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A Distributed Parameter Physiologically-Based Pharmacokinetic Model for Dermal and Inhalation Exposure to Volatile Organic Compounds

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Estimates of dermal dose from exposures to toxic chemicals are typically derived using models that assume instantaneous establishment of steady-state dermal mass flux. However, dermal absorption theory indicates that this assumption is invalid for short-term exposures to volatile organic chemicals (VOCs). A generalized distributed parameter physiologically-based pharmacokinetic model (DP-PBPK), which describes unsteady state dermal mass flux via a partial differential equation (Fickian diffision), has been developed for inhalation and dermal absorption of VOCs. In the present study, the DP-PBPK model has been parameterized for chloroform, and compared with two simpler PBPK models of chloroform. The latter are lumped parameter models, employing ordinary differential equations, that do not account for the dermal absorption time lag associated with the accumulation of permeant chemical in tissue represented by permeability coefficients. All three models were evaluated by comparing simulated post-exposure exhaled breath concentration profiles with measured concentrations following environmental chloroform exposures. The DP-PBPK model predicted a time-lag in the exhaled breath concentration profile, consistent with the experimental data. The DP-PBPK model also predicted significant volatilization of chloroform, for a simulated dermal exposure scenario. The end-exposure dermal dose predicted by the DP-PBPK model is similar to that predicted by the EPA recommended method for short-term exposures, and is significantly greater than the end-exposure dose predicted by the lumped parameter models. However, the net dermal dose predicted by the DP-PBPK model is substantially less than that predicted by the EPA method, due to the post-exposure volatilization predicted by the DP-PBPK model. Moreover, the net dermal dose of chloroform predicted by all three models was nearly the same, even though the lumped parameter models did not predict substantial volatilization.

KEY WORDS: Chloroform; volatile organic compounds; dermal; diffusion; PBPK; skin-absorption.

1. INTRODUCTION

Dermal absorption of environmental contaminants has been shown to contribute significantly to internal dose in many exposure scenarios.[1–4] Consequently, there is a need for improved methods of estimating the dermal uptake of these chemicals. Since dermal exposures are often of short duration, dermal mass flux does not reach steady state for many commonly experienced dermal exposure scenarios, such as showering and swimming.[5–7] It is therefore particularly important for dermal absorption estimation methods to be able to account for unsteady-state dermal mass flux.

Since the fundamental mechanism of dermal mass transport is passive diffusion,[8] unsteady state dermal mass flux is most naturally described by a Fickian diffusion equation. In this paper, we present a generalized distributed parameter physiologically based pharmaco-

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kinetic (PBPK) model that describes dermal transport of volatile organic compounds (VOCs) through the stratum corneum (the outermost layer of the skin) based on a numerical solution to the one-dimensional Fickian diffusion equation.

2. BACKGROUND

The propensity of a chemical to be dermally absorbed from a given environmental medium is commonly characterized by the skin permeability of the chemical, $K_{media \rightarrow skin}$. Skin permeability is usually estimated from *in* vitro experiments based on:[7]

$$J_{ss} = K_{media \rightarrow skin} \Delta C \quad (1)$$

where J_{ss} is the steady state in vitro dermal mass flux, and ΔC is the difference in concentration of the permeant chemical in the media on either side of the skin. Equation (1) is derived from the steady-state solution to the onedimensional Fickian diffision equation, and is valid only when the chemical has ceased to accumulate in the skin. Equation (1) will not accurately predict the dermal mass flux under conditions in which the skin has not fully equilibrated with the media on either side. In recognition of this, EPA has recommended that dermall dose be estimated using the Cleek and Bunge method,[7,9] in which resistance to dermal mass transport is manifested in terms of diffisivity, rather than directly in terms of skin permeability. The skin is not a homogeneous tissue, and a brief review of the structure of the skin will facilitate a discussion on the estimation of diffusivity in the skin.

2.1. Structure of the Skin

Skin tissue may be broadly classified into:

- the stratum corneum, a 10- to 40-pm-thick outermost epidermal layer, comprised of dead,, keratinized cells, held together in a lipid matrix,, and
- the viable skin, comprised of (a) the viable epidermis, a 50 to 100 μm thick nonvascularized layer of partly differentiated, living cells, and (b) the dermis, a 500 to 3000 pm thick layer that is highly vascularized.

Two properties of the stratum corneum distinguish it from other skin tissues. First, due to the lipophilic nature of the stratum corneum, the media:stratum comeurn partition coefficient for organic chemicals is generally much higher than the media:viable skin partition coefficient,[10] and so organic chemicals tend to accumulate in the stratum corneum. This has been termed the "epidermal reservoir" effect."') Second, the stratum corneum is generally accepted as being the main barrier to dermal transport across the skin,[8] due to the low diffusivity of chemicals through this layer as compared with diffusivity in the viable skin.

2.2. Estimation of Absorbed Dose

The parabolic Fickian partial differential diffusion equation describes the process of passive diffusion through the skin.[8] The EPA recommended Cleek and Bunge method for estimating dermal dose, is based on the approximate analytical solution to the one-dimensional Fickian diffision equation:[7,9]

$$\frac{\partial c_{s.c.}}{\partial t} = D_{s.c.} \frac{\partial^2 c_{s.c.}}{\partial x^2} \quad (2)$$

with initial and boundary conditions given by:

$$c_{s.c.}(x,0) = 0;\ 0 \le x \le L_c \quad (3)$$

$$c_{s.c.}(0,t) = C_{media} P_{s.c\ media};\ t > 0, \text{ and} \quad (4)$$

$$c_{s.c.}(L_c,t) = c_{v.s.}/P_{v.s./s.c.};\ t > 0 \quad (5)$$

where $c_{s.c}$ is the concentration of the chemical in the stratum corneum, which is a function of time, t, and distance from the surface of the skin, x, and C_{media} is the concentration of the permeant chemical in the media. The quantity L_c is the characteristic diffusion pathlength in the stratum corneum, and as explained in Appendix A.3, L_c may be greater than L, the thickness of the stratum corneum. However, in the Cleek and Bunge approach it is assumed that L_c is the same as L.

The solution of the one-dimensional Fickian diffision equation gives the concentration profile of the permeant chemical in a direction normal to the surface of the skin, which can then be used to calculate the mass flux at any depth within the stratum corneum through:

$$J(x,t) \equiv -D_{s.c.} \frac{\partial c_{s.c.}}{\partial x} \quad (6)$$

Thus, the mass flux from the media into the stratum corneum is given by $J(0, t)$, the mass flux from the stratum corneum into the viable skin is given by $J(L_c, t)$, and the difference between these quantities gives the accumulation in the stratum corneum.

