NOVA
SCIENCE PUBLISHERS, INC.

DISTRIBUTED PARAMETER ESTIMATION OF DERMAL ABSORPTION OF CHEMICALS USING A PHYSIOLOGICALLY INSPIRED BOUNDARY CONDITIONS

L. Simon

In: "Skin Anatomy and Physiology Research Developments"
Editor: Leon F. Bukowsky

ISBN: 978-1-60741-469-8 2010

400 Oser Avenue, Suite 1600
Hauppauge, N. Y. 11788-3619
Phone (631) 231-7269
Fax (631) 231-8175
E-mail: main@novapublishers.com
http://www.novapublishers.com

In: Skin Anatomy and Physiology Research Developments ISBN: 978-1-60741-469-8
Editor: Leon F. Bukowsky

Chapter 9

Distributed Parameter Estimation of Dermal Absorption of Chemicals using a Physiologically Inspired Boundary Conditions

L. Simon [*]
Otto H. York Department of Chemical, Biological and Pharmaceutical Engineering
New Jersey Institute of Technology, University Heights, Newark, NJ 07102, USA

Abstract

A spatial-temporal framework representing dermal absorption of chemicals is important for toxicological risk assessment. Failure to adequately estimate the amount of chemicals entering the body through the skin may compromise the ability of physiologically-based pharmacokinetic (PBPK) models to predict concentration-time profiles in individual tissue compartments. This contribution considers the conventional PBPK model equations as a boundary condition to a diffusive mass transport problem. The partial differential equation (PDE), representing the uptake of dibromomethane (500 to 10000 ppm) in the skin, is discretized into ordinary differential equations (ODEs) by orthogonal collocation techniques. The resulting system is solved in the Mathematica® environment to evaluate the fate of dibromomethane in the liver, fat, rapidly and slowly perfused compartments and to monitor its evolution in the different layers of the skin. This approach, which uses published physicochemical properties, predicts laboratory data very well. Cumulative amounts of dibromomethane into and out of the skin are also computed and compared to those obtained by applying a perfect sink boundary condition at the skin-capillary interface. Discrepancies between the two model predictions become more pronounced with increased exposure time. The steady-state dibromomethane concentration and the time to reach equilibrium values increased with the exposure level and stratum corneum depth. The proposed methodology may help to explore and

[*] Corresponding author. Tel.: 973-596-5263; fax: 973-596-8436; e-mail: laurent.simon@njit.edu

elucidate potential links among exposure-time, concentration, skin depth and the onset of skin irritation.

1. Introduction

Physiologically based pharmacokinetic (PBPK) models have been applied, successfully, to assess risk posed by toxic chemicals and to elucidate their biological mechanisms as they are transported to specific organs and tissues. In the PBPK modeling framework, the body is divided into several physiological compartments, such as the liver and lung. Material balance equations are written to represent chemical uptake in the various tissues. The transport phenomena, occuring in each organ, are complex and involve convection and diffusion contributions that are rigorously described using partial differential equations (PDEs). Assumptions (e.g., homogeneous compartments, perfusion- or diffusion-limited processes) are usually made to address certain aspects of the problem and to limit the scope of modeling. The well-mixed compartment approach, often adopted by researchers in the field, leads to stiff ordinary differential equations (ODEs) that are solved using softwares such as acslXtreme® (AEgis Technology Group) and Berkeley Madonna™ (Macey & Oster). Since a comprehensive database of biochemical, physiological and physicochemical parameters are compiled for a large number of compounds [1], model developers can easily compare their predictions with experimental concentration data. The findings of such investigations are instrumental in promoting a better understanding of the dominant mechanisms that control the absorption and distribution of toxic agents throughout the body. Nestorov (2003) offered a comprehensive review of PBPK structures that describes model development methodologies, implementations, limitations and research orientation [2].

PBPK models, developed to predict biological tissue distribution of chemicals, are often applied to describe percutaneous absorption. Such approaches allow researchers to assess dermal absorption from soil contamination by Volatile Organic Compounds (VOCs), such as perchloroethylene (PCE) [3]. The mathematical framework also facilitated the simulation of worst-case scenarios for dermal exposures to methyl chloroform found in contaminated soil [4]. In those examples, ordinary differential equations were written to explain chemical concentration changes in subcutaneous tissues. Although the skin offers a complex heterogenous medium, the simplified representations have been successful in explaining laboratory data collected from rats and humans. Work on drug release from transdermal systems shows that PDE-based models are more suitable to describe the transport of medicaments via this route. The skin is composed of the epidermis (stratum corneum and viable epidermis), the dermis and the subcutaneous fat region. The stratum corneum, consisting of dead cells, constitutes the main resistance to drug permeation [5]. The nature of the epidermis (i.e., aqueous and lipid regions) has a profound impact on drug diffusivity [6]. However, only a few examples in the literature use PDEs because of the relative simplicity of PBPK models, the physiologically meaningful nature of the parameters [7], and the large database of information for animal species and humans,

The “well-stirred” homogeneous skin model has been critical in the generation of model parameters that can be determined experimentally [8]. As in distributed-parameter systems,

the accumulation of penetrants in homogeneous skin models is governed by Fick's laws of diffusion as they traverse the dermal layers and blood flow rate. However, in the common PBPK framework, mass transfer resistance is mainly due to a very thin-layer representation of the stratum corneum. An implication of this analogy, unsubstantiated by experimental work with volatile organic compounds, is that chemicals do not accumulate in the skin's main barrier [9]. A drawback of this approach is that risk assessment, based on such analysis, only provides temporal concentration data. Poet and McDougal (2002) noted that accurate information, concerning both the absorption and penetration of chemicals into and through the layers of the skin, is indispensable for reliably predicting local and systemic toxicity [10]. In studies addressing jet prollant-8 (JP-8) irritation potential, researchers reasoned that the ability to ascertain the JP-8 concentration, that induces dermal irritation, is important and may result in the development of therapeutic intervention strategies to help individuals exposed to jet fuel [11]. Elucidating the mechanism of skin irritation in a spatial-temporal context is a critical step to fully comprehend the toxicity and irritation potency of chemicals. A firm understanding of the concentration and location of chemicals in the skin layers and how they relate to biological responses may promote perspectives not found in the well-stirred compartment model. In addition, the ability to predict the time it takes a compound, in each skin layer, to reach a steady-state concentration, is paramount to efforts toward a comprehensive risk assessment of dermal exposure to toxic compounds. Similar investigations were undertaken to estimate brain equilibrium half-life (i.e., time to reach 50% of its plateau level after single intravenous bolus dose) based on PBPK models [12].

2. Pbpk Modeling of Dermal Chemical Absorption

Physiologically-based pharmacokinetic skin models were initially proposed in an effort to standardize and simplify parameter estimation through laboratory experiments and enable the extrapolation of results across species [8]. Dermal absorption is modeled using skin permeation values in lieu of Fick's second law of diffusive transport adopted in drug-delivery research. Chinery and Gleason (1993) employed different skin permeability coefficients to construct a PBPK model for dermal absorption of chloroform from exposure to an aqueous medium [13]. Guidance on how PBPK models can be used to study toxicity after dermal exposure can be found in the work of Anderson and Keller [14].

