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INVESTIGATIONS ON VENTILATION EQUATION STRUCTURE IN PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING OF INHALED TOXICANTS

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Abstract: Physiologically based pharmacokinetic (PBPK) models translate external concentrations into internal dose estimates. Most PBPK models use multiple assumptions when modeling toxicant uptake through ventilation. This study uses existing human PBPK models of xylene and perchloroethylene to investigate the effect of the structure of air and blood concentration equations on compartmental predictions. Differences in ventilation equation structure do have an effect on model predictions and may affect parameter estimates found through inverse problems.

AMS Subject Classification: 92B05
Key Words: PBPK, xylene, perchloroethylene

1. Introduction

Physiologically based pharmacokinetic (PBPK) models were developed in order to translate external concentrations into internal dose estimates. These differential equation models were formed by taking into account absorption,

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distribution, metabolism, and excretion and incorporating physiological measurements. PBPK models can be constructed to reflect certain assumptions, such as considering the transfer of some chemicals to be at equilibrium. This study aims to investigate changes in model output due to common ventilation assumptions.

PBPK models have been developed to estimate internal doses for various toxicants in rodents [1, 2, 3, 4, 5, 6, 7, 8, 9] and in humans [10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. The appropriate use of PBPK model estimates in risk assessment is dependent on the biological basis of the model structure and parameters, among other factors [20]. Most PBPK models for inhaled toxicants use assumptions about the transfer of the toxicant from the inhaled/exhaled air to the alveolar space in order to simplify model equations. This study intends to investigate the effect of these assumptions on model output using simulations with existing PBPK models of two toxicants, xylene and perchloroethylene.

Xylene is an widely used industrial solvent and is a component of paints, paint thinners, and related products [21]. Although occupational exposure may often be relatively small, workers in specific industries or exposed to xylene in poorly ventilated areas may be at risk of exposure to high xylene concentrations [22]. Additionally, xylene potentially increases the toxicity of other chemicals when present in mixtures [23].

Internal dose estimates of perchloroethylene (or tetrachloroethylene) are of interest because perchloroethylene is used as a solvent in the dry-cleaning industry [24]. Perchloroethylene has been observed to induce hepatocellular carcinoma in mice [25], and exposure to perchloroethylene was found to affect motor function behavior in both rats and humans, although a relationship between exposure conditions and function impairment was not established [26, 27]. Additionally, dry-cleaning workers exposed to perchloroethylene have been found to have overall excess cancer mortality [28, 29, 30, 31].

PBPK models for xylene and perchloroethylene were chosen for the simulations for the simplicity in their structure and for their metabolic similarities and differences. Both xylene and perchloroethylene are primarily metabolized by the same cytochrome enzyme, CYP2E1. The PBPK model used for xylene predictions only considers the parent chemical in four primary compartments [18] (see Figure 1). Metabolism of perchloroethylene is believed to contribute to toxicity [32], and the PBPK model for perchloroethylene used for simulations incorporates modeling of one metabolite [16] (see Figure 2). Additionally, these chemicals have different metabolic rates, with perchloroethylene being metabolized relatively slower than xylene [18, 16].

In order to determine the effect of inhalation equation structure on PBPK

modeling, PBPK models of xylene and perchloroethylene are used for simulations with different ventilation equations. The model simulations for the different ventilation structures are compared for each compartment of both PBPK models. The differences in model output are of interest because many internal parameters are estimated using inverse problems with data from inhalation exposures.

2. Methods

2.1. Computational Methods

All computational solutions were produced using MATLAB (version 7.6) and its *ode15s* solver [33]. Exposure scenarios were chosen to be similar to the source material for each model but to be the same for both models (50 ppm for 7 hours). Coding for both models was verified to satisfy mass balance and produce similar results to the original studies [16, 18].

2.2. Ventilation and Blood Equations

The concentration in the alveoli (or respiratory space) can be described by considering what enters from inhalation and the venous blood and what leaves through exhalation and the arterial blood

$$\frac{dA^i_{alv}}{dt} = Q_p \left(C^i_{inh} - \frac{A^i_{alv}}{V_{alv} P^i_{bl:air}} \right) + Q_c \left(C^i_{ven} - \frac{A^i_{alv}}{V_{alv} P^i_{alv}} \right) . \tag{1}$$

Further, the corresponding blood concentrations can be described

$$\frac{dC^i_{art}}{dt} = Q_c \left(\frac{A^i_{alv}}{V_{alv} P^i_{alv}} - C^i_{art} \right) \tag{2}$$

$$\frac{dC^i_{ven}}{dt} = \frac{1}{V_{ven}} \left(\sum_j Q_j \frac{A^i_j}{P^i_j V_j} - Q_c C^i_{ven} \right) \tag{3}$$

where j ranges over all compartments (except the respiratory space) and i indicates the toxicant being modeled. A^i_j and C^i_j indicate the amount or concentration of toxicant i in compartment j, respectfully; V_j is the volume of compartment j; P^i_j represent partition coefficients; Q_p and Q_c represent alveolar ventilation and cardiac flow, respectively; and C^i_{inh} is the concentration

of toxicant i in the inhaled air. The notation used above is consistent with PBPK modeling and is defined more fully in Appendix A.1. In most PBPK models, equations (1)-(3) are simplified using a few assumptions [4, 16, 18]. As in [34], the amount of toxicant leaving the alveolar space into the atmosphere is assumed to be equal to the amount eliminated through the blood. In these cases, (1) is set equal to zero. Additionally, the alveolar concentration is assumed to be equal to the arterial concentration and that $P^i_{alv} = 1$. Under these assumptions, (1) can be reduced to the algebraic expression for C^i_{art} as follows:

$$C^i_{art} = \frac{Q_c C^i_{ven} + Q_p C^i_{inh}}{Q_c + \frac{Q_p}{P^i_{bl:air}}} \tag{4}$$

Equation (4) is then used with the following algebraic representation for the concentration of toxicant in venous blood:

$$C^i_{ven} = \frac{\sum_j Q_j \frac{A^i_j}{P^i_j V_j}}{Q_c} \ . \tag{5}$$

The purpose of this study is to investigate the affect of using Equations (1)-(3) instead of Equations (4) and (5). The term "non-equilibrium" is used here to indicate simulations using Equations (1)-(3), and "equilibrium" results are formulated using (4) and (5). All investigations in the current study focus on human models.