The time required for dermal mass flux to reach steady state is a function of t_{lag}:

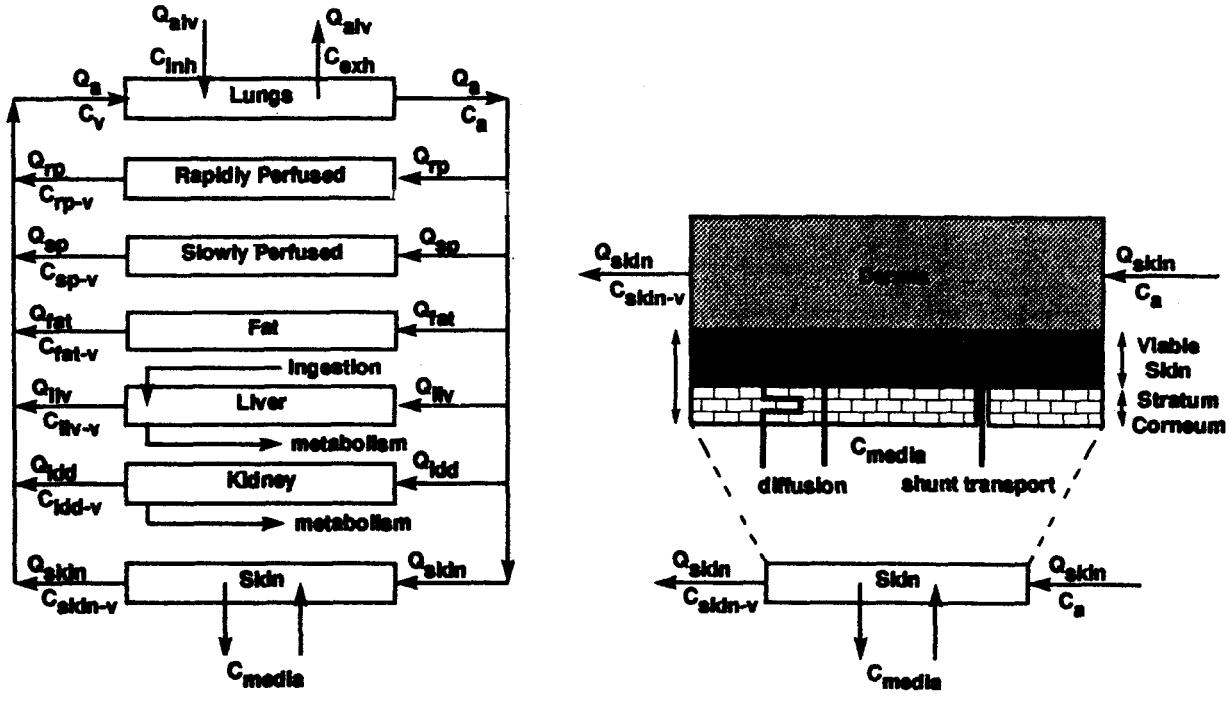

Fig. 1. Schematic of basic PBPK model for inhalation and dermal exposure to **VOCs,** showing three possible pathways of dermal mass transport.

$$t_{lag} = \frac{L_c^2}{6D_{s.c.}} \quad (7)$$

where $D_{s.c}$ is stratum corneum diffusivity, and L_c is the characteristic difision pathlength through the stratum corneum.

It has been estimated that mass flux reaches 99% of its steady-state value for exposures greater than 2.7 t_{lag}.[12] The EPA has tabulated t_{lag} values for approximately 70 organic compounds, most have t_{lag} values greater than 30 min.[7] Therefore, as noted by Bogen[5] the time required for the establishment of steady state, and for accumulation to cease in the bamer layer, appears to be greater than 1 hour for most environmental contaminants.

The formulation of dermal mass transport in existing PBPK models[13,14] is based on Eq. (1), in which mass transfer resistance is represented by skin permeability. Therefore, by analogy with Eq. (1), these PBPK models do not consider accumulation of the permeant chemical in the bamer layer. This is not physiologically realistic, since it is well established that the main bamer layer in the skin is the stratum corneum, and that organic chemicals tend to form an "epidermal reservoir" in this layer.[11,15]

This paper presents a distributed parameter PBPK model, in which dermal mass flux is estimated from the concentration gradient in the stratum corneum, which is obtained by solving the one-dimensional Fickian diffision equation numerically. The distributed parameter PBPK model has been demonstrated by parameterizing the model for chloroform; the predictions of this model are compared with those of two existing lumped parameter PBPK models. The dermal dose predicted by the distributed parameter PBPK model is also compared with the dermal dose predicted by the method currently recommended by EPA for estimating dermal dose for short-term exposures. Finally, an evaluation of the distributed parameter PBPK model is presented, using data resulting from short-term human exposure to chloroform.

3. PBPK MODEL **DESCRIPTIONS**

A schematic representation of the basic structure of the PBPK models described in this paper is given in Fig. 1. This basic structure has been adapted from the flow-limited PBPK model first proposed by Bischoff,[16,17] and subsequently applied to a variety of VOCs by Andersen and colleagues.[18,19] **Also** shown in Fig. 1, are the three possible paths by which chemicals may pass through the stratum corneum and enter the viable skin. The permeant

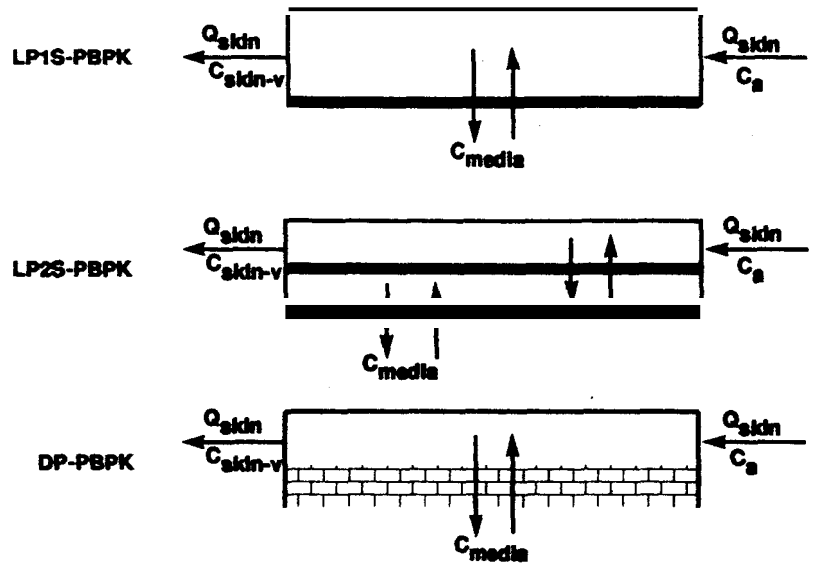

Fig. 2. Schematic of the skin compartment in alternative PBPK models of dermal absorption.

chemical may diffuse through the lipid matrix, or may diffuse through the keratinized cells, or may follow a shunt pathway via hair follicles or sweat glands. Of these, the lipid matrix pathway is considered to be the predominant route for dermal absorption of organic chemicals.[20]

3.1. The Lumped Parameter One Skin Compartment (LP1S-PBPK) Model

A PBPK model for dermal absorption with one skin compartment was first proposed by McDougal *et al.*[13] The McDougal et al. model may be generalized to a lumped parameter one slun compartment (LP1S-PBPK) model to describe the uptake of VOC contaminants from any media. In the LP1S-PBPK model, the skin is conceptualized as a single homogeneous compartment, with the mass transfer resistance located at an infinitesimally thin layer at the media–skin interface, as shown in Fig. 2.