The steady-state permeation flux can be calculated using Fick's first law of diffusion:

$$J_{ss} = \frac{DK}{l}\Delta C = P\Delta C \tag{1}$$

where D is the diffusion coefficient of the penetrant, l is the thickness of the membrane, K is the membrane/donor partition coefficient, ΔC is the difference between the concentration in the vehicle and the concentration in the sink (i.e., receiver chamber), P is the permeability coefficient. The dermal uptake and assessment of potential toxicity of chemical agents are

based on the *P* value, the applied concentration and the surface area and time of exposure. An average flux is usually calculated in animal studies [15]:

$$J_{ave} = \frac{M}{A \times t} \tag{2}$$

In this formulation, *M* is the total mass of chemical absorbed, *t* is the time and *A* is the exposed area. It is customary to express the permeability coefficient as:

$$P = \frac{J_{ave}}{C_{sfc}} \tag{3}$$

where C_{sfc} is the vehicle concentration. Combining Eqs. (2) and (3) gives:

$$M = PAC_{sfc}t \tag{4}$$

Methodologies are proposed to relax the assumption of steady-state conditions embedded in Eq. (4) and to account for the fact that, in a PBPK model, mass balance equations have to include chemicals entering the skin from the arterial blood and exiting via the venous blood [15].

2.1. Homogeneous One Compartment Skin Model (1-CSM)

A single homogeneous compartment is developed to represent the skin [8]:

$$V_{sk}\frac{dC_{sk}}{dt} = P_{sk}A_{sk}\left(C_{sfc} - \frac{C_{sk}}{R_{sk/sfc}}\right) + Q_{sk}\left(C_a - \frac{C_{sk}}{R_{sk/b}}\right) \tag{5}$$

Equation (5), based on mass conservation, describes the accumulation of permeant. The lumped-parameter approach treats the skin as a process unit in which concentration changes due to a) the blood flow to the skin (Q_{sk}), the skin permeability and area (P_{sk}, A_{sk}, respectively), b) concentrations in the arterial blood and in the skin (C_a and C_{sk}, respectively), and c) the skin to surface and skin to blood partition coefficients ($R_{sk/sfc}$ and $R_{sk/b}$). Compound accumulation in the skin is the result of material transported by the blood flow and mass transfer from the surface. The model assumes an infinitely thin resistance layer and tends to underestimate the amount of chemical initially absorbed into the skin [16].

2.2. Homogeneous Two-Compartment Skin Model (2-CSM)

Booktout et al. (1996) wrote a two-subcompartment model made up of the stratum corneum (I) and a lumped region (II) composed of the viable epidermis, dermis and subcutaneous fat. Blood only flows in the latter region (II). In this approach, the stratum corneum and subcompartment II are described by:

$$V_{sc}\frac{dC_{sc}}{dt} = P_{sc}A_{sc}\left(C_{sfc} - \frac{C_{sc}}{R_{sc/sfc}}\right) + P_{cd}A_{cd}\left(C_{cd} - \frac{C_{sc}}{R_{sc/cd}}\right) \tag{6}$$

and

$$V_{cd}\frac{dC_{cd}}{dt} = P_{cd}A_{cd}\left(C_{cd} - \frac{C_{sc}}{R_{sc/cd}}\right) + Q_{cd}\left(C_{a} - \frac{C_{cd}}{R_{cd/b}}\right), \tag{7}$$

respectively. Volumes of regions I and II are V_{sc} and V_{cd}; C_{sc} and C_{cd} are the concentration in regions I and II; P_{sc} and P_{cd} are the drug permeability in sections I and II; A_{sc} and A_{cd} are the surface areas of I and II; $R_{sc/sfc}$, $R_{sc/cd}$ and $R_{cd/b}$ are the blood partition coefficients at the following interfaces: stratum corneum to surface, stratum corneum to compartment II, and region II to blood, respectively; Q_{cd} is the blood flow rate to region II. The mass transfer resistance of the stratum corneum is at a thin interfacial layer between the exposure medium and the stratum corneum [9]. An additional mass transport resistance is due to a similarly thin layer, situated between the stratum corneum and the viable skin. Although the model defined by Eqs. (6) and (7) may lead to more accurate predictions than the one-compartment construct, the dermal resistances, represented by two infinitesimally thin layers, underestimate the chemical accumulation in the stratum corneum [9]. In addition, since not all of the new parameters are measurable, regression techniques are usually applied to estimate the permeability constants and partition coefficients [8]. However, the 2-CSM does not allow the monitoring of compounds at different depths of the skin layers. A three subcompartment skin model, derived from the homogeneous representation, was also described in [8]. It should be noted that one of the main attractions of PBPK models is the presence of meaningful and measurable parameters in the mathematical description of permeant uptake through the body. Consequently, the results of increasingly complex models have to be interpreted and extrapolated with caution. In section 2.4, Fickian diffusion and orthogonal collocation methods are used to estimate the dermal absorption at different skin layers.

2.3. Homogeneous Three-Compartment Skin Model (3-CSM)

The 2-CSM was expanded to a three sub-compartment skin model [8]:

$$V_{sc}\frac{dC_{sc}}{dt} = P_{sc}A_{sc}\left(C_{sfc} - \frac{C_{sc}}{R_{sc/sfc}}\right) + P_{ve}A_{ve}\left(C_{ve} - \frac{C_{sc}}{R_{sc/ve}}\right) \tag{8}$$

$$V_{ve}\frac{dC_{ve}}{dt} = P_{ve}A_{ve}\left(\frac{C_{sc}}{R_{sc/ve}} - C_{ve}\right) + P_{cd}A_{cd}\left(C_{cd} - \frac{C_{ve}}{R_{ve/cd}}\right) \tag{9a}$$

and

$$V_{cd}\frac{dC_{cd}}{dt} = P_{cd}A_{cd}\left(\frac{C_{ve}}{R_{ve/cd}} - C_{cd}\right) + Q_{cd}\left(C_a - \frac{C_{cd}}{R_{cd/b}}\right). \tag{9}$$

Equations (8), (9a) and (9) are written for the stratum corneum (*sc*), viable epidermis (*ve*), and composite dermal compartment (*cd*), respectively. The latter compartment is composed of the dermis and subcutaneous fat. These equations were written by Bookout et al. (1996) and are repeated here for completeness. Definitions of the quantities are provided in the Nomenclature section. It is worth noticing that blood only flows through the composite dermal. Experiments show that the three sub-compartment model results in more accurate blood concentration estimations of dibromomethane [8]. The disadvantage of this procedure is that some of the new parameters would have to be estimated or optimized.