With the added complexity of using the non-equilibrium formulation comes the requirement for more information. In order to use equations (1)-(3) instead of (4) and (5), the following additional parameters are needed: V_{alv} (alveolar/lung compartment volume), V_{ven} (volume of venous blood), and P^i_{alv} (lung:blood partition coefficient for chemical i). The volume of the alveolar space/lung compartment is described by 0.8% body weight (the lung tissue balance value from Table 21 of [35]). This value is presented in [35] with the caveat "because the lung is a vascular tissue, some percentage of the lung weight will consist of residual blood, even in reasonably drained tissues." The value 0.8% of body weight most likely describes the entire lungs and not just the alveolar space. However, only considering the respiratory compartment as a significantly smaller percentage of the overall lung tissue may not be reasonable either. The authors of [36] point out that solubility and reactivity of the toxicant play a large role in how they are absorbed in the respiratory tract. In the current study, $V_{alv} = 0.008BW$ is assumed to be sufficient. A value of 7.9% of body weight was assumed to describe the total volume of blood [35] (if not

defined otherwise in the model being considered). If arterial and venous blood are defined separately, a fractional division is set to be 80% venous, 20% arterial based on [35], which lists percentages for the arterial portion of blood to be 15% and 19% (not including pulmonary circulation and heart cavities) and an alternative approach of a 25:75 division of blood volume between arterial and venous circulations. Compartmental volumes are set to sum to 100% including blood and lung volumes, regardless of which condition ("non-equilibrium" or "equilibrium") is used.

3. Model Simulations

3.1. Xylene Model

In order to investigate ventilation changes, simulations are generated using a human PBPK model of xylene from [18]. The flow-limited model contains four compartments: slowly perfused tissues, rapidly perfused tissues, fat, and liver. A schematic of the PBPK model for xylene is presented in Figure 1, and model equations are presented in Section A.3. The compartmental volumes (V_i) were altered slightly in order to sum to 100% of body weight similar to [37] for toluene for the "non-equilibrium" case. The volume of rapidly perfused tissues was lowered in order to subtract out volumes for blood and for the lung. The value for V_r used in the current study is between previously used values [35, 18], and compartmental volumes are presented in Table **??**. Identical compartmental volumes were used for all simulations presented in Section 3.3 under the assumption that the blood and lung volumes should not be part of the total in the "equilibrium" case. More information about compartmental volumes and other parameters is contained in Appendix A.2. Metabolism is assumed to be limited to the liver and to behave according to Michaelis-Menten kinetics. No metabolites were modeled. As with the simulations in [37], the exposure conditions were set to be 50 ppm inhalation for 7 hours. The lung:air partition coefficient ($P^{xyl}_{alv:air}$) was obtained from [21] and was used with the blood:air partition coefficient from [18] in order to find P^{xyl}_{alv} (i.e., $P^{xyl}_{alv} = P^{xyl}_{alv:air}/P^{xyl}_{bl:air}$).

3.2. Perchloroethylene Model

In order to provide another toxicant for investigation, the human perchloroethylene model from [16] is modified to make predictions on using both the "equilibrium" and "non-equilibrium" equations for blood concentrations. The per-

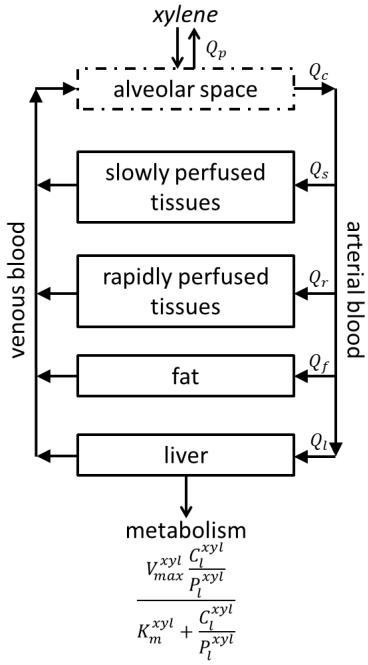

Figure 1: A schematic of the PBPK model for xylene.

chloroethylene model incorporates compartments for the liver, kidneys, fat, deep fat, brain, muscle, skin, rapidly perfused tissue, and slowly perfused tissue. A schematic of the PBPK model for perchloroethylene is presented in Figure 2, and model equations are presented in Section A.3. The compartmental blood flow and volume fractions are modified slightly as is described in [37] for the standard adult case except for V_m. The parameter V_m is treated as a "rest of the body" compartment in [16] and therefore the additional volumes used with the "equilibrium case" (V_{bl} and V_{alv}) were subtracted out of V_m from [37]. Parameter volumes used in the perchloroethylene model are presented in Table **??**, and other parameter values are defined as described in Appendix A.2. As with the xylene model, compartmental volumes remained the same for all simulations. Metabolism is assumed to be limited to the liver and is described using Michaelis-Menten kinetics. The concentration of one metabolite (trichloroacetic acid, TCA) in the plasma is modeled using a percentage rate of metabolism in the liver. The value of P_{alv}^{perc} is calculated as described for xylene in Section 3.1 and is based on the lung:air partition coefficient from