The accumulation of the VOC permeant in the skin compartment of this model is given by the following mass balance:

$$V_{\text{skin}} \frac{dc_{\text{skin}}}{dt} = Q_{\text{skin}} \left(c_{\text{arterial}} - \frac{c_{\text{skin}}}{P_{\text{skin/blood}}} \right) + K_{\text{media}\leftrightarrow\text{skin}} A \left(C_{\text{media}} - \frac{c_{\text{skin}}}{P_{\text{skin/media}}} \right) \quad (8)$$

The quantities in the above equation are described in Table I. The first term on the r.h.s. represents the net accumulation of the VOC in the skin compartment due to blood flow, and the second term on the r.h.s. represents the rate of dermal mass transport of the contaminant.

It is important to note that the assumption of an infinitesimally thin resistance layer is necessary, since by analogy with Eq. (1), Eq. (8) is subject to the restriction that no accumulation of the permeant chemical occurs in the barrier layer. The location of the infinitesimally thin barrier layer in the skin compartment of the LP1S-PBPK model corresponds to the location of the stratum corneum in the skin. However, as noted in Sec. 2.1, accumulation of chemical in the stratum corneum can be significant for lipophilic compounds such as VOCs. McKone[6] has shown that the LP1S-PBPK model will underestimate the total amount of chemical that is initially absorbed into the skin.

3.2. The Lumped Parameter Two Skin Compartment (LP2S-PBPK) Model

Chinery and Gleason[14] proposed a PBPK model for dermal absorption of chloroform from aqueous media, in which the skin is represented by two homogeneous compartments: an outer compartment, the stratum corneum, and an inner compartment, the viable skin. This two-compartment approach may be generalized to a lumped parameter two-skin-compartment (LP2S-

Table I. Description of Parameters Used in the PBPK Models

Symbol	Description	Value	Reference
	Parameters common to LP1S-PBPK, LPZSPBPK, and DP-PBPK		
A	surface area (cm^2)	18,000	ICRP[30]
BW	body weight (Kg)	70	Corley[26]
Km	Michalis-Menten constant for metabolism (mg/liter)	0.448	Corley[26]
$P_{blood/air}$	blood:air partition coefficient	7.43	Corley[26]
$P_{fat/blood}$	fat:blood partition coefficient	37.7	Corley[26]
$P_{sp/blood}$	slowly perfused tissue:blood partition coefficient	1.6	Corley[26]
$P_{rp/blood}$	rapidly perfused tissue:blood partition coefficient	2.3	Corley[26]
$P_{liv/blood}$	liver:blood partition coefficient	2.3	Corley[26]
$P_{kid/blood}$	kidney:blood partition coefficient	1.5	Corley[26]
Q_c	cardiac output (liters/min)	5.8	Corley[26]
Q_p	alveolar ventilation (liters/min)	5.8	Corley[26]
Q_{fat}	blood flow to fat (litershin)	5% Q_c	Corley[26]
Q_{sp}	blood flow to slowly perfused tissue (liters/min)	15.6% Q_c	Corley[26]
Q_{rp}	blood flow to rapidly perfused tissue (liters/min)	26% Q_c	Corley[26]
Q_{liv}	blood flow to liver (liters/min)	25% Q_c	Corley[26]
Q_{kid}	blood Bow to kidney (liters/min)	25% Q_c	Corley[26]
Q_{skin}	blood flow to skin (liters/min)	3.4% Q_c	Section A
V_{fat}	mass of fat compartment (Kg)	23.1%	Corley[26]
V_{sp}	mass of slowly perfused tissue compartment (Kg)	51.05% BW	Corley[26]
V_{rp}	mass of rapidly perfused tissue compartment (Kg)	3.27% BW	Corley[26]
V_{liv}	mass of liver compartment (Kg)	3.14% BW	Corley[26]
V_{kid}	mass of kidney compartment (Kg)	0.44% BW	Corley[26]
V_{skin}	mass of skin compartment (Kg)	10% BW	McDougal[14]
Vmax	maximum rate of metabolism (mg/min)	5.117	Corley[26]
	Parameters specific to LP1S-PBPK		
$K_{water\leftrightarrow skin}$	overall skin permeability of chloroform in water (cm/min)	1.48×10^{-4}	Appendix A.1
$K_{air\leftrightarrow skin}$	overall skin permeability of chloroform in air (cmimin)	9.09×10^{-4}	Appendix A.l
$P_{sk/blood}$	skin:blood partition coefficient	1.6	Appendix A.l
$P_{skin/water}$	skin:water partition coefficient	1.94	Appendix A.1
$P_{skin/air}$	skin:air partition coefficient	11.9	Appendix A.1
	Parameters specific to LPZSPBPK and DP-PBPK		
$P_{v.s./blood}$	viable skin:blood partition coefficient	1.6	Appendix A.2
$P_{s.c./water}$	stratum corneum:water partition coefficient	25	Appendix A.2
$P_{s.c./air}$	stratum corneum:air partition coefficient	153	Appendix A.2
$P_{v.s./s.c.}$	viable skin:stratum corneum partition coefficient	0.1	Appendix A.2
	Parameters specific to LPZSPBPK		
$K_{water\leftrightarrow s.c.}$	stratum corneum permeability of chloroform in water (cmimin)	1.54×10^{-4}	Appendix A.2
$K_{air\leftrightarrow s.c.}$	stratum corneum permeability of chloroform in air (cm/min)	9.41×10^{-4}	Appendix A.2
$K_{s.c.\leftrightarrow v.s.}$	viable skin permeability of chloroform (cm/min)	$1.64 \times 10^{-}$	Appendix A.2
	Parameters specific to DP-PBPK		
$D_{s.c}$	effective stratum comeum diffisivity of chloroform (cm^2/min)	$0.6\text{-}2.4 \times 10^{-4}$	Appendix A.3
L	nominal stratum corneum thickness (μm)	10-40	Appendix A.3
L_c	stratum corneum diffusion pathlength (μm)	10-40	Appendix A.3

PBPK) model, to describe the dermal uptake of VOC contaminants with respect to any media. As shown in Fig. 2, the stratum corneum mass transfer resistance is assumed to be located at an infinitesimally thin layer at the media-stratum corneum interface, and the viable skin mass transfer resistance is assumed to be located at an infinitesimally thin layer at the stratum corneum–viable skin interface.