2.4. Membrane Skin Model (MSM)

Equations (5)-(9) are useful in addressing the resistance offered by the skin layers and the contribution of skin physiology in influencing the distribution of a chemical through tissues. The skin tissues include i) the stratum corneum, the outermost epidermal layer, that has a thickness ranging from 10 to 40 μm and is composed of dead cells containing keratin; ii) the viable skin made of the viable epidermis (50-100 μm) and the dermis (500-3000 μm) [9]. The stratum corneum offers the most significant mass transfer resistance for most compounds [17]. Describing chemical absorption through the skin using the structures outlined above assumes that the major resistance to the transport of molecules simply occurs at some interfaces. The spatial variation of drugs in the layers is not captured by these models. To maintain the PBPK modeling framework and to represent the physiology of the skin, Roy et al. (1996) proposed a distributed parameter (DP-PBPK) representation of dermal absorption where the resistance is distributed all throughout the stratum corneum [9]. The accumulation

of mass in the viable skin is a function of the mass flux at the stratum corneum/viable skin interface. The equations used can be summarized as:

$$\frac{\partial C_{sc}}{\partial t} = \frac{\partial}{\partial x}\left(D_{sc} \frac{\partial C_{sc}}{\partial x} \right) \tag{10}$$

$$C_{sc}\ \ 0,t\ \ = C_{sfc} R_{sc/sfc} \tag{11}$$

$$C_{sc}\ \ h,t\ \ = \frac{C_{vs}}{R_{vs/sc}} \tag{12}$$

$$C_{sc}\ \ x,0\ \ = 0 \tag{13}$$

$$V_{vs} \frac{dC_{vs}}{dt} = J\ \ h,t\ \ A_{vs} + Q_{sk}\left(C_a - \frac{C_{vs}}{R_{vs/b}} \right) \tag{14}$$

Equation (10) is Fick's second law applied to the stratum corneum. The diffusion coefficient in the stratum corneum, D_{sc}, is not a function of time or the drug concentration. The donor cell concentration, C_0, does not change significantly during the course of exposure. As a result, the concentration on the surface of the stratum corneum, $C_{sc}\ \ 0,t$, remains constant (Eq. (11)). Equation (12) is a local equilibrium partition condition at the stratum corneum/viable skin interface. The skin is initially free of drug (Eq. (13)). The mass accumulation in the viable skin is represented by Eq. (14) and $J\ \ h,t$ is the transient flux at the stratum corneum/viable skin interface. Roy et al. (1996) proposed a numerical scheme based on a central difference formula to convert Eqs. (10)-(14) into a set of ODEs. An orthogonal collocation methodology, that provides increased accuracy, is implemented in this contribution.

3. Orthogonal Collocation Techniques

The method of orthogonal collocation consists of writing the concentration of chemicals in the stratum corneum as a finite series:

$$C_{sc}(\zeta,t) \approx a(t) + \zeta b(t) + \zeta(1-\zeta)\sum_{i=1}^{N} a_i(t) P_{i-1}(\zeta) \tag{15}$$

after scaling the thickness of the layer to 1. In this formulation, $\{P_i(\zeta)\}$ represents a set of polynomials such that $P_n(\zeta)$ is orthogonal to $P_m(\zeta)$ when $m \neq n$, over some interval. The locations of the collocation points (ζ) are given by the roots of $P_n(\zeta)$. System nonlinearities and the level of model accuracy required by the user influence the selection of the number of internal collocation points (N). A system of ODEs is generated by substituting Eq. (15) in the original partial differential equation.

A dimensionless version of Eqs. (10)-(13) is first written and solved by the orthogonal collocation method and by the built-in solver, *NDSolve* in Mathematica®. According to this method, the normalized concentration of the dissolved chemical (C_{1sc}) in the stratum corneum is expressed by linear combinations of Jacobi polynomials, $P_i(\zeta_j)$, as the basis functions. A weight function $W(\zeta)$ was written to satisfy the orthogonality condition:

$$\left\langle P_m(\zeta), P_n(\zeta) \right\rangle_W = \int_0^1 W(\zeta) \times P_m(\zeta) \times P_n(\zeta)\, d\zeta = 0 \tag{16}$$

where $\langle f_1, f_2 \rangle_W$ stands for the inner product of functions f_1 and f_2 with respect to $W(\zeta)$. The internal collocation points, ζ_j, were chosen as the positive roots of the equation:

$$P_N(\zeta) = 0 \tag{17}$$

Equation (15) is rewritten as:

$$C_{1sc}(\zeta_j, \tau) = \sum_{i=1}^{N+2} d_i(\tau)\, \zeta_j^{(i-1)} \tag{19}$$

The first derivative of Eq. (19) with respect to ζ is:

$$\frac{\partial}{\partial \zeta} C_{1sc}(\zeta_j, \tau) = \sum_{i=1}^{N+2} d_i(\tau)\,(i-1)\,\zeta_j^{i-2} \tag{18}$$

The vector-matrix forms of Eq. (19) and (18) are:

$$\mathbf{c} = \mathbf{Z}\,\mathbf{d} \tag{19}$$

and

$$\frac{\partial \mathbf{c}}{\partial \boldsymbol{\zeta}} = \mathbf{Q}\,\mathbf{d} \tag{20}$$

where $\mathbf{c} = C_{1sc}\ \zeta_j, \tau$ and $\mathbf{d} = d_i\ \tau$ represent vectors; $\mathbf{Z} = \zeta_j^{i-1}$, $\mathbf{Q} = i-1\ \zeta_j^{i-2}$ are matrices. The solution of $\mathbf{d}$ in Eq. (19) is substituted in eq. (20) to yield:

$$\frac{\partial \mathbf{c}}{\partial \boldsymbol{\zeta}} = \mathbf{Q}\,\mathbf{Z}^{-1}\mathbf{c} = \mathbf{A}\,\mathbf{c} \tag{21}$$

With these results, the normalized PDE problem is reduced to a system of ODEs in $C_{1sc}\ \zeta_j, \tau$ from which a set of $dC_{sc}\ x_j, t\ \big/ dt$ can be easily obtained after converting the transformed variables back to their original scale. All the boundary conditions are incorporated in the ODEs, which are now written in terms of C_{vs}. Because C_{vs} is connected to other tissue compartments, such as liver and brain, the whole-body PBPK representation can be effectively formulated as a biologically-inspired boundary condition to a diffusive mass transport problem. Although no numerical benefit is gained from this perspective, the new paradigm has the advantage of placing the skin at the center of the analysis. In this framework, the design of novel and more complex transdermal drug-delivery devices can be fully investigated. The difficulty with this approach is that it involves a mixed system of ODEs and PDEs, which are not easily solved by software packages. However, this method makes it easy to visually represent the spatial-temporal evolution of toxic chemicals in the skin following dermal exposure and to explore potential links among exposure-time, concentration, skin depth and the onset of skin irritation.

A more detailed description of orthogonal collocation techniques is offered in [18] and [19]. Implementations of the method and advances can be found in [20-22]. The solution strategy significantly reduced the number of spatial nodes used in finite difference-based methods and required less computational resources to achieve similar performance [18]. The methodology is carried out using in-house codes written in Mathematica®.

4. Tissue Compartments in the Body

The PBPK model used in this work is similar to the one described by Bookout et al. [8]. The transport equations apply to solutes with large permeability across the capillary wall.