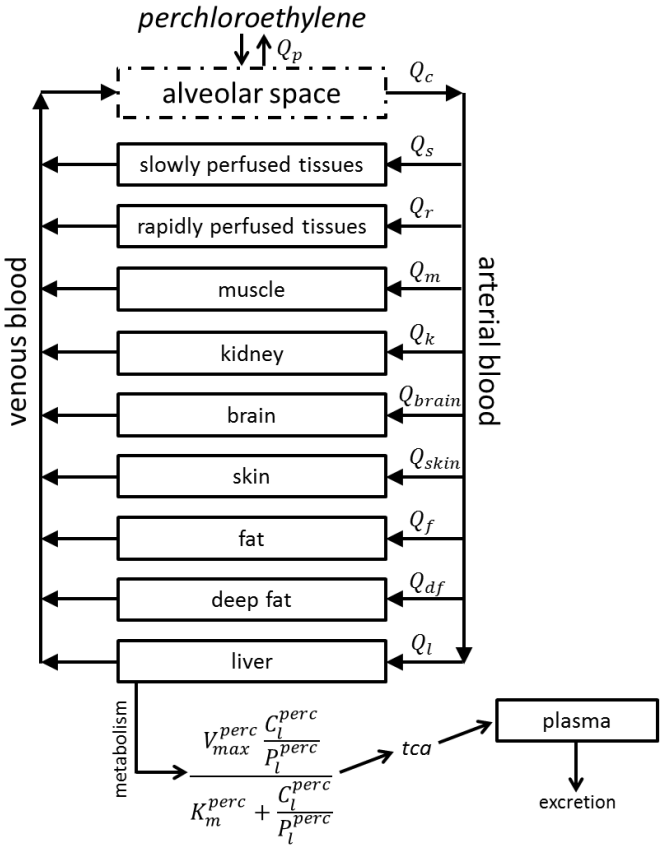

Figure 2: A schematic of the PBPK model for perchloroethylene.

[21]. (Note: $P_{alv}^{perc} = P_{alv:air}^{perc}/P_{bl:air}^{perc}$.)

3.3. Computational Investigations

Both the values for P_{alv}^{perc} and P_{alv}^{xyl} based on literature are greater than 1, but the accuracy of the model output in the "non-equilibrium" case is likely dependent on the accuracy of P_{alv}^{i}. In order to investigate the differences in model output, the following three cases will are considered:

- **Case 1:** the "equilibrium" case using equations (1)-(3),

- **Case 2:** the "non-equilibrium" case using equations (4) and (5) with P^i_{alv} based on [21],
- **Case 3:** the "non-equilibrium" case using equations (4) and (5) with $P^i_{alv} = 1$ or (a "hybrid" case).

4. Results

Compartmental simulations were produced using the xylene model are contained in Figures 3-9. Note that different plots have different scales. Predictions for xylene for the "equilibrium" case are very similar to that of the "hybrid" case for the main four compartments, and simulations of xylene predictions are lower for the "non-equilibrium" case with $P^{xyl}_{alv} \neq 1$ than for the "equilibrium" case for internal compartments. The predictions for the concentration of xylene in exhaled air are higher for Case 2 than the other two cases. The predictions for xylene concentrations for blood are highest for the "hybrid" case and lowest for the "equilibrium" case. However, when the "equilibrium" case was simulated with slightly different compartmental volumes (such that the rapid, slow, liver, and fat compartments totaled 100% body weight), the resulting graphs are very similar to the "hybrid" simulations for all graphs. The graphs for the "equilibrium" case with different compartmental volumes are not presented for more direct comparison and because the graphs were so similar to those from Case 3.

Simulations made using the perchloroethylene model are presented in Figures 10-22. Again, the graphs are presented on different scales. Simulations were generated over longer periods for predictions of perchloroethylene in the fat, perchloroethylene in the deep fat, and TCA in the blood. As with the xylene simulations, predictions are similar for Case 1 and Case 3. Additionally, the predicted compartmental perchloroethylene concentrations are lower for the non-equilibrium case (Case 2) than for the other cases (except for concentration in exhaled air). The "non-equilibrium" conditions also lead to lower predictions for TCA in the blood.

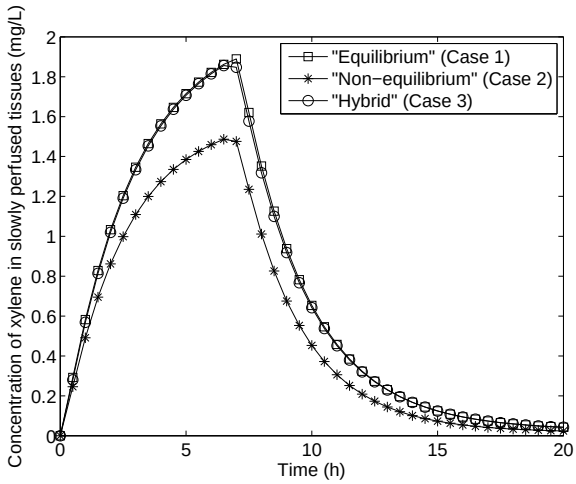

Figure 3: The PBPK predicted concentrations of xylene in the slowly perfused tissues using the three cases listed in Section 3.3.