The accumulation of the VOC permeant in the stratum corneum compartment is given by the following mass balance:

$$V_{s.c}\frac{dc_{s.c}}{dt} = {}_{media\leftrightarrow s.c}\,A\left(C_{media} - \frac{c_{s.c.}}{P_{s.c./media}}\right) - K_{s.c.\leftrightarrow v.s.}\,A\left(c_{s.c.} - \frac{c_{v.s.}}{P_{v.s./s.c.}}\right) \quad (9)$$

and the accumulation of VOC in the viable skin is given by:

$$V_{v.s.}\frac{dc_{v.s.}}{dt} = Q_{skin}\left(c_{arterial} - \frac{c_{v.s.}}{P_{v.s.\,blood}}\right) + K_{s.c.\leftrightarrow v.s.}A\left(c_{s.c.} - \frac{c_{v.s.}}{P_{v.s./s.c.}}\right) \quad (10)$$

The quantities in the above equations are described in Table I.

The quantities $K_{media\leftrightarrow s.c}$ and $K_{s.c.\leftrightarrow v.s}$ are related to the overall skin permeability $K_{media\leftrightarrow skin}$ by[21]:

$$\frac{1}{K_{media\leftrightarrow skin}} = \frac{1}{K_{media\leftrightarrow s\,c}} + \frac{1}{K_{s\,c\leftrightarrow v\,s.}P_{s\,c\ media}} \quad (11)$$

The quantity $P_{s.c\ media}$ appears in the above equation because the viable skin permeability $K_{sc\leftrightarrow vs}$ has been defined with respect to the stratum corneum and not with respect to the media.[8] Using this relation it can be shown that the steady-state dermal mass flux predicted by this model is identical to the steady-state dermal mass flux predicted by the LP1S-PBPK model.

The compartmentalization in the LP2S-PBPK model is physiologically based, since the stratum corneum is not perfused, and is highly lipophilic (in contrast to the hydrophilic and mostly perfused viable skin). Although the LP2S-PBPK model does attempt to distinguish between accumulation of permeant in two very different types of skin tissue, the drawback of this model is that the representation of dermal mass transfer resistances by two infinitesimally thin layers is artefactual, The LP2S-PBPK model will underestimate the accumulation of chemical in the stratum corneum, since the entire stratum corneum resistance is concentrated at the media-stratum corneum interface.

3.3. The Distributed Parameter (DP-PBPK) Model

The,distributed parameter (DP-PBPK) model represents a refinement over the LP1S-PBPK and LP2S-PBPK models because the resistance to dermal mass transport is distributed throughout the stratum corneum, In the DP-PBPK model, the skin is divided into two compartments, as in the LPZS-PBPK model. However in the DP-PBPK model, the concentration of the permeant chemical in the stratum corneum compartment changes with distance from the stratum corneum–media interface.

In the DP-PBPK model the Fickian diffusion equation (Eq. 2) is solved numerically to obtain the concentration profile of the permeant chemical in the stratum corneum, following which the mass flux at the media–stratum corneum interface and at the stratum comeum–viable skin interface can be calculated by numerically solving Eq. (6).

The concentration profile of the permeant chemical within the stratum corneum is calculated by discretizing the stratum corneum compartment to obtain $N + 2$ equidistant nodes, and by using the central difference formula to give:

$$\frac{dc_{s.c.,i}}{dt} = \frac{D_{s.c.}}{(L_c/(N+1))^2}(c_{s.c.,i+1} - 2c_{s.c.,i} + c_{s.c.,i-1}),\ i = 1, \ldots, N \quad (12)$$

where, $c_{s\,c.,i}$ is the concentration at the ith node. The concentrations at the two extreme nodes in the stratum corneum are given by boundary conditions to Eq. (2):

$$c_{s.c.,0} = C_{media}P_{s.c./media} \quad (13)$$

$$c_{s.c.,N+1} = c_{v.s.}/P_{v.s./s.c.} \quad (14)$$

The accumulation of mass in the viable skin is given by:

$$V_{v.s.}\frac{dc_{v.s.}}{dt} = Q_{skin}\left(c_{arterial} - \frac{c_{v.s.}}{P_{v.s./blood}}\right) + J(L_c,t)A \quad (15)$$

where, $J(L_c, t)$ is the mass flux at the stratum corneum–viable skin interface. The mass flux at the stratum corneum–viable skin interface is calculated by a numerical approximation of Eq. (6):

$$J_{s.c.,N+1} = -D_{s.c.}\left(\frac{c_{s.c.,N+1} - c_{s.c.,N}}{L_c/(N+1)}\right) \quad (16)$$

3.4. Numerical Methodology

The lumped parameter models (LPS1-PBPK and LPS2-PBPK) are mathematically represented by a set of coupled ordinary differential equations (ODEs), one differential equation for each non-equilibrium physiological compartment describing the accumulation of VOC in the compartment, The only equilibrium compartment in the model is the lung, in which venous blood and exhaled air are assumed to be in equilibrium and no accumulation of the VOC is assumed to occur. Since the rate of VOC accumulation in the various compartments of the body can vary by orders of magnitude, the set of ODEs must be solved by a method appropriate for a set of stiff equations. In this study, the governing ODEs have been solved using Gear's backward differentiation formula (BDF),[22] as implemented in SimuSolv.[23]

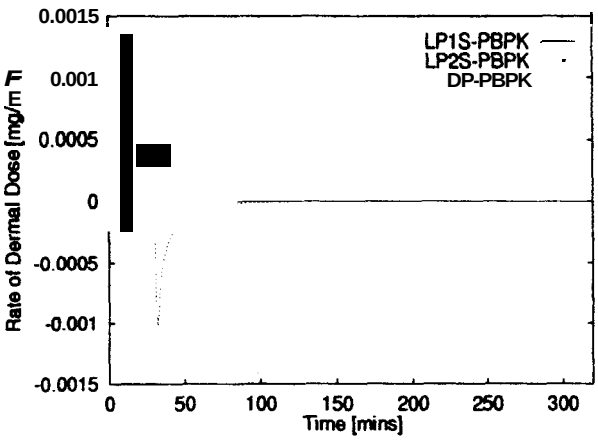

Fig. 3. Simulated rate of dermal dose resulting from a 30-min dermal-only exposure to 100.0 μg/l chloroform in water, predicted by the LPIS-PBPK. LPZS-PBPK, and DP-PBPK models.

The distributed parameter model (DP-PBPK) is represented by a set of coupled ODEs which is coupled with a partial differential equation (PDE). The ODEs in the DP-PBPK model are identical to those in the lumped parameter models, except for the ODE representing the skin compartment(s). In the DP-PBPK model, the stratum corneum compartment is represented by a PDE that has been solved by approximating the PDE by a set of N ODEs, as described in Sec. 3.3. The DP-PBPK model was implemented with $N = 100$, and this set of equations is now solved using Gear's BDF method.