Except for the lung, absorption of the compound into the various tissues is only limited by the blood perfusion rate (i.e., perfusion-limited PBPK). Material balances around the tissues yield (Fig. 1):

$$V_r \frac{dC_r}{dt} = Q_r \left(C_a - \frac{C_r}{R_{r/b}} \right) \tag{22}$$

$$V_l \frac{dC_l}{dt} = Q_l \left(C_a - \frac{C_l}{R_{l/b}} \right) - \frac{k_f C_l V_l}{R_{l/b}} - \frac{V_{\max} C_l}{K.R_{l/b} + C_l} \tag{23}$$

$$V_s \frac{dC_s}{dt} = Q_s \left(C_a - \frac{C_s}{R_{s/b}} \right) \tag{24}$$

$$V_f \frac{dC_f}{dt} = Q_f \left(C_a - \frac{C_f}{R_{f/b}} \right) \tag{25}$$

$$C_a = \frac{Q_c C_v}{\left(\frac{Q_a}{R_{b/air}} + Q_c \right)} \tag{26}$$

$$C_v = \frac{1}{Q_c} \left(\frac{Q_p C_p}{R_{p/b}} + \frac{Q_r C_r}{R_{r/b}} + \frac{Q_l C_l}{R_{l/b}} + \frac{Q_s C_s}{R_{s/b}} + \frac{Q_f C_f}{R_{f/b}} \right) \tag{27}$$

Equations (22)-(27) are solved along with models 1-CSM, 2-CSM, 3-CSM, or MSM. The subscript "*p*" stands for "*sk*", "*cd*" or "*vs*". The composite dermal compartment "*cd*" is represented by Eq. (7) (2-CSM) or Eq. (9) (3-CSM); "sk" and "*vs*" are used for models 1-CSM and MSM, respectively. Subscript "*a*" represents arterial, "*v*", venous and "*c*" stands for cardiac blood. Equations (22)-(25) are the mass-balance equations around the rapidly perfused tissue ("*r*"), liver ("*l*"), slowly perfused tissue ("*s*") and fat tissue ("*f*"). By assuming that the amount of chemical in the lung does not change with time, and that concentration in

the surrounding air is negligible, Eq. (26) is written [23]. Equation (27) is employed to show the solute behavior in the large venous compartment; a steady-state assumption is made [23].

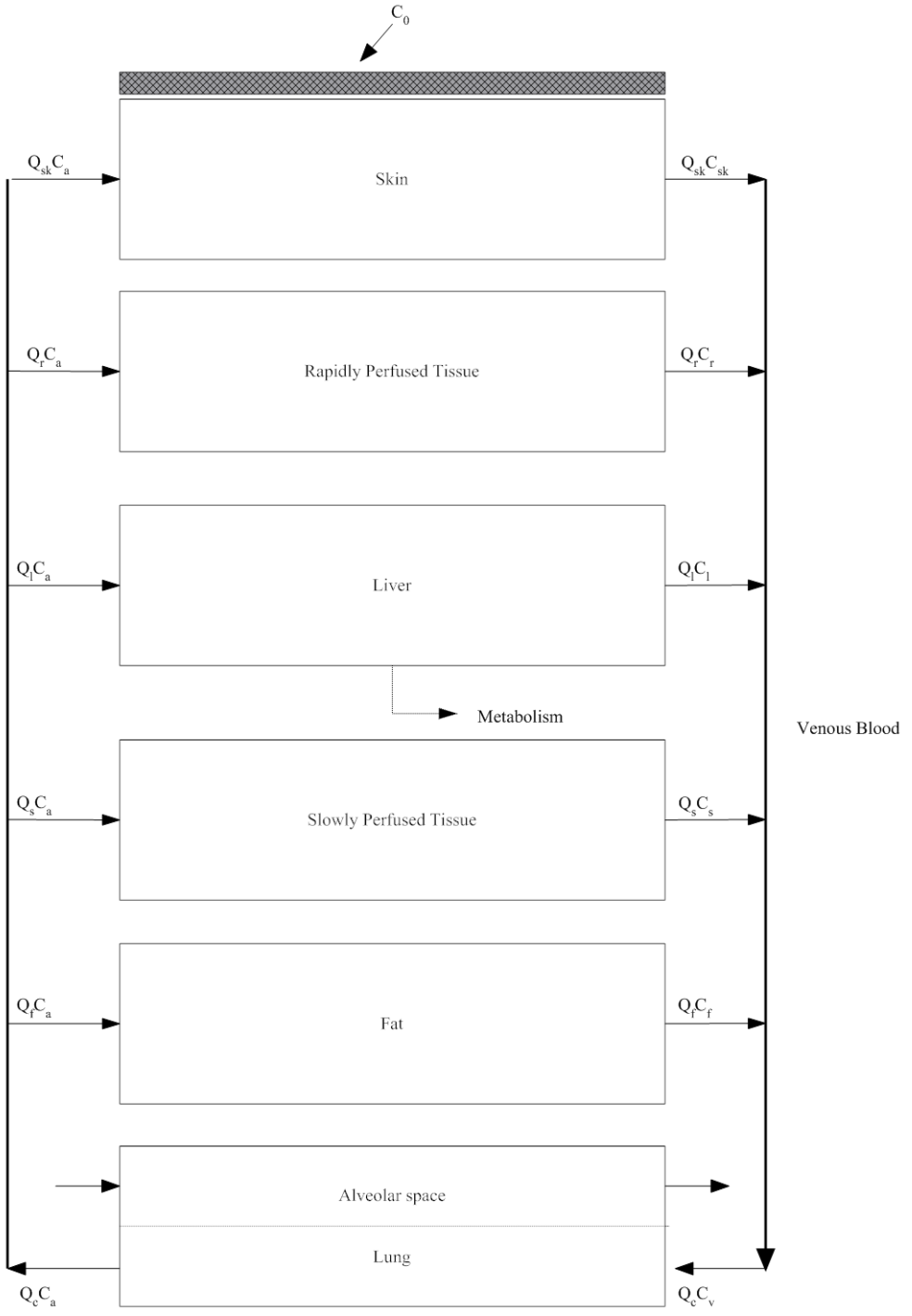

Figure 1. PBPK schematic representing the different tissues.

5. Numerical Results

The lumped-parameter models were solved using Mathematica®, which offers an integrated environment for statistical analysis, visualization and solutions for stiff and non-stiff ordinary equations. Physiologically-based pharmacokinetic modeling studies, such as the one conducted by Loizou et al. [24], are essential for a better understanding of the dermal absorption of solvent liquids and vapors. In that study, *m*-Xylene (50 ppm) was absorbed in humans by the inhalation and dermal routes. The compartments were liver, fat, skin and richly- and poorly-perfused tissues. Numerical simulations facilitated the estimation of dermal concentration exposure necessary to produce the same body burden from inhalation of 50 ppm *m*-Xylene [24].

In this contribution, the study was based on the work by Bookout et al. (1996). Because results of 1-CSM, 2-CSM, 3-CSM approaches are already shown in [8], only the 1-CSM is reproduced here for illustration. Second, the membrane skin model was solved for the absorption of dibromomethane by using orthogonal collocation techniques. The spatial-temporal concentration profiles at different skin depths were plotted. Third, values for the cumulative amounts of the chemical into and out of the skin were computed and compared to those obtained by applying a "perfect sink" boundary condition at the skin-capillary interface. Fourth, the time it would take distinct skin layers to become saturated with dibromomethane was investigated.