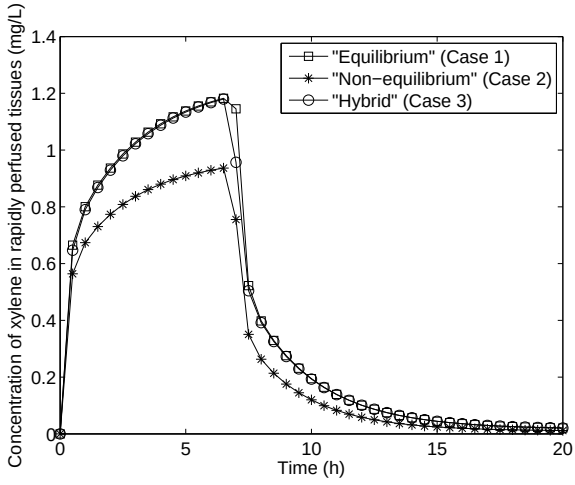

Figure 4: The PBPK predicted concentrations of xylene in the rapidly perfused tissues using the three cases listed in Section 3.3.

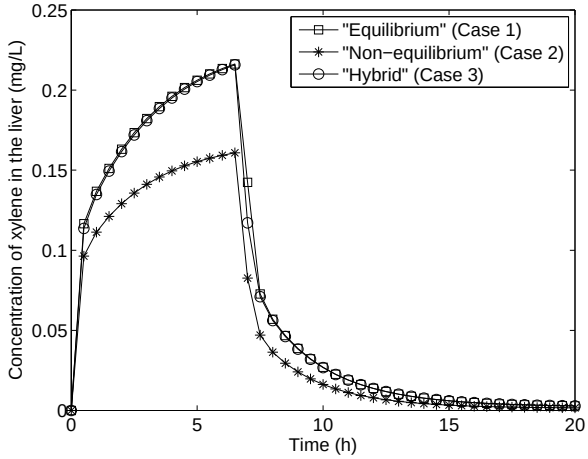

Figure 5: The PBPK predicted concentrations of xylene in the liver using the three cases listed in Section 3.3.

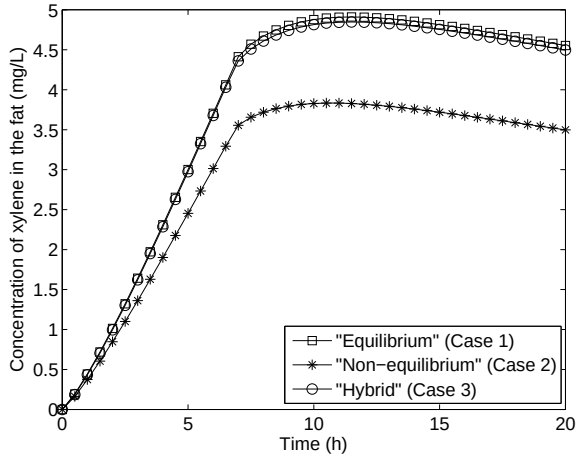

Figure 6: The PBPK predicted concentrations of xylene in the fat using the three cases listed in Section 3.3.

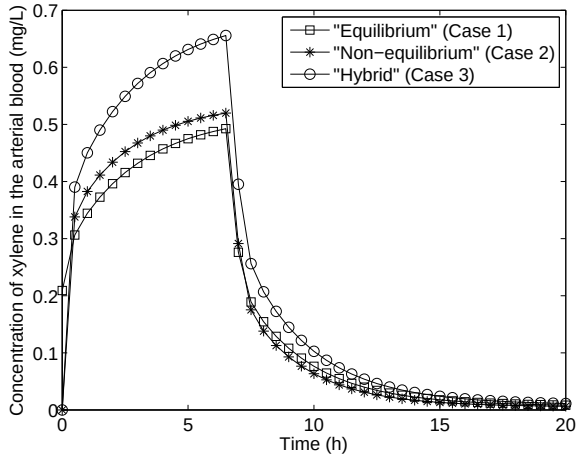

Figure 7: The PBPK predicted concentration of xylene in arterial blood using the three cases listed in Section 3.3.

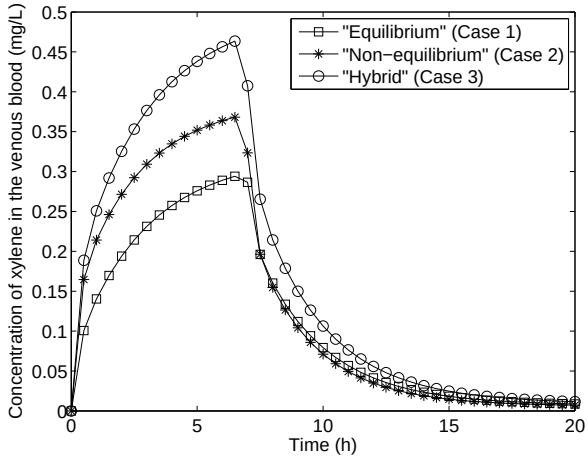

Figure 8: The PBPK predicted concentrations of xylene in venous blood using the three cases listed in Section 3.3.