Approximating the PDE by a set of N = 100 ODEs introduced errors of approximately 0.02% and 0.5% for 30-min and 10-min chloroform exposures, respectively. The numerical error was estimated by comparing the peak dermal dose predicted by the DP-PBPK model with that predicted by the analytical solution to Eq. (2). The analytical solution to Eq. (2) is available for constant concentration boundary conditions,[24] and the numerical implementation of Eq. (2) was disassociated from the other PBPK model equations and solved with constant concentration boundary conditions to facilitate a comparison with the analytic solution.

4. COMPARISON OF THE MODELS

To facilitate comparison, the three PBPK models described in Sec. 3 have been parameterized for chloroform, which is a typical VOC that is well suited to studying the dynamics of exposure–dose relationships relevant to VOC contaminants of municipal tap water. Chloroform is formed by the reaction of naturally occurring humic material in ground water with chlorine (added as a disinfectant during water treatment), and has been shown to be a carcinogen in rats and mice. In humans, chloroform is known to induce depression of the central nervous system, and cause toxic effects in the liver and kidney.[25,26] Each of the three PBPK models were used to simulate 30 min of dermal exposure to 100 μg/l chloroform in water. This level of exposure to chloroform is typical of that experienced in a swimming pool.[27] Following the end of exposure the skin is assumed to be in contact with air in which the concentration of the chemical is zero. This assumption proved to be a significant factor in the determination of the extent of volatilization from the skin.

The dermal dose rates predicted by the three PBPK models is compared in Fig. 3. There does not appear to be any difference between the dermal dose rate predicted by the LPIS-PBPK and LP2S-PBPK models, whereas the rate of dermal dose predicted by the DP-PBPK model during exposure is significantly greater than that for the other two models. Furthermore, all three PBPK models predict that the dermal dose rate is negative following the end of exposure, indicating that chloroform is volatilized from the skin. This volatilization of chloroform is to be expected, since the model assumes that dermal absorption is a passive process, the driving force for which is the concentration gradient. However, it is apparent from Fig. 3 that the extent of volatilization is appreciable only for the DP-PBPK model.

The dermal dose rate predicted by the DP-PBPK model during exposure is much greater than that for the lumped parameter models because in the latter the resistance to dermal absorption is located at the media–skin interface, which limits the rapid uptake of chloroform. In contrast, the resistance to dermal absorption in the DP-PBPK model is distributed throughout the stratum corneum, and therefore uptake into the outer region of the stratum corneum is much more rapid. This is also one of the reasons why the rate of volatilization in the lumped parameter models is less than that for the distributed parameter model. Another reason that volatilization is less in the lumped parameter models, is that skin concentrations are averaged out in these models, whereas in the DP-PBPK model, the concentration of the chemical in stratum comeurn compartment at the end of exposure is highest at the media–skin interface.

To account for the phenomenon of volatilization of a dermally-absorbed chemical, net dermal dose is defined as the total amount of the chemical that is absorbed into skin in a given time period, less the total amount of the chemical that is volatilized from skin in the same time period. The net dermal doses predicted by the three

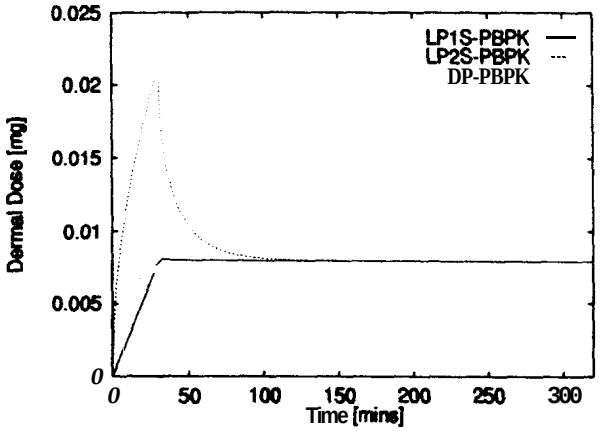

Fig. 4. Simulated dermal dose resulting from a 30-min dermal-only exposure to 100.0 μg/l chloroform in water, predicted by the LP1S-PBPK, LPZSPBPK, and DP-PBPK models. Peak dermal dose corresponds with the end of exposure, whereas the net dermal dose is the dose remaining in skin following volatilization.

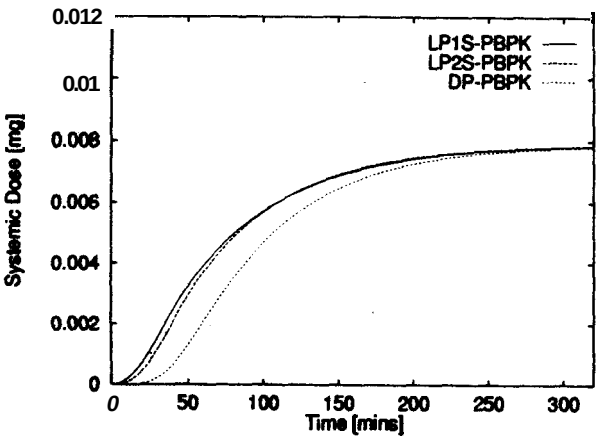

Fig. 5. Simulated systemic dose (dermal dose to blood) resulting from a 30-min dermal-only exposure to 100.0 μg/l chloroform in water, predicted by the LPIS-PBPK, LP2S-PBPK, and DP-PBPK models.

Table II. Comparison of Dose due to Transient Dermal Exposure, Estimated by the DP-PBPK Model and the EPA Recommended Method

Exposure duration (min)	Dermal dose (pg)		
	EPA method	DP-PBPK (peak)	DP-PBPK (net)
10	12.4	12.2	2.6
30	21.5	21.2	7.9
60	30.5	30.6	15.9

PBPK models are shown in Fig. 4. The peak in dermal dose predicted by the models coincides with the end of exposure, following which the chloroform accumulated in the skin either volatilizes or is transported into the viable skin. Although the net dermal doses predicted by the lumped parameter models (LP1S-PBPK and LP2S-PBPK) differ from that predicted by the distributed parameter model (DP-PBPK) at intermediate times, the net dermal doses predicted by all three models appear to converge to similar values at longer times for this exposure scenario, provided the post-exposure air concentration is assumed to be zero.

However, it should be noted that the net dermal dose predicted by the DP-PBPK model may differ significantly for cases in which volatilization is restricted. Post-exposure volatilization may be restricted due to total or partial occlusion of the skin. For example, clothing may cause air to be trapped next to the skin, resulting in an increase in the concentration of the chemical in the air, due to volatilization. This will gradually suppress volatilization. Therefore, actual net dermal dose will probably lie somewhere in between the DP-PBPK peak dermal dose shown in Fig. 4 and the final net dermal dose predicted by assuming zero post-exposure air concentration.