5.1. Well-stirred Single Compartment Model

The model parameters were found in [8]. Dibromomethane vapor concentrations varied from 500 to 10,000 ppm. As expected, the amount of chemical in the venous blood increased with the time and level of dibromomethane exposure (Fig. 2). The profiles are identical to those generated in [8]. The model validity was tested, in the original work, by comparing experimental data with simulated values. A good agreement was achieved. One of the advantages of this effort is that other exposure scenarios can be tested, as well, and the findings extrapolated across various species. The mathematical framework can be used to estimate dermal exposure concentration.

5.2. Diffusive Transport Model

The 1-CSM did not provide information about chemical concentration in the skin layers. Orthogonal collocation techniques were applied using a total of 8 internal collocation points. A higher number did not increase model accuracy. The various tissues were assumed free of the drug at the beginning of the experiment. Estimation of the stratum corneum diffusion coefficient is based on the steady-state permeability of the stratum corneum from the environmental medium ($K_{sc/sfc}$), the effective thickness of the stratum corneum (h) and the

equilibrium partition coefficient between the stratum corneum and the environmental medium ($R_{sc/sfc}$) [25]:

$$D_{sc} = \frac{K_{sc/sfc} h}{R_{sc/sfc}} \tag{28}$$

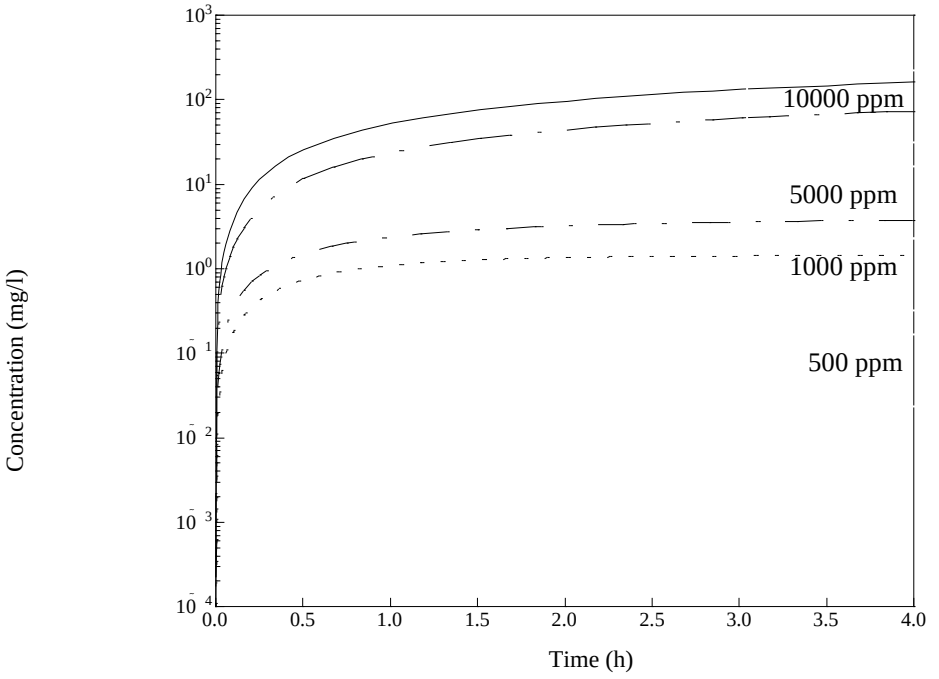

Figure 2. Venous blood concentration of dibromomethane using a well-stirred single compartment model. The exposure level varied from 500 to 10000 ppm.

The value for $R_{sk/b}$ was used in place of $R_{vs/b}$ in this example. This approximation should not introduce significant error in the calculation based on reported values of skin/air and viable epidermis-dermis-subcutaneous fat/air partition coefficients (266.0 and 259.3, respectively) [8]. The overall skin permeability ($K_{sk/sfc}$) was employed in Eq. (28) as an estimation of $K_{sc/sfc}$. Simulation results (Fig. 3) show that the diffusive transport model predicts well the chemical concentration in venous blood when compared to experimental data in [8]. In addition, Fig. 3 agrees with the trend shown in Fig. 2. The detailed description makes it possible to monitor the evolution of chemicals in the different skin layers. Such a feature was tested with the same conditions as in the single compartment model (i.e., 500 to

10000 ppm). The results are shown in Figs. 4 to 7. Steady-state dibromomethane concentration increased with the stratum corneum depth and exposure level.

Investigators outline other benefits associated with the distributed parameter model. Roy et al. (1996) reported that the end-exposure dose estimated by such methodologies is more consistent with the prediction of EPA-recommended Cleek and Bunge method for short-term exposure [25]. More recently, studies, using chloroform as a test compound, show that the homogeneous skin model predicts a very rapid initial uptake, as indicated by the quick appearance of chloroform in exhaled breath once the exposure begins [26]. The initial lag, supported by experimental data, was not observed.

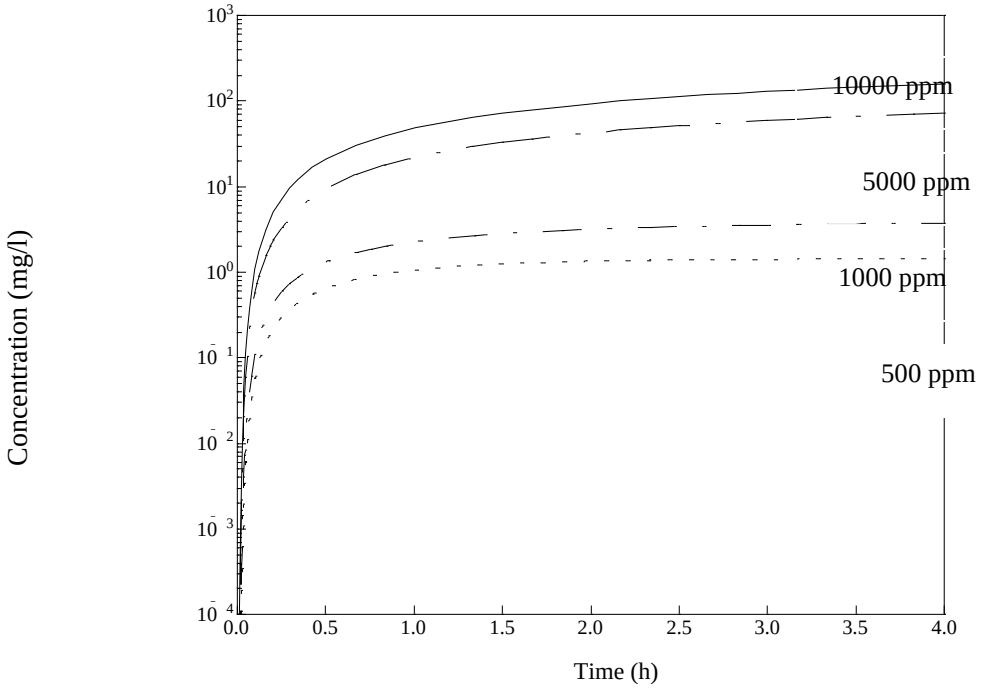

Figure 3. Venous blood concentration of dibromomethane using a membrane model of the skin. The exposure level varied from 500 to 10,000 ppm.