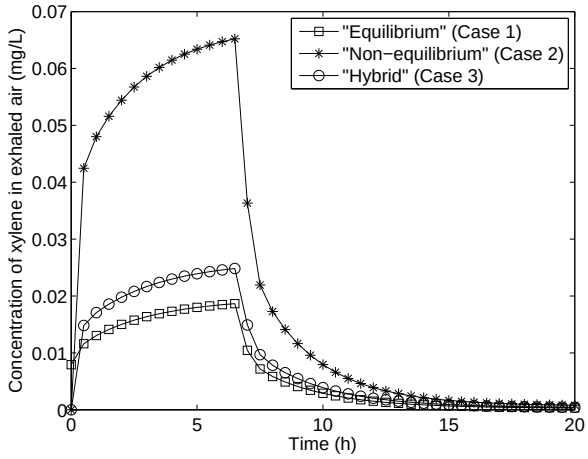

Figure 9: The PBPK predicted concentrations of xylene in exhaled air using the three cases listed in Section 3.3.

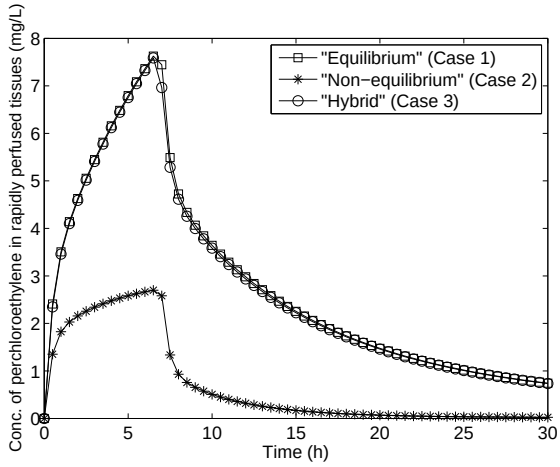

Figure 10: The PBPK predicted concentrations of perchloroethylene in the rapidly perfused tissues using the three cases listed in Section 3.3.

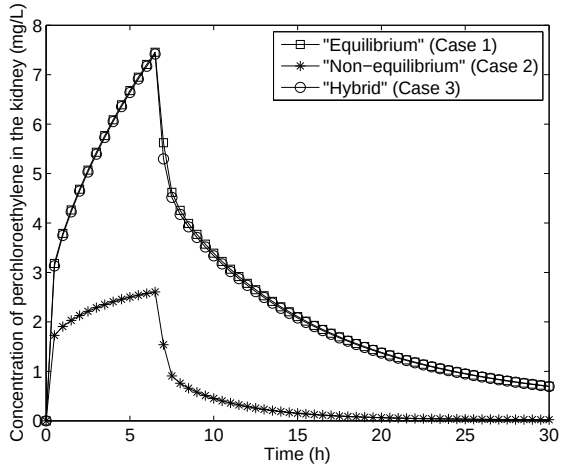

Figure 11: The PBPK predicted concentrations of perchloroethylene in the kidney using the three cases listed in Section 3.3.

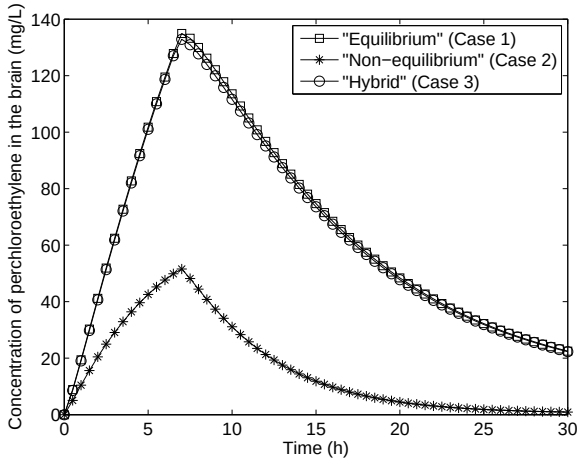

Figure 12: The PBPK predicted concentrations of perchloroethylene in the brain using the three cases listed in Section 3.3.

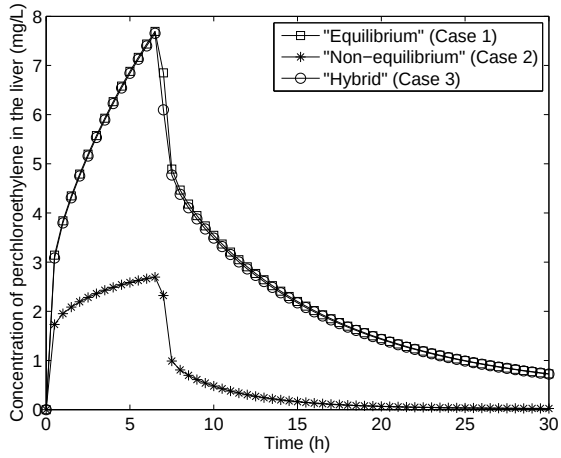

Figure 13: The PBPK predicted concentrations of perchloroethylene in the liver using the three cases listed in Section 3.3.

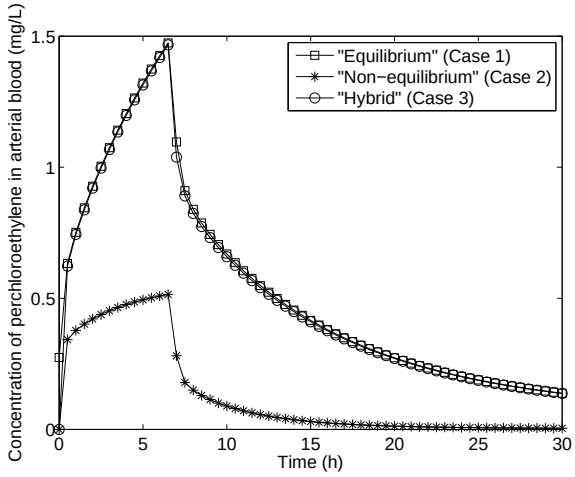

Figure 14: The PBPK predicted concentrations of perchloroethylene in arterial blood using the three cases listed in Section 3.3.

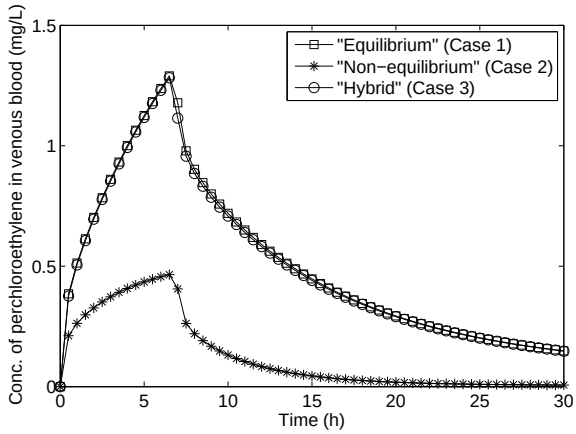

Figure 15: The PBPK predicted concentrations of perchloroethylene in venous blood using the three cases listed in Section 3.3.

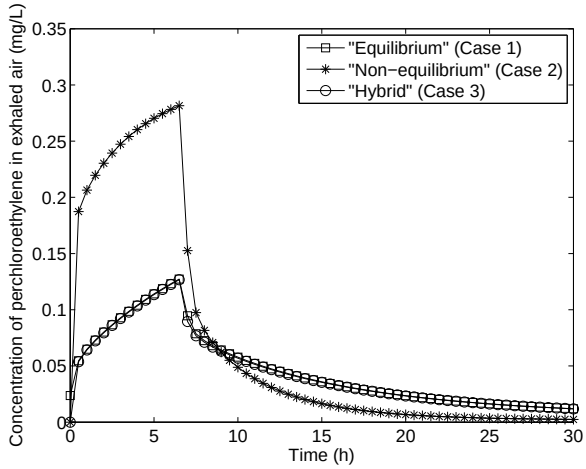

Figure 16: The PBPK predicted concentrations of perchloroethylene in exhaled air using the three cases listed in Section 3.3.

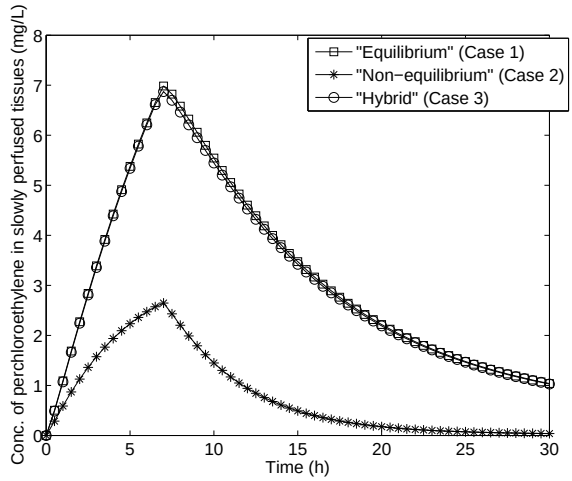

Figure 17: The PBPK predicted concentrations of perchloroethylene in the slowly perfused tissues using the three cases listed in Section 3.3.

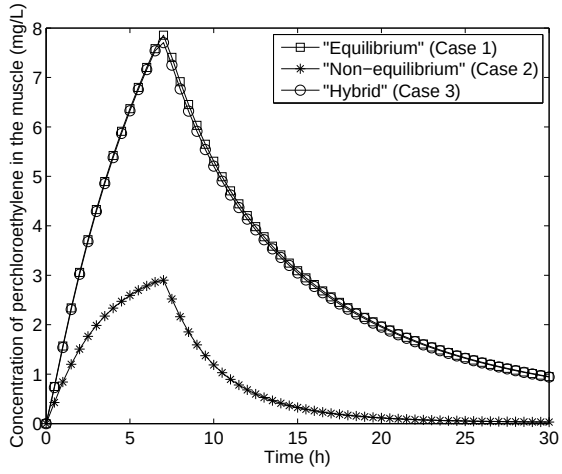

Figure 18: The PBPK predicted concentrations of perchloroethylene in the muscle using the three cases listed in Section 3.3.

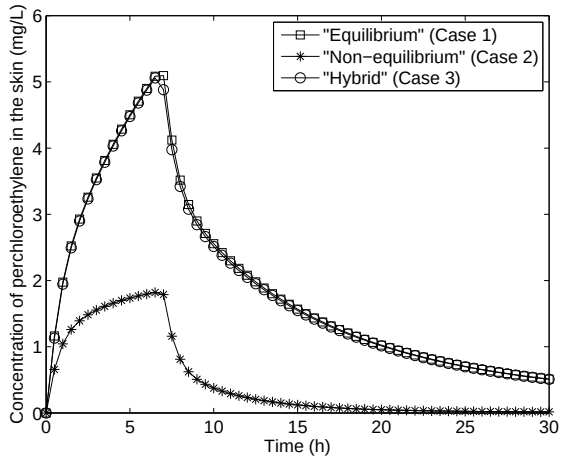

Figure 19: The PBPK predicted concentrations of perchloroethylene in the skin using the three cases listed in Section 3.3.