There is also a significant difference in the systemic dose predicted by the three PBPK models; systemic dose being the dermal dose that is transported away from the skin and into the rest of the body. The systemic dose predicted by the three PBPK models for the simulated exposure scenario is shown in Fig. 5. The systemic dose predicted by the DP-PBPK model initially lags behind that predicted by the lumped parameter models, but eventually it marginally exceeds the systemic doses predicted by the lumped parameter models.

5. COMPARISON WITH CURRENTLY ACCEPTED ESTIMATES OF TRANSIENT DERMAL DOSE

A comparison of the dermal dose estimated by the DP-PBPK model and by the Cleek and Bunge method has been made for the specific case of dermal exposure to 100 μg/l chloroform in water. The dermal dose predictions for three exposure durations (10, 30, and 60 min) are given in Table II, and the simulation results for the 30-min exposure is shown in Fig. 6.

There is very good agreement in the end-exposure dermal dose computed by the DP-PBPK model and the dermal dose predicted by the Cleek and Bunge method.

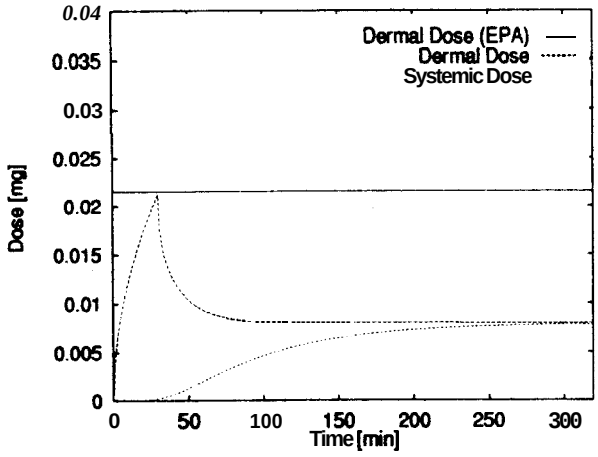

Fig. 6. Comparison of dermal and systemic dose of chloroform predicted by the DP-PBPK model with the dermal dose estimated using the EPA recommended procedure.[7] Comparison is for a 30-min dermal-only exposure to 100.0 μg/l chloroform in water.

The difference in the predicted doses increases as the exposure duration decreases, but even for an exposure duration as short as 10 min, the difference is only 2%. However, there is a significant difference between the net dermal dose predicted by the DP-PBPK model, and the dermal dose estimated by the Cleek and Bunge method. This difference is due to the post-exposure volatilization predicted by the DP-PBPK model, which is not considered in the Cleek and Bunge method. Since it was assumed that the post-exposure air concentration is zero, the volatilization predicted in these simulations represents an upper limit.

6. EVALUATION OF THE PBPK MODELS

Each of the three PBPK models for chloroform described in Sec. 3, have been applied to "inhalation only," and "inhalation and dermal" exposure scenarios. Exhaled breath concentration data from two series of experiments were used to evaluate the models:[21,27]

- inhalation only exposure in a shower chamber, and
- inhalation and dermal exposure in a swimming pool.

First, data from the "inhalation only" experiment were used to evaluate the overall structure and parameters in each of the PBPK models. Subsequently, the "inhalation and dermal" exposure experiment data were used to evaluate differences in doses predicted by the different skin compartments in the three PBPK models. This is the first reported evaluation of a chloroform PBPK model with human concentration-time profile data. Earlier evaluations of chloroform PBPK models for humans were based on experiments in which only a single exhaled breath concentration measurement was taken per exposure.[6,14] It should be noted that these experiments were primarily designed to estimate the internal dose of chloroform under "real-world" conditions, and, due to imperfect mixing in the microenvironment, the reported concentrations have a high degree of variability. Notwithstanding this, the model calculations show fairly good agreement with the data.

6.1. Experimental Methodology

The shower chamber experiment was conducted on a subject wearing protective clothing to ensure that there was no water–skin contact. The swimming pool experiment was conducted on a subject participating in light exercise. The duration of exposures in the shower chamber and swimming pool were 10 min and 30 min, respectively. The shower was allowed to run for 2 min prior to the start of the exposure, to allow the shower water temperature to stabilize at a predetermined value of 40°C.

Chloroform concentrations in air and water were measured during both experiments, and samples of exhaled breath were collected from the subjects following the exposure and analyzed for chloroform concentration in exhaled breath. A portable sampling apparatus, designed to collect primarily alveolar air and described by Raper *et al.*,[28] was used to collect exhaled breath. The fraction of alveolar air collected by the apparatus is approximately 95%, the balance 5% being air from the upper airways. Adsorbent traps filled with 0.5 grams of Tenax GC were used to concentrate the organic fraction of the of exhaled breath collected by the apparatus, and were then thermally desorbed into a gas chromatograph/mass spectrometer for analysis. The volume of exhaled breath concentration sampled was increased from approximately 0.5 to 2.0 liter as the duration of sampling was varied from 30 sec to 3.0 min. A detection limit of 0.3 $\mu g/m^3$ of chloroform in a 2-min breath sample was achieved. Ambient air samples were also collected in Tenax traps, at a flow rate of approximately 70 cm^3/min for 10 min. Water samples were collected in clean glass bottles, which were immediately capped and analyzed within 3 h of collection.

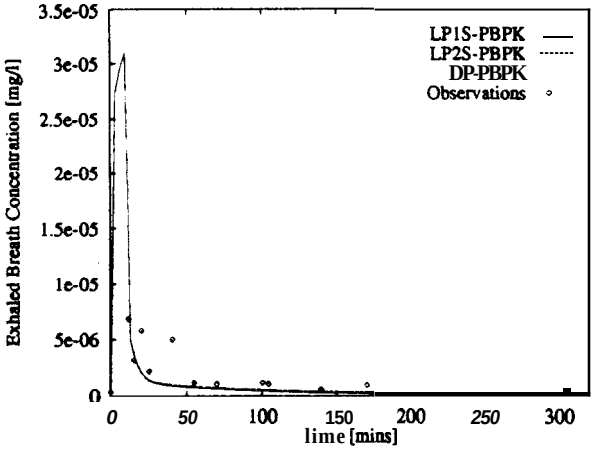

Fig. 7. Comparison of simulated and observed exhaled breath concentration data for a 10-min inhalation-only exposure to chloroform in a shower (measured air concentration = 120 μg/m³).

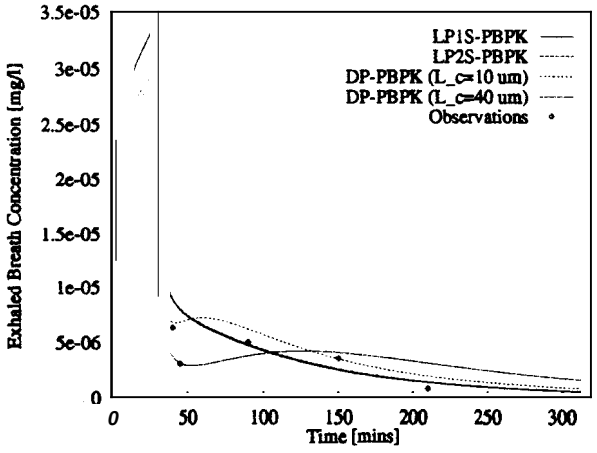

Fig. 8. Comparison of simulated and observed exhaled breath concentration data for a 30-min inhalation and dermal exposure to chloroform in a swimming pool (measured air concentration = 100 μg/m³; measured water concentration = 150 μg/l).

6.2. Evaluation of the PBPK Models with "Inhalation Only" Data

Since the three models under consideration are identical in all respects other than in their representation of dermal absorption, the exhaled breath concentrations predicted by all three models are expected to be very nearly identical for the "inhalation only" exposures. As shown in Fig. 7, this was indeed found to be the case for the "inhalation only" experiment in a shower chamber. The simulated exhaled breath concentration profiles are virtually indistinguishable for all three models. The model predictions also appear to agree reasonably well with the data. given the expected scatter due to microenvironmental fluctuations and measurement uncertainties for these "real-world" samples.

As noted earlier, all three models are derived from the PBPK model for chloroform developed by Corley et *al.*[26] in which parameters for humans were estimated by scaling parameters in animals. This is the first time that the parameters in that model have been evaluated using human concentration profile data.

6.3. Evaluation of the PBPK Models with "Inhalation and Dermal Absorption" Data

The exhaled breath concentration profiles predicted by the three models for "inhalation and dermal" exposure to chloroform in a swimming pool are shown in Fig. 8, together with the experimental data. Two profiles for the DP-PBPK model are shown, corresponding to characteristic stratum corneum diffusion pathlengths of 10 μm and 40 μm. The exhaled breath concentration profiles predicted by the lumped parameter models, LPI S-PBPK and LP2S-PBPK, are once again very similar. However, the DP-PBPK model exhaled breath concentration profiles show a significant time lag over the profiles predicted by the lumped parameter models, and the time lag increases as the diffusion pathlength is increased.

An examination of the data suggests that the exhaled breath concentration profile falls sharply at 30 min, when the exposure was terminated, followed by a gradual shallow rise before finally decreasing to background levels. This pattern of a sharp fall in exhaled breath concentration, followed by a shallow rise, is also suggested by data from other similar experiments reported by Weisel and Shepard.[27] Among the three models evaluated here only the DP-PBPK model simulates this phenomenon. This is due to the fact that the DP-PBPK model alone accounts for the unsteady state flux which results in a time-lag in systemic dose. Although the present set of data is not adequate to determine the correct characteristic length to use in the DP-PBPK model, Fig. 8 suggests that the value lies between 10 and 40 μm.

7. DISCUSSION

According to our current understanding of dermal absorption, dermal transport occurs due to passive diffusion, and mass flux into the viable skin is greater than

99% of the steady state value only for $t \geq 2.7\ t_{lag}$. At shorter times, the permeant chemical accumulates in the stratum corneum, and consequently the mass **flux** into the viable skin is less than the steady state value, whereas that into the stratum corneum is greater. Since t_{lag} for many environmentally relevant chemicals is greater than 0.5 h, it is expected that steady state will not be achieved under most commonly experienced dermal exposure scenarios. However, most existing **PBPK** models that account for dermal absorption do not account for this time lag. To address this problem McKone[6] proposed a modification to the **LP1S-PBPK** type model, in which an effective skin permeability replaces skin permeability. The effective skin permeability proposed by McKone[6] is a function of exposure duration, such that it increases as exposure duration decreases, and in this manner accounts for the initial accumulation in the stratum corneum. The disadvantage of this approach is that effective skin permeability must be estimated specifically for each exposure scenario, and this can be particularly involved when the exposure concentration is variable, or when volatilization needs to be considered.

The **DP-PBPK** model proposed in this paper accounts for accumulation in the stratum corneum based on the intrinsic properties of this tissue and on fundamental equations of transport phenomena. Since the **DP-PBPK** model is solved numerically, arbitrary exposure scenarios can be simulated, including post-exposure scenarios to estimate volatilizations. **As** a performance test, the **DP-PBPK** model was parameterized for chloroform, and compared with two lumped parameter **PBPK** models in which the skin is represented by one and two compartments (**LP1S-PBPK** and **LP2S-PBPK**, respectively). The three **PBPK** models are identical in all respects except in the representation of the skin and the processes associated with dermal absorption. The skin compartment in each of the three **PBPK** models was parameterized such that all the models had identical steady-state solutions. However, the dermal doses predicted by the three models were not the same for short-term dermal exposures.

The end-exposure dermal dose predicted by the **DP-PBPK** model for a 30-min exposure was significantly greater than that predicted by the two lumped parameter models. Furthermore, the **DP-PBPK** model predicts a significant time lag in the systemic dose, which is in accordance with dermal absorption theory. No significant time lag is observed in the estimates of either **of** the lumped parameter **PBPK** models. Measured exhaled concentration data from a subject exposed in a swimming pool appear to corrobate the existance of a time lag.

The **DP-PBPK** model predicts that a significant portion of the dermal dose is volatilized in the post-exposure period, assuming that there is no chloroform in the air in contact with skin following exposure. Without the volatilization the net dermal dose predicted by the **DP-PBPK** model would have been very nearly the same as that predicted by the **EPA** recommended Cleek and Bunge method.[9] However, due to volatilization, the net dermal dose predicted by the **DP-PBPK** model is approximately 37% of the end-exposure dose. Therefore, the **DP-PBPK** model provides an estimate of the degree of conservativeness inherent in the Cleek and Bunge method.

In contrast to the **DP-PBPK** model, the lumped parameter models predict negligible volatilization **of** chloroform. However, since the end-exposure dose predicted by these models was less than that predicted by the **DP-PBPK** model, the serendipitous result is that the net dermal dose predicted by the lumped parameter models are very nearly the same as that predicted by the **DP-PBPK** model, provided that it is reasonable to assume that the skin is in contact with uncontaminated air. However, there may be situations in which the concentration **of** chloroform in post-exposure air is not negligible, and under these conditions the net dermal dose predicted **by** the **DP-PBPK** model will be significantly greater than that predicted by the lumped parameter models. The true net dermal dose will lie somewhere between the peak end-exposure dermal dose and the net dermal dose predicted by assuming maximum volatilization.

8. CONCLUSIONS

This is the first evaluation **of** chloroform **PBPK** models with temporal profiles of exhaled breath concentration measurements in humans. Three **PBPK** models representing different levels of detail in the description of dermal absorption were evaluated by comparing the predicted post-exposure exhaled breath concentrations with measured values for two exposure scenarios. **As** expected, all three models gave very nearly identical results for the inhalation-only exposure in a shower chamber. All three models also exhibited generally acceptable agreement with the measured post-exposure exhaled breath time-concentration values **for** dermal and inhalation exposure in a swimming pool. However, the post-exposure exhaled breath concentration data seem to confirm the time lag in systemic dose predicted by the **DP-PBPK** model. Additional data are needed to better clarify the dynamics of the dermal absorption process.

APPENDIX A. PARAMETERIZATION OF THE PBPK MODELS FOR CHLOROFORM

The parameters proposed by Corley *et al.*,[26] have been used as the basis for parameterizing each of the three PBPK models for chloroform; these parameters are given in Table I. All the parameters common to the three PBPK models, and not associated with the skin compartment, are identical with the parameters in the Corley *et al.* PBPK model for chloroform, with the exception of the mass and blood flow of the slowly perfused compartment, which have been reduced to accommodate the skin compartment. The mass of slowly perfused compartment has been reduced by 10% of body weight, and corresponds to the mass assumed for the skin compartment;[14] the blood flow to the slowly perfused compartment was proportionally reduced.

A.1. Parameters Used in the LP1S-PBPK Model

The LP1S-PBPK model requires several parameters in addition to the parameters that are common with the PBPK model for chloroform developed by Corley *et al.*[26] The estimation of these parameters is outlined below, and the values are given in Table I.

The skin:blood partition coefficient $P_{skin/blood}$ was estimated to be in the range 1.6–1.7 by Chinery and Gleason,[14] which is similar to the $P_{sp/blood}$ partition coefficient of 1.6 in the Corley *et al.* model. The skin:air partition coefficient of chloroform was estimated using:

$$P_{skin/air} = P_{skin/blood} P_{blood/air} \tag{17}$$

and the skin:water partition coefficient was estimated using:

$$P_{skin/water} = P_{skin/air} P_{air/water} \tag{18}$$

where $P_{air/water} = 0.0163$ is the Henry's Law constant for chloroform.[25]

The skin permeability of chloroform in water was estimated using the semi-empirical Potts and Guy correlation:

$$\log K_{water \leftrightarrow skin} = -2.72 + 0.71 \log P_{octanol/water} - 0.0061\ MW \tag{19}$$

where $P_{octanol/water}$ is the octanol:water coefficient, and MW is the molecular weight of the chemical. The skin permeability of chloroform in air was obtained from:

$$K_{air \leftrightarrow skin} = K_{water \leftrightarrow skin} \frac{P_{skin/air}}{P_{skin/water}} \tag{20}$$

A.2. Parameters Used in the LP2S-PBPK Model

The LPZS-PBPK model requires parameters characterizing stratum corneum and the viable skin, in addition to the parameters common to the Corley *et al.* PBPK model.

The stratum corneum:water partition coefficient was estimated using a relation suggested by Potts and Guy:[20]

$$P_{s.c./water} = P^{0.71}_{octanol/water} \tag{21}$$

where $P_{octanol/water}$ is the octanol:water coefficient, which has a value of 93.3 for chloroform.[25] The above value of $P_{s.c./water}$ agrees fairly well with the $P_{s.c./water} = 20$ estimated by the correlation developed by Raykar.[10] The value suggested by the Potts and Guy correlation was used to be consistent with the skin permeability calculations.

The stratum corneum:air partition coefficient was estimated by:

$$P_{s.c./air} = \frac{P_{s.c./water}}{P_{air/water}} \tag{22}$$

and the viable skin:water partition coefficient was estimated by:

$$P_{v.s./water} = \frac{P_{skin/water} V_{skin} - P_{s.c./water} AL}{V_{skin} - AL} \tag{23}$$

where AL gives the volume of the stratum corneum. The viable skin:air partition coefficient was estimated by:

$$P_{v.s./air} = P_{v.s./water} / P_{air/water} \tag{24}$$

and the viable skin:blood partition coefficient was estimated by:

$$P_{v.s./blood} = P_{v.s./air} / P_{blood/air} \tag{25}$$

The stratum corneum permeability with respect to a given media $K_{media \leftrightarrow s.c.}$, and the viable skin permeability $K_{s.c. \leftrightarrow v.s.}$, are related by:[21]

$$K_{media \leftrightarrow skin} = \frac{K_{media \leftrightarrow s.c.} K_{s.c. \leftrightarrow v.s.} P_{s.c./media}}{K_{media \leftrightarrow s.c.} + K_{s.c. \leftrightarrow v.s.} P_{s.c./media}} \tag{26}$$

and Cleek and Bunge[9] have suggested estimating the relative permeability in the stratum corneum and viable skin by:

$$B = \frac{K_{water \leftrightarrow s.c}}{K_{s.c \leftrightarrow v.s} P_{s.c/water}} = K_{water \leftrightarrow skin} \frac{\sqrt{MW}}{2.6} \tag{27}$$

B was computed to be 3.75×10^{-2}, which is consistent with the notion that the main resistance to dermal absorption of chloroform is in the stratum corneum. The

stratum corneum permeability of chloroform in water, $K_{water \leftrightarrow s.c.}$, and the viable skin permeability $K_{s.c. \leftrightarrow v.s.}$, were calculated from Eqs. (26) and (27), given the value of $K_{water \leftrightarrow skin}$ used in the LPIS-PBPK model. The stratum corneum permeability of chloroform from air was estimated by:

$$K_{air \leftrightarrow s.c.} = K_{water \leftrightarrow s.c.} \frac{P_{s.c./air}}{P_{s.c./water}} \quad (28)$$

A.3. Parameters Used in the DP-PBPK Model

The DP-PBPK model requires parameters specifying the distributed stratum corneum compartment and the lumped viable skin compartment, in addition to the set of common parameters listed in Table I.

In this model, the resistance to dermal absorption across the stratum corneum is represented by the effective stratum corneum diffisivity, rather than by a permeability coefficient. The stratum corneum diffusivity can be estimated from the overall skin permeability from:[20]

$$D_{s.c.} = \frac{K_{media \leftrightarrow skin} L_c}{P_{s.c./media}} \quad (29)$$

The Potts and Guy correlation is based on the assumption that diffusion in the stratum corneum occurs through the lipid matrix, which implies that the chemical follows a tortuous path between the keratinized cells. Therefore the characteristic difision pathlength through in the stratum corneum could be 4–5 times its nominal thickness of 10 μm.[29] Cleek and Bunge[9] based their estimate of stratum corneum diffisivity on the assumption that the diffision pathlength was equal to the thickness of the stratum corneum, and this assumption has been adopted here as well. However, in Fig. 8, we also show the effect that a longer difision pathlength would have on exhaled breath concentrations.

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