A membrane model, implemented using a finite-difference scheme, exhibited a better fit to actual data [26] than the homogenous representation. Similar to findings made by Roy et al. (1996), a lag-time was apparent in the exhaled breath concentration profile [9]. In studies conducted by Norman et. al. (2008), a lower cumulative uptake was also reported when the well-stirred skin approach was used [26]. PBPK model prediction capability improved, significantly, when the skin was represented by a membrane where diffusive transport took place. With fewer nodes than finite difference formula, the orthogonal collocation method gives a more accurate estimation of fluxes and concentrations. This feature may help increase the popularity of Fickian diffusion equation in aqueous dermal exposure. In addition, the reduced number of nodes, necessary to achieve acceptable model accuracy, makes the procedure easily transportable to other software packages.

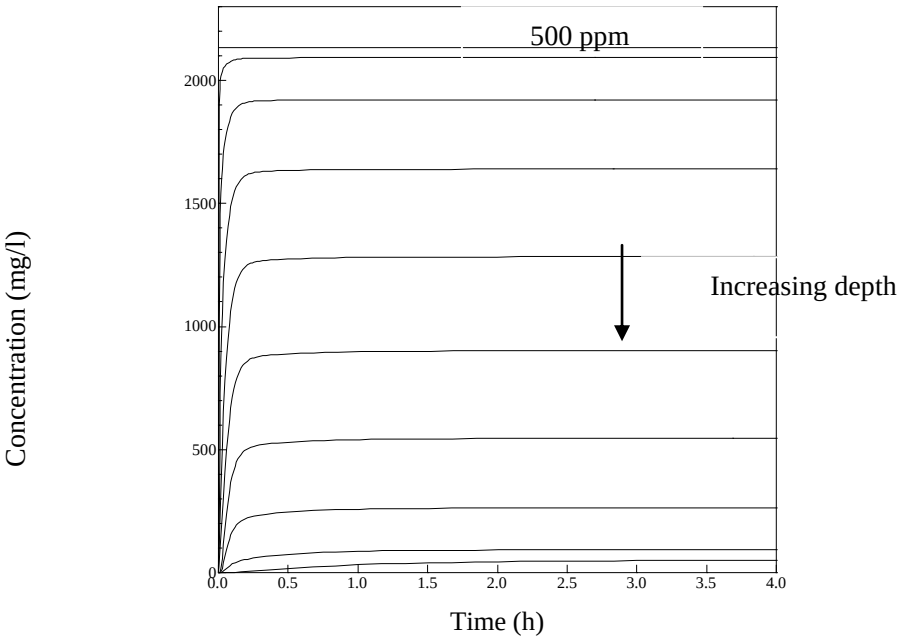

Figure 4. Dibromomethane concentration in the stratum corneum. The depths (dm), based on the internal collocation points, are 0, 2.055×10-6, 1.052×10-5, 2.455×10-5, 4.226×10-5 6.124×10-5, 7.895×10-5, 9.298×10-5, 1.014×10-4, 1.035×10-4. An exposure level of 500 was used.

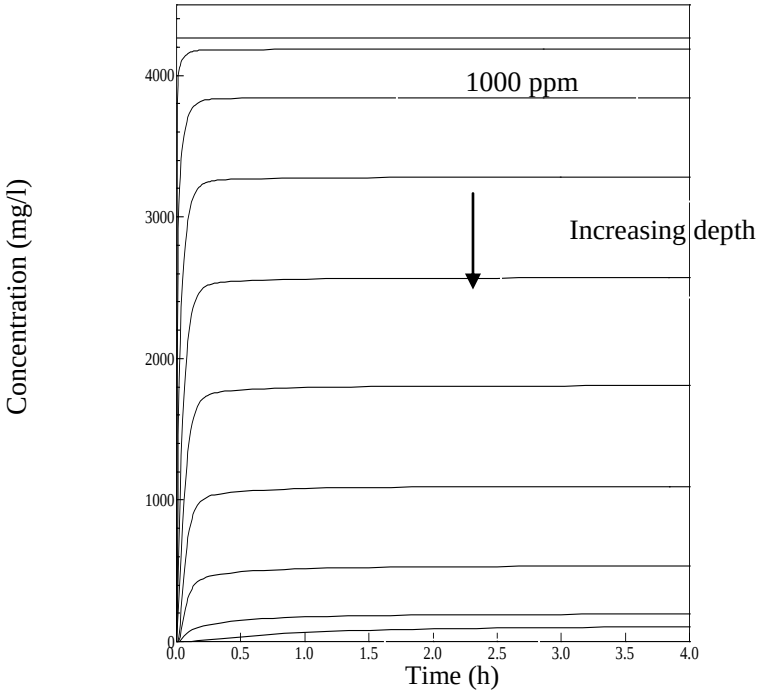

Figure 5. Dibromomethane concentration in the stratum corneum. The depths (dm), based on the internal collocation points, are 0, 2.055×10^{-6}, 1.052×10^{-5}, 2.455×10^{-5}, 4.226×10^{-5} 6.124×10^{-5}, 7.895×10^{-5}, 9.298×10^{-5}, 1.014×10^{-4}, 1.035×10^{-4}. An exposure level of 1000 was used.

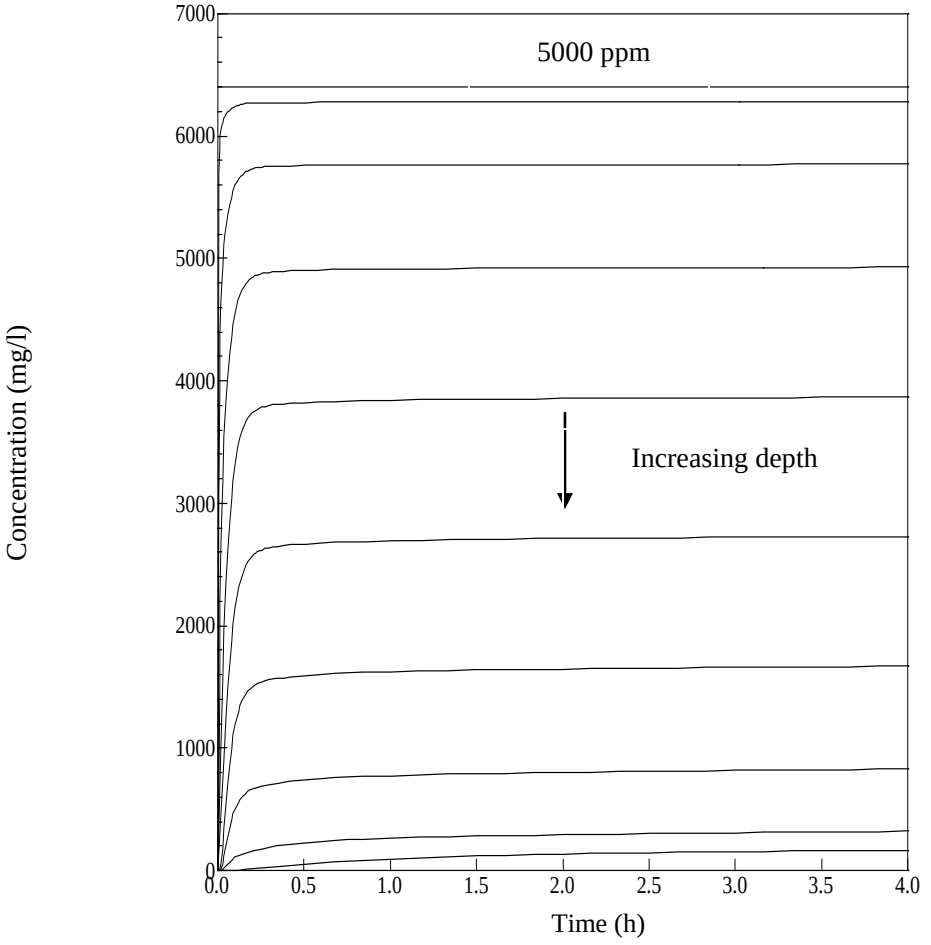

Figure 6. Dibromomethane concentration in the stratum corneum. The depths (dm), based on the internal collocation points, are 0, 2.055×10^{-6}, 1.052×10^{-5}, 2.455×10^{-5}, 4.226×10^{-5} 6.124×10^{-5}, 7.895×10^{-5}, 9.298×10^{-5}, 1.014×10^{-4}, 1.035×10^{-4}. An exposure level of 5000 was used.

5.3. Amount of Chemical Released Through the Skin

The incorporation of a non-homogeneous skin model into the whole body PBPK structure can alternatively be represented as a Fickian diffusion transport problem. One of the boundary conditions is set by the remaining ODEs. It would be enlightening to compare the widely used "perfect sink" condition, assumed in the modeling of controlled-release systems, to the physiologically-based boundary condition. Amounts of chemical from the environment into the stratum corneum (M_{sc}) and from the stratum corneum into the viable skin (M_{vs}), or a receiver, are chosen to guide the analysis since the difference (M_{sc}-M_{vs}) represents chemical accumulation in the stratum corneum. In the long run, the "perfect sink" assumption overestimates the total dose absorbed in both layers as a result of the infinitely fast clearance,

which creates a higher driving force (Fig. 8). The exposure level was fixed at 500 ppm for this simulation.

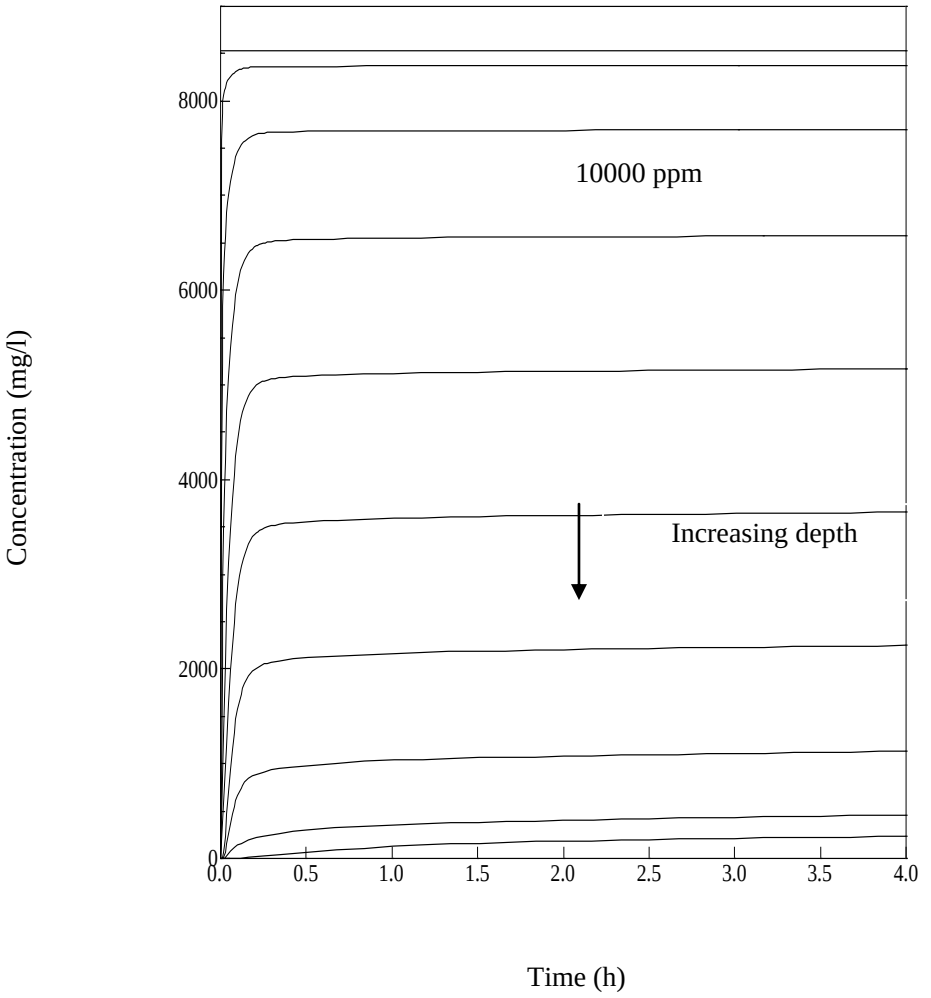

Figure 7. Dibromomethane concentration in the stratum corneum. The depths (dm), based on the internal collocation points, are 0, 2.055×10^{-6}, 1.052×10^{-5}, 2.455×10^{-5}, 4.226×10^{-5} 6.124×10^{-5}, 7.895×10^{-5}, 9.298×10^{-5}, 1.014×10^{-4}, 1.035×10^{-4}. An exposure level of 10,000 was used.

5.4. Time Required to Reach Equilibrium Concentrations

The speed at which the skin becomes saturated after coming in contact with a chemical agent is a question of utmost importance for toxicological assessment. It is well known that thermal relaxation time varies with the distance along a uniformly insulated bar when one end is brought to a new temperature [27]. In designing novel patches for drug release, the time to reach a constant delivery rate is also critical [28]. For the above mentioned systems, it was possible to estimate a time constant directly from the closed-form solution in the Laplace or

time domain. Such options are not available for the present distributed-parameter model due to the nonlinear Michaelis-Menten equation for the liver. To address the problem, a response time defined by how long it takes to reach 98% of the steady-state value is chosen in agreement with process control theory. The exposure concentration of dibromomethane was allowed to vary from 500 to 1000 ppm for the illustration. The routine "FindRoot"' in Mathematica® was invoked to estimate the time elapsed (t) when $C_{sc}\ x_i, t\ = 0.98 C_{sc,ss}\ x_i, t_{\text{large}}$. In this formulation, x_i represents the stratum corneum depth of interest (i.e., scaled collocation point); the subscript "*ss*" implies a steady-state value and t_{large} is set at 100 hours. The result of the investigation is shown in Fig. 9. The response time increases with the depth and exposure level.

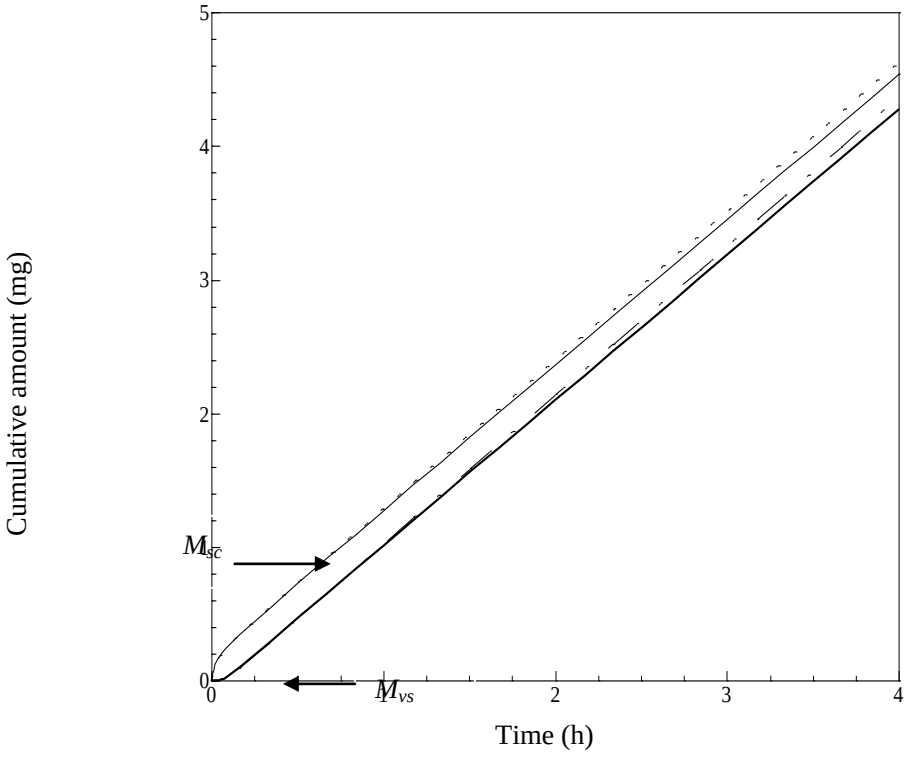

Figure 8. Amount of dibromomethane from the environment into the stratum corneum (M_{sc}) and from the stratum corneum into the viable skin (M_{vs}). The "perfect sink" assumption (--- and ___ _ ___) was compared to the physiologically based boundary condition (___ and ___)

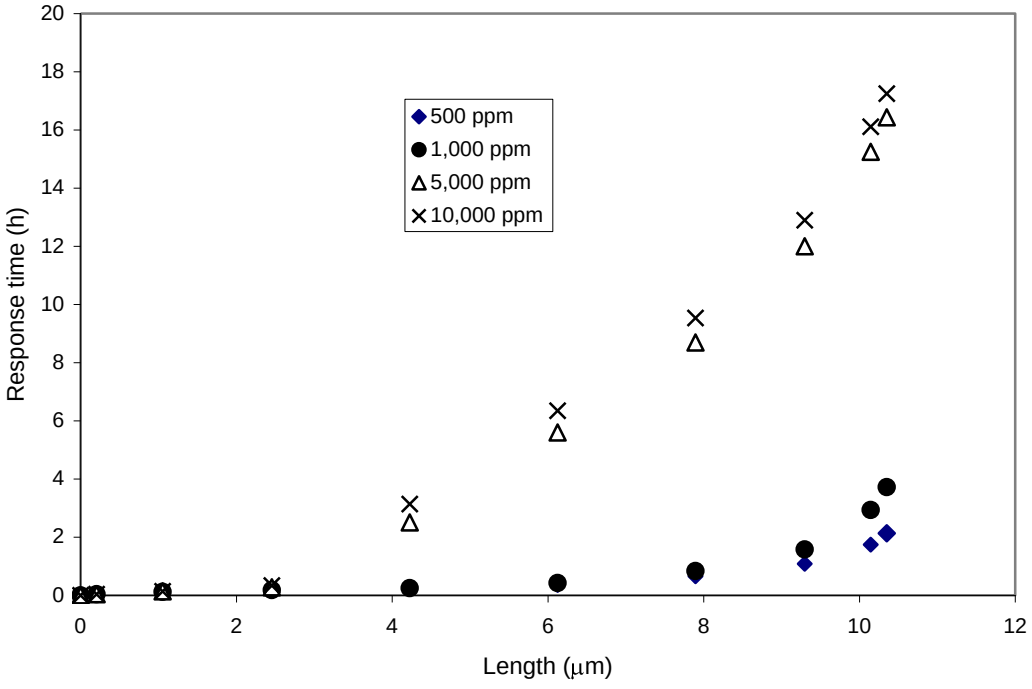

Figure 9. Response time for stratum corneum layers to become saturated with dibromomethane following exposure.

6. Conclusion

Fick's second law was used to analyze diffusive chemical transport through the skin. The boundary condition corresponded to a physiologically-based pharmacokinetic model. Orthogonal collocation procedures were implemented to discretize the partial differential equation in a Mathematica® environment and the results compared to a 1-compartment homogeneous skin model. The diffusive transport model predicted venous blood dibromomethane concentrations very well when compared to experimental data and results from the well-stirred 1-compartment model. This framework facilitated the monitoring of the chemical concentration at various stratum corneum depths. A rise in the exposure level was accompanied by an increase in the equilibrium dibromomethane concentration as the chemical penetrates deeper layers of the tissue. The relaxation time toward saturation in this region was an increasing function of depth and dibromomethane concentration in the environment. Compared to the "perfect sink" assumption, the cumulative amount of chemicals absorbed in the stratum corneum and the viable skin was less when the PBPK boundary condition was invoked.

Nomenclature

J permeation flux (mg/h)
D diffusion coefficient (dm^2/h)
K membrane/donor partition coefficient
l membrane thickness (dm)
P permeability coefficient (dm/h)
C concentration (mg/l)
M total mass of chemical absorbed (mg)
t time (h)
A exposed area (dm^2)
V volume (l)
R partition coefficient
Q blood flow (l/h)
x space variable (dm)
h stratum corneum thickness (dm)
a coefficient in Eq. (15)
b coefficient in Eq. (15)
P Jacobi polynomial
d coefficient in Eq. **Error! Reference source not found.**
W weight function

Subscripts

ss steady state
ave average
sfc vehicle
sk skin
a arterial
b blood
sc stratum corneum
cd composite dermal (2-CSM and 3-CSM)
ve viable epidermis
vs viable skin
i series index in Eq. (15)
1sc scaled value in the stratum corneum
r rapidly perfused tissue
l liver
s slowly perfused tissue
f fat tissue
ss steady state

Greek letters

ζ scaled space variable

References

[1] Meulenberg, C. J. W. & Vijverberg, H. P. M. (2003). Empirical relations predicting human and rat tissue: Air partition coefficients of volatile organic compounds. *Toxicol. Appl. Pharmacol.*, 165, 206-216.

[2] Nestorov, I. (2003). Whole body pharmacokinetic models. *Clin. Pharmacokinