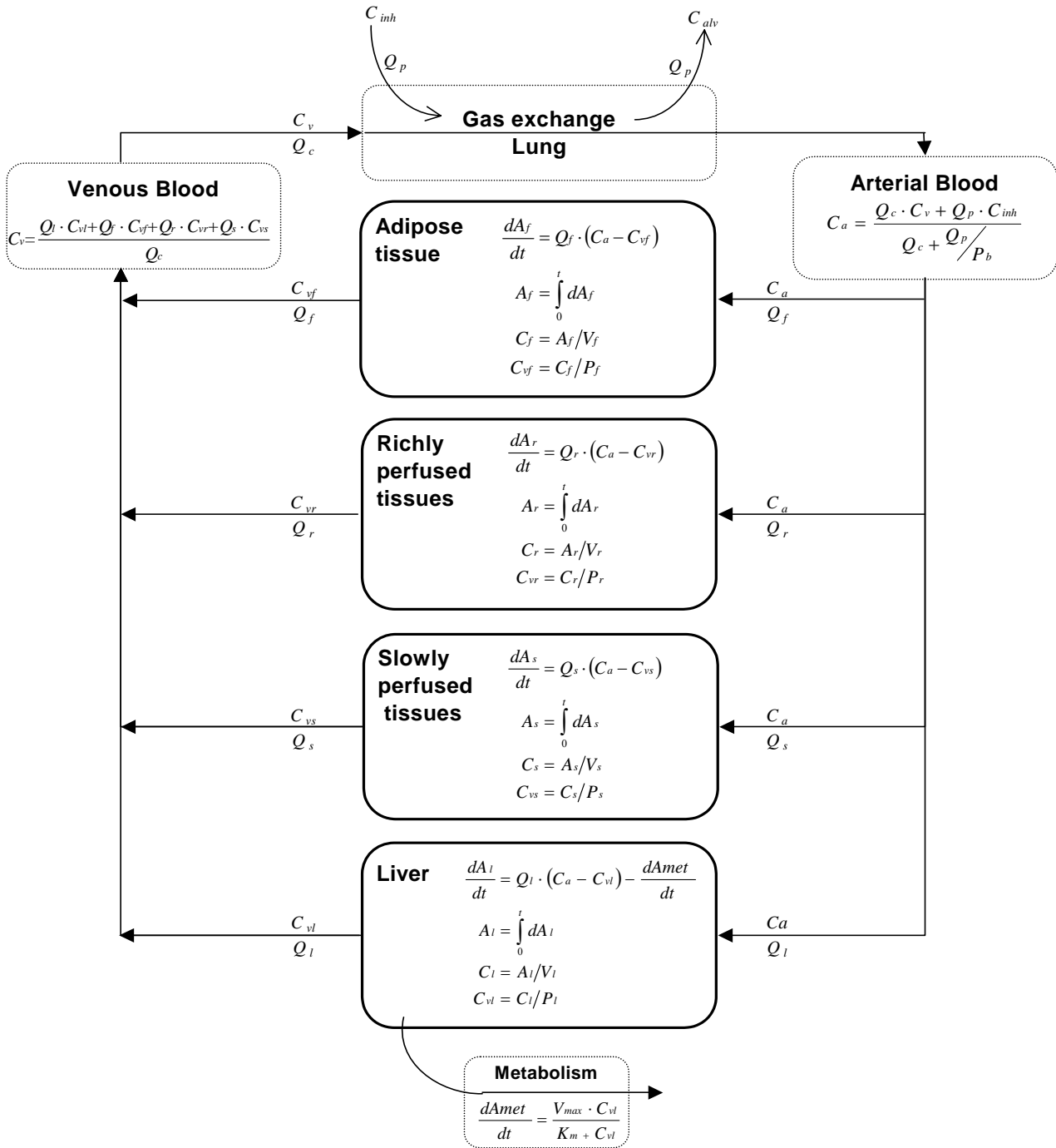


FIGURE 2.2: Conceptual and fundamental representations of the PBPK model for toluene



Legend: C_{inh} and C_{alv} refer to inhaled and exhaled toluene concentrations. C_v and C_a refer to venous and arterial blood concentrations. P_b refers to blood:air partition coefficient. Q_p and Q_c refer to alveolar ventilation and cardiac output. C_{vi} , V_i , P_i , A_i and Q_i refer to venous blood concentrations leaving tissue compartments, tissue volumes, tissue: blood partition coefficients, amount in tissues and blood flow to tissues (i.e., f: adipose tissue, s: slowly perfused tissues, r: richly perfused tissues, and l: liver). V_{max} , K_m and A_{met} refer to the maximal velocity of metabolism, Michaelis affinity constant, and amount metabolized. dt refers to integration interval.

3.0 PBPK Modeling Results

This section describes how the existing PBPK models for toluene were expanded and utilized for the Toluene VCCEP Exposure and Risk Assessments. This includes the expansion of the existing rat and human inhalation models to include the oral route of exposure and the estimation of human milk concentrations and lactational transfer of toluene.

3.1 Rat Model with Integrated Oral Dosing Route

The PBPK model of Tardif et al. (1993a) for toluene inhalation exposure in rats was implemented in MS Excel® with physiological and physicochemical parameters as described in Tables 1 and 2 of that publication. The model was modified to incorporate oral dosing by adding a virtual gastrointestinal tract compartment with a first-order absorption process to the liver. The model was parameterized against two sets of data.

First, to confirm that the model was implemented correctly, predictions from the model were compared to results reported in Tardif et al. (1993a), Figure 2A, which showed blood data and model simulations of 5-hr rat inhalation exposure to three concentrations of toluene. Figure 3.1 reproduces Figure 2A from Tardif et al. (1993a) and presents the results of the same simulation using the current model implementation: the curves are identical.

Second, to parameterize the absorption from oral dosing, the gastrointestinal absorption rate was calibrated visually against data from Sullivan and Conolly (1988) for the time course of blood toluene concentrations following oral gavage at four different dose levels in Sprague-Dawley rats. The absorption rate from the rat gastrointestinal tract was adjusted to result in peak blood concentrations between 2 and 2.5 hours post-gavage, as reflected in the Sullivan and Conolly (1988) data set. All other parameters were retained as reported by Tardif et al. (1993a). Figure 3.2 presents a comparison of Figure 2 from Sullivan and Conolly (1988) (which shows measured values and a set of fitted empirical curves) and model predictions from the current modified PBPK model incorporating the oral dosing route. The maximal levels attained and the general behavior of the curves matched the experimental data well.

The parameters used in the rat oral and inhalation toluene PBPK model are presented in Table 3.1.

3.2 Adult Human Model with Integrated Oral Dosing Route

The validated human PBPK model of Tardif et al. (1995) with parameters as reported by Nong et al. (2006, Table 1) for toluene inhalation exposure was similarly implemented in MS Excel® with parameters identical to those reported in the publication. This model was modified in the same way as the rat model to incorporate the oral dosing route. The model was validated for inhalation exposure by simulating a data set from Pierce et al. (1998) (see Figure 3.3). The model was able to accurately

reproduce the central tendency of the measured blood and exhaled air concentrations in volunteers exposed to 50 ppm toluene for 2 hours.

However, very few data were available for validation of the oral dosing component of the model. Only one data set was found reporting on controlled oral exposure to toluene. Baelum et al. (1993) administered toluene at measured drip rates for specified periods of time to human volunteers via nasal-gastric tube and measured the concentration of toluene in exhaled “alveolar” air samples; blood samples were not taken. The experiment involved 1 or 4 individuals, depending on the dose rates administered. At the dose level with 4 individuals sampled, the measured air levels varied by more than 3 orders of magnitude among the four individuals examined, and are essentially uninformative about true air or blood concentrations. However, the data do indicate an apparent time course for the maximal concentrations following the exposure regimen that is similar across 3 of the 4 individuals, peaking approximately 15 to 30 minutes following cessation of exposure. This time course was used to calibrate the oral absorption rate to liver in the human model. The resulting predicted blood and air levels were within, but on the higher end, of the reported range of exhaled air concentrations from Baelum et al. (1993). The full set of model parameters for the adult human model is included in Table 3.1.

3.3 Infant and Child Models with CYP2E1-Related V_{max} (Implementation of Nong et al. 2006)

Nong et al. (2006) recently published a quantitative analysis of the impact of the time course of ontogeny of CYP2E1 in infants and children on the predicted pharmacokinetics of toluene. Nong et al. (2006) implemented PBPK models using age-specific physical parameters and the previously-established physicochemical parameters for toluene. The maximal metabolism rate, V_{max} , was calibrated based on data on hepatic CYP2E1 content in samples collected from autopsies of infants and children of varying ages (from Johnsrud et al. 2003). V_{max} for each age was estimated as a fraction of the adult V_{max} based on the relative amount of total hepatic CYP2E1 (hepatic protein concentration times liver volume, V_L) for that age compared to adults:

$$V_{\max_child} = \frac{[CYP2E1]_{child} V_{L_child}}{[CYP2E1]_{adult} V_{L_adult}} V_{\max_adult}$$

Nong et al. (2006) reported the means and ranges for all relevant physiological parameters for four age groups: neonates (<1 month), infants (1 m to 1 yr, parameters corresponding to approximately 6 to 8 months old), children (1 to 11 yrs, parameters corresponding to approximately a 3-yr-old), and adolescents (12 to 17 yrs). Using these reported means and ranges, a PBPK model for two additional age groups of 1 to 3 months and 6 to 12 yrs (parameters corresponding to approximately a 9-yr-old) were implemented to correspond to the additional age groups of interest for the VCCEP exposure and risk assessment. The absorption rate from the gastrointestinal tract to liver was fixed at the same rate identified above for the adult human model. The full set of parameters for all of the age group models is presented in Table 3.1. The models were

implemented in MS Excel® and tested against results reported in Nong et al. (2006) to ensure that implementation was correct.

Table 3.1: Model parameters for integrated oral and inhalation PBPK models for rats and humans across different ages.

Parameter	Rat ^a	Adult ^b	Neonate (<1m) ^c	Infant (1 to 3m) ^d	Infant (4m to 1y) ^c	Child (1 to 5y) ^c	Child (6-13y) ^d	Adolescent (14 to 18y) ^c
<i>Physiological parameters</i>								
Body weight (kg)	0.25	70	1.8	3	8	20.9	30	62.1
Tissue Volumes (L)								
Liver	0.01225	1.82	0.07	0.1	0.23	0.61	1	1.42
Fat	0.0225	13.3	0.36	0.6	0.84	3.57	5.5	11.43
Richly perfused	0.0125	3.5	0.74	1	1.84	2.88	3.3	5.12
Poorly perfused	0.18	43.4	0.35	0.5	2.02	11.38	16.5	37.85
Cardiac output (L/hr)	5.3	417.60	19.80	29.4	69.00	218.40	263.4	400.20
Alveolar ventilation (L/hr)	5.3	417.60	27.00	39.0	56.4	142.2	200	374.40
GI Tract emptying rate (hr ⁻¹) ^e	0.23				0.69			
Tissue blood flow rates (L/hr)								
Liver	1.33	108.58	5.40	7.2	10.80	28.80	42	82.20
Fat	0.48	20.88	1.80	2.4	5.40	17.40	19.8	26.40
Richly perfused	2.70	183.74	12.00	18	48.60	145.20	159	201.00
Poorly perfused	0.80	104.40	0.60	1.8	4.20	27.00	42.6	90.60
<i>Partition coefficients</i>								
Blood:air	18				15.6			
Liver:blood	4.64				2.98			
Fat:blood	56.7				65.8			
Richly perfused:blood	4.64				2.66			
Poorly perfused:blood	1.54				1.37			
<i>Metabolic constants</i>								
V _{max} (mg/hr)	1.7	116.2	0.8	2.0	12.1	34.6	60	115.3
K _m (mg/L)	0.55					0.55		

^a From Tardif et al. (1993a)

^b From Tardif et al. (1995) and Nong et al. (2006)

^c From Nong et al. (2006), Table 1

^d Interpolated from Nong et al. (2006), Table 1

^e Fit to data sets as described in text

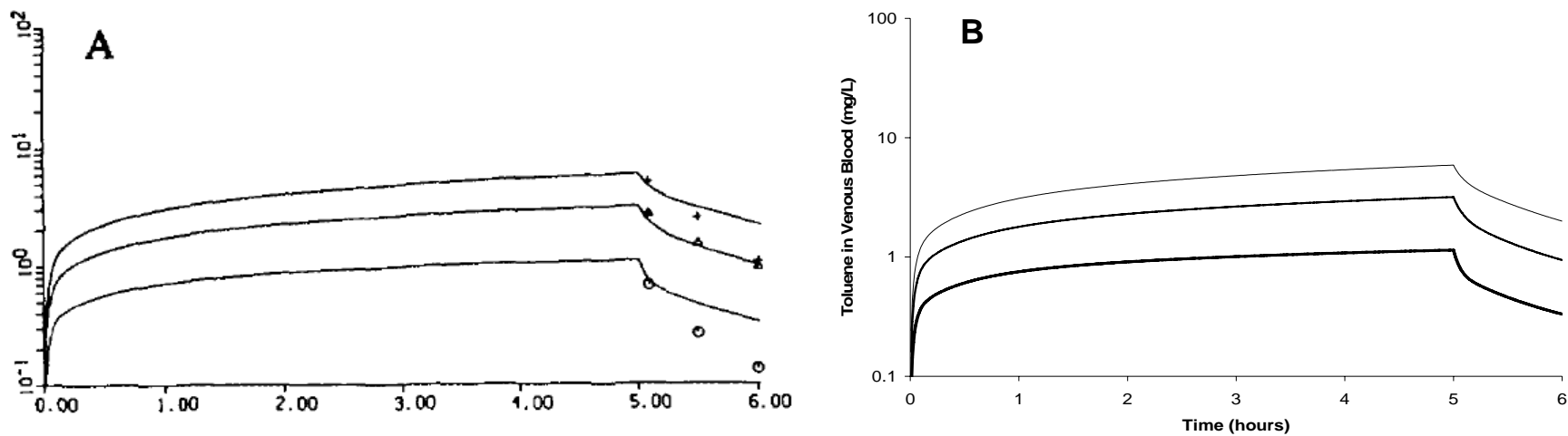


Figure 3.1: Replication of Tardif et al. (1993a) PBPK model simulations. Panel A, Figure 2A from Tardif et al. (1993a), shows data and model simulations for 5 hours of inhalation exposure at 75, 150, and 225 ppm. Panel B demonstrates replication of the model.

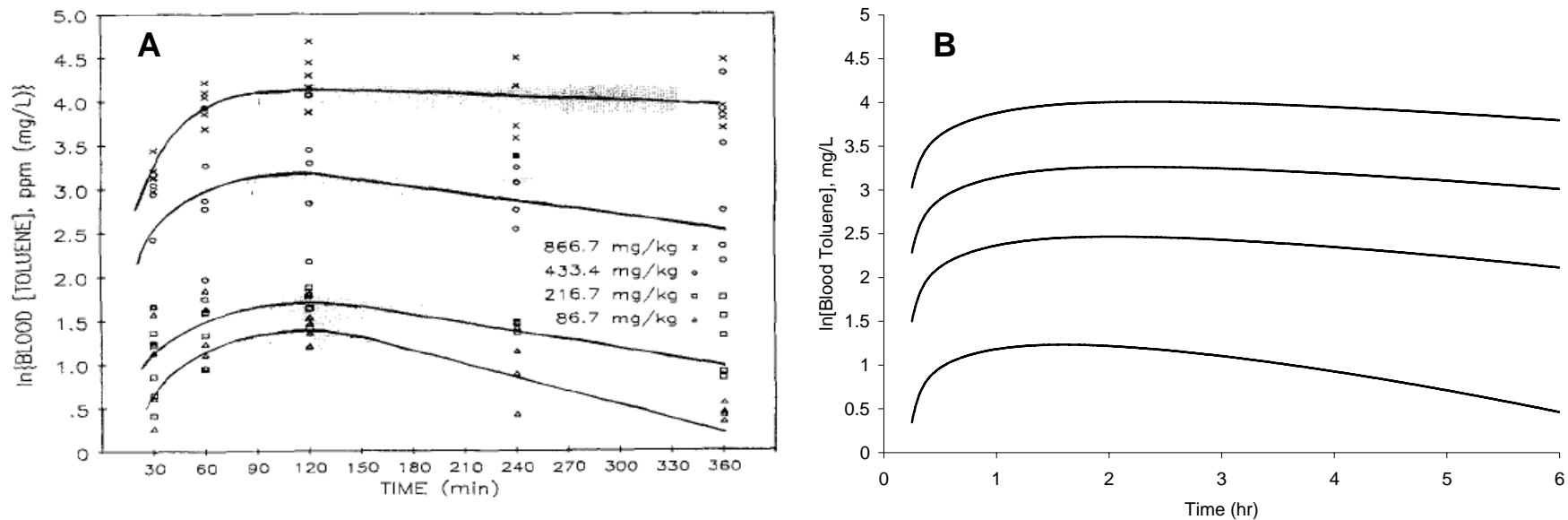


Figure 3.2: Verification of rat oral toluene PBPK model. Panel A displays measured blood concentrations following gavage dosing with 86.7, 216.7, 433.4, or 866.7 mg/kg in Sprague-Dawley rats (Figure 2 from Sullivan and Conolly 1988). Note the wide spread in measured blood concentrations at each time point and dose level. Panel B displays the predicted blood concentration profiles for the same gavage doses using the rat inhalation PBPK model as modified to include a gastrointestinal compartment and first-order absorption to the liver.

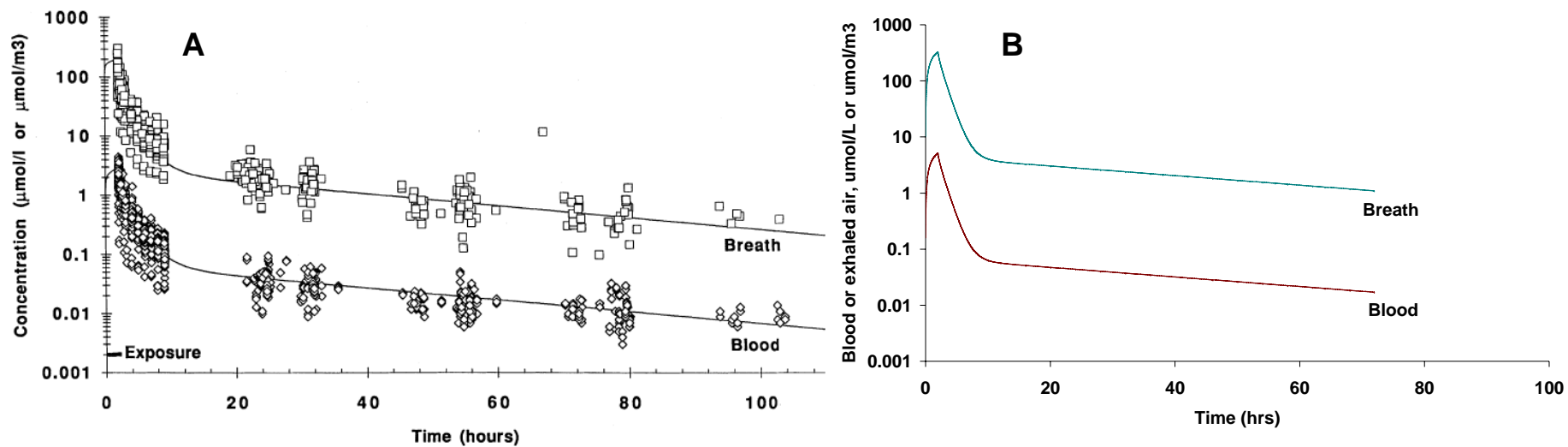


Figure 3.3: Verification of human oral toluene PBPK model. Panel A displays data for 33 individuals exposed to 50 ppm (188 mg/m³) toluene for 2 hours (Pierce et al., 1998). Model results in Panel B were generated using the Tardif et al. (1995) PBPK model as described in the text.

3.4 PBPK modeling of human lactational (milk) transfer of Toluene

The objectives of this work were: (1) to reconstruct the PBPK model for simulating lactational transfer of toluene, and (2) to calculate toluene dose ingested by infants through the nursing exposure pathway. The milk concentrations and infant exposure dose associated with maternal exposure to toluene were obtained using human PBPK models. The maternal exposure data used in this modeling is from the Toluene VCCEP Exposure Assessment (Section 7).

The PBPK model was used to simulate the lactational transfer of toluene based on information on maternal exposure from Toluene VCCEP Exposure Assessment (Section 7). The exposure concentration and duration specified in the model are presented in Table 3.2.

The simulation of breast feeding and lactational transfer of toluene was done according to a conservative schedule described by Fisher et al. (1997). Accordingly, during the workday, the mother was assumed to be exposed at the respective workplace TWA concentrations for 8 hours and background concentrations of toluene for the remainder of the day. Eight nursing events were assumed to occur each day, lasting 12 minutes each, with 115 mL of milk ingested per nursing event, yielding a daily milk consumption of 0.92 L. Three individual nursing events were assumed to occur during working hours and the remainder five nursing events were assumed to occur after working hours. The nursing events that occurred during working hours all occurred after the toluene blood concentrations had reached steady-state with the workplace exposures and occurred at 2.1, 4.1 and 7.1 hours into the workday. The remaining five nursing events occurred at 2, 5, 10, 13 and 15 hours post-work-shift. If the working day were assumed to begin at 8:00 a.m., this would amount to nursing events occurring at 2:00 a.m., 5:00 a.m., 7:00 a.m., 10:00 a.m., 12:00 p.m., 3:00 p.m., 6:00 p.m., and 9:00 p.m. The exposure concentration and duration specified in the model are presented in Table 3.2.

Table 3.2. Summary of Mothers' Toluene Exposures

Exposure Scenario	Milk Concentration (µg/L)	Mother's Exposure Duration (hrs)
Rural, typical	0.0019	24
Rural, high end	0.0069	24
Urban, typical	0.0022	24
Urban, high end	0.0077	24
Occupational, Typical	24	8
- Background, Urban typical	0.021	16
Occupational, high end	87	8
- Background, Urban high end	0.065	16

All parameters for the PBPK model of toluene were obtained from Fisher et al. (1997), except the metabolic rate constants for toluene which were obtained from Tardif et al. (1995). The Fisher et al. (1997) model was reproduced successfully before using it to simulate the lactational transfer of toluene according to the defined exposure scenarios. The parameters of the model and the simulations of lactational transfer are included in Section 3.5. Additionally, all model codes in MS Excel® and modeling results are recorded in the Compact Disc accompanying this report.

The PBPK modeling results are presented in Table 3.3. The model predicted that the mass of toluene transferred via human milk in the lactating mother ranges 2.6×10^{-5} mg/kg/day for a 3-12 month old of a typically exposed rural mother to 7.4×10^{-2} for a 7-12 week old child of an upper-bound occupational exposed, urban mother.

Table 3.3. PBPK model predictions of amount transferred to milk in lactating mothers exposed to toluene.

Exposure Category	Mass of Toluene Consumed by Child (mg/day)	0-6 wk Dose mg/kg-d	7-12 wk Dose mg/kg-d	3 – 12 months Dose mg/kg-d
Rural, typical	0.0002	6.1E-05	4.1E-05	2.6E-05
Rural, Upper Bound	0.0008	2.2E-04	1.5E-04	9.5E-05
Urban, typical	0.0003	7.0E-05	4.7E-05	3.0E-05
Urban, Upper Bound	0.0009	2.5E-04	1.6E-04	1.1E-04
Occupational, Typical Background, Urban typical	0.1	7.0E-05	2.0E-02	1.3E-02
Occupational, Upper Bound Background, Urban Upper Bound	0.4	2.5E-04	7.4E-02	4.8E-02

* Note that the human milk ingestion rate is similar across age groups, thus for each age group, the dose was calculated by dividing the mass ingested by the age-specific body weights.

3.5 Model Parameters and the Simulations of Lactational Transfer

In order to establish the amount transferred via milk following inhalation exposure to toluene, the contractor used the PBPK model and the parameters published by Fisher et al. (1997). These PBPK models describe the lactating mother as a set of tissue and milk compartments interconnected by systemic circulation and a gas-exchange lung. The tissue compartments refer to liver, slowly perfused tissues, richly perfused tissues and adipose tissue (fat). The rate of change in the amount of toluene in each non-metabolizing tissue compartment was described as follows (Note: all abbreviations are defined following Equation 14):

$$V_t \frac{dC_t}{dt} = Q_t(C_a - C_{vt}) \quad (7)$$

The rate of change in toluene concentration in liver was described as follows:

$$V_t \frac{dC_t}{dt} = [Q_t(C_a - C_{vt})] - \frac{dA_{met}}{dt} \quad (8)$$

In lay terms, the above equation signifies:

Rate of change in the amount of the chemical in the tissue = (blood flow x arteriovenous concentration difference) – rate of loss due to metabolism

The rate of the amount metabolized was described as a saturable process as follows:

$$\frac{dA_{met}}{dt} = \frac{V_{max} C_{vt}}{K_m + C_{vt}} \quad (9)$$

The mixed venous blood concentration of toluene was calculated as follows:

$$C_v = \frac{\sum_t^n Q_t C_{vt} + Q_m C_{vm}}{Q_c} \quad (10)$$

The above equation represents the steady-state solution of the mass-balance differential equation for venous blood:

$$\left[V_b \left(\frac{dC_b}{dt} \right) = \sum_t^n Q_t C_{vt} + Q_m C_{vm} - C_v Q_c \right] \quad (11)$$

The arterial blood concentration of toluene was computed with the following equation:

$$C_a = \frac{Q_p C_{inh} + Q_c C_v}{Q_c + \left(\frac{Q_p}{P_b} \right)} \quad (12)$$

The equation describing the rate of change in the amount of toluene in breast milk (mg/hr) was calculated as:

$$RA_{milk} = Q_m (C_a - C_{vm}) - R_{nurse} \quad (13)$$

where,

$$R_{nurse} = C_{milk} \times V_{milk} \times \text{Nurse} \times S_{zone} \quad (14)$$

The amount of milk in the mammary tissue lumen was computed as the difference between the rate of production and rate of loss. The loss rate was set equal to the nursing rate and the volume of milk in the mammary tissue.

In the above equations, C_{inh} , C_v and C_a refer to inhaled, venous and arterial blood concentrations of toluene. P_b refers to blood:air partition coefficient. Q_p and Q_c refer to alveolar ventilation and cardiac output. C_{vi} , V_i , P_i , A_i and Q_i refer to venous blood concentrations leaving tissue compartments, tissue volumes, tissue:blood partition coefficients, amount in tissues and blood flow to tissues (t). V_{max} , K_m and A_{met} refer to the maximal velocity of metabolism, Michaelis affinity constant, and amount metabolized. dt refers to integration interval.

Regarding the milk-related parameters, the abbreviations are as follows:

RA_{milk} = rate of change in amount of chemical in breast milk

R_{nurse} = rate of change in amount of chemical ingested by nursing infant

C_{milk} = concentration of chemical in breast milk

V_{milk} = volume of milk currently in the mammary tissue lumen

N_{nurse} = infant nursing rate

S_{zone} = switch function to turn on or turn off the nursing over a 24-hr period

C_{vm} = venous blood leaving the milk compartment

Q_m = blood flow to the mammary tissue

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