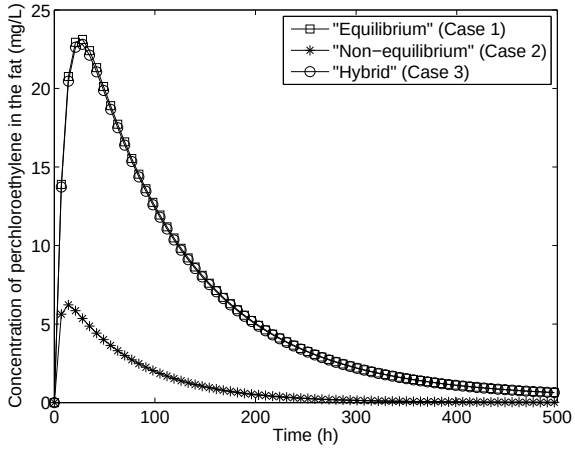

Figure 20: The PBPK predicted concentrations of perchloroethylene in fat using the three cases listed in Section 3.3.

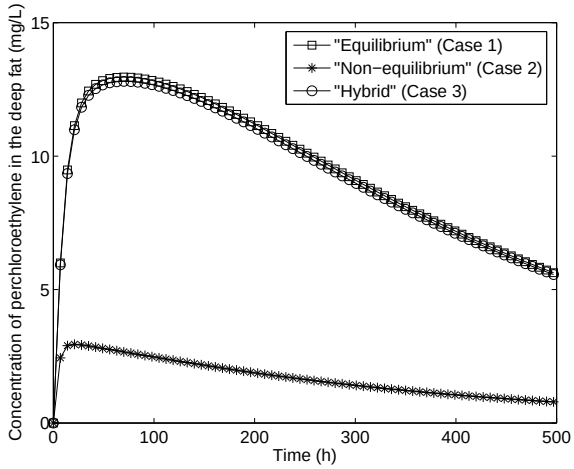

Figure 21: The PBPK predicted concentrations of perchloroethylene in deep fat using the three cases listed in Section 3.3.

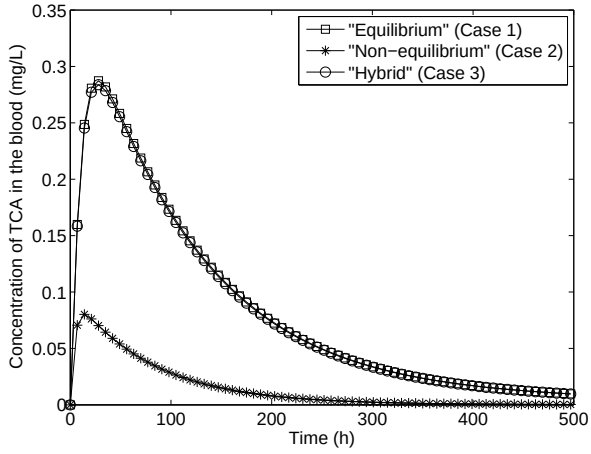

Figure 22: The PBPK predicted concentrations of the perchloroethylene metabolite TCA in the blood using the three cases listed in Section 3.3.

5. Conclusions

The current study uses established human PBPK models for xylene and perchloroethylene in order to investigate how equations for ventilation affect model predictions for inhaled toxicants. Structural differences in equations that predict blood concentrations result in different predicted compartmental concentrations if P^i_{alv} is calculated based on lung tissue experiments. Equilibrium assumptions result in higher compartmental concentrations and lower concentrations in exhaled air than for the non-equilibrium conditions if the literature-based values are used for P^i_{alv}. The model predictions for the non-equilibrium case when $P^i_{alv} = 1$ are often similar to the predictions using the equilibrium case, indicating that the steady state assumption ($\frac{dA^i_{alv}}{dt} = 0$) may not significantly change predictions if $P^i_{alv} = 1$.

Internal dose estimates are predicted to be higher for the equilibrium case than for the non-equilibrium case with a literature-based lung partition coefficient ($P^i_{alv} > 1$). Hence, if (1), (2), and (3) are better for modeling the inhalation of xylene and perchloroethylene than (4) and (5), then the use of (4) and (5) may result in over predictions of internal doses. One could argue that this is a moot point in that if internal doses are *over predicted* then measures of risk will be overestimated. The literature based non-equilibrium condition results in the higher predictions of xylene and perchloroethylene concentrations in exhaled air. The differences in the exhaled air predictions are of interest because data of toxicant concentrations in exhaled air are often used in optimizations of PBPK models to data. Additionally, TCA predictions are also different with the "equilibrium" and "non-equilibrium" cases which could affect inverse problems using blood or excretion data

If a more complicated system of equations for respiration and blood concentrations (as presented in Equations (1), (2), and (3)) better represents the physiological system when toxicants are inhaled, then the more commonly used equations in (4) and (5) may be inadequate if $P^i_{alv} \neq 1$. More developed ventilation models are beginning to be used with PBPK modeling [38] which could assist in avoiding the problems associated with the currently used ventilation assumptions. However, some internal parameters may need to be estimated with the more developed models to be accurate.

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A. Appendix

A.1. Model Notation

Chemicals:

xyl	xylene
perc	perchloroethylene

Compartments:

s	slowly perfused tissues
f	adipose tissue or fat
r	rapidly perfused tissues
k	kidney
l	liver
ven	venous blood
art	arterial blood
bl	blood (mixed)
alv	alveolar space or respiratory compartment
brain	brain
df	deep fat
skin	skin

General Notation:

BW	Body weight (kg)
MW	Molecular weight
Q_j	Blood flow in/to compartment j (L/h)
Q_c	Cardiac flow, $\sum_j Q_j$ (L/h)

Q_p	Pulmonary flow/alveolar ventilation (L/h)
V_j	Volume of compartment j (L)
P_j^i	The partition coefficient for chemical i in tissue j $(dimensionless)$
$P_{bl:air}^i$	The blood/air partition coefficient for chemical i $(dimensionless)$
$P_{alv:air}^i$	The lung/air partition coefficient for chemical i $(dimensionless)$
A_j^i	The amount of chemical i in tissue j (mg)
C_j^i	The concentration of chemical i in compartment j (mg/L)
C_{inh}^i	The concentration of chemical i inhaled (mg/L)
V_{max}^i	The maximum rate of metabolism for chemical i (mg/h)
K_m^i	The concentration of i at half saturation (mg/L)
K_e	The elimination constant of perchloroethylene $(1/h)$
K_u	Urinary excretion constant of perchloroethylene $(1/h)$
SY	Stoichiometric yield of perchloroethylene metabolized $(dimensionless)$

A.2. Parameter Values

All simulations used body weight, BW, as 70 kg under the assumption that 1 L=1 kg is a sufficient conversion. Physiological parameters used in the xylene and perchloroethylene models are presented in Tables **??**, **??**, and **??**. Cardiac output and alveolar ventilation were assumed to follow allometric scaling with scaling factors used from the respective models:

Xylene: $Q_c = 18.0BW^{0.70} = Q_p$ [18]

Perchloroethylene:

$Q_c = 15.9BW^{0.81}$,
$Q_p = 18.6BW^{0.74}$, see [16]

Metabolic values from the PBPK source models were used ($V_{max}^{xyl} = 8.4BW^{0.75}$, $K_m^{xyl} = 0.2$ [18]; $V_{max}^{perc} = 0.28BW^{0.7}$, $K_m = 7.7$ [16]).

Compartmental flow	Value (% Q_c)	Source
Xylene		
Fat	5	[18]
Slowly perfused	25	[18]
Richly perfused	44	[18]
Liver	26	[18]
Perchloroethylene		
Brain	10.2	[16]
Kidney	24	[16]
Fat	4	[16]
Deep fat	1	[16]
Skin	3.4	[16]
Rapidly perfused	10.1	(mass balance)
Slowly perfused	4.2	[35]
Liver	24	[16]
Muscle	19.1	[35]

Table 1: The compartmental flows used in simulations of the xylene and perchloroethylene models.

Additional values specific to the perchloroethylene model, unless otherwise stated, are the same as in [16].

Partition coefficient	Value	Source
Xylene		
Blood:air	26.4	[18]
Fat:blood	77.8	[18]
Slowly perfused:blood	3.0	[18]
Richly perfused:blood	4.42	[18]
Liver:blood	3.02	[18]
Lung:air	87.4	[21]
Perchloroethylene		
Blood:air	11.58	[16]
Fat:air	1450	[16]
Deep fat:air	3020	[16]
Slowly perfused:air	70.45	[16]
Rapidly perfused:air	61.1	[16]
Liver:air	61.1	[16]
Kidney:air	58.6	[16]
Brain:air	1450	[16]
Muscle:air	70.45	[16]
Skin:air	41.5	[16]
Lung:air	73.3	[21]

Table 2: The partition coefficients used in simulations of the xylene and perchloroethylene models.

A.3. PBPK Model Equations

The following are equations used in the PBPK modeling for xylene or perchloroethylene with either equations (1)-(3) or (4) and (5).

Compartmental concentration:

$$C_j^i = \frac{A_j^i}{V_j}$$

Differential equation for an internal compartment j (excluding the liver):

$$\frac{dA_j^i}{dt} = Q_j \left(C_{art}^i - \frac{C_j^i}{P_j^i} \right)$$

Volume	Value
Xylene	
V_l	$0.026BW$
V_f	$0.214BW$
V_s	$0.613BW$
V_r	$0.06BW$
V_{bl}	$0.079BW$
Perchloroethylene	
V_l	$0.03BW$
V_{brain}	$0.02BW$
V_k	$0.0044BW$
V_f	$0.15BW$
V_{df}	$0.09BW$
V_m	$0.4186BW$
V_{skin}	$0.037BW$
V_s	$0.143BW$
V_r	$0.04BW$
V_{bl}	$0.059BW$
All	
V_{alv}	$0.008BW$
V_{art}	$0.2V_{bl}$
V_{ven}	$0.8V_{bl}$

Table 3: The compartmental volumes used in simulations of the xylene and perchloroethylene models. All values are the same as used for the "Non-aged adult" in [37] except for V_r and V_{bl} for xylene, V_m for perchloroethylene, and V_{alv}, V_{art}, and V_{ven} for both models. V_r for xylene and V_m for perchloroethylene were altered to have all volumes sum to 100%. V_{bl} used for xylene, V_{alv}, V_{art}, and V_{ven} are based on [35].

Differential equation for the liver compartment:

$$\frac{dA_l^i}{dt} = Q_l \left(C_{art}^i - \frac{C_l^i}{P_l^i} \right) - \frac{V_{max}^i \frac{C_l^i}{P_l^i}}{K_m^i + \frac{C_l^i}{P_l^i}}$$

Additional equations for perchloroethylene involving TCA in the body, in an

intermediate compartment (int), and in the urine (u):

$$\frac{dA^{tca}}{dt} = SY\left(\frac{MW_{tca}}{MW_{perc}}\right)\left(\frac{V^{i}_{max}\frac{C^{perc}_{l}}{P^{perc}_{l}}}{K^{perc}_{m}+\frac{C^{perc}_{l}}{P^{perc}_{l}}}\right) - K_e A^{tca}$$

$$\frac{dA^{tca}_{int}}{dt} = K_e A^{tca} - K_u A^{tca}_{int}$$

$$\frac{dA^{tca}_{u}}{dt} = K_u A^{tca}_{int}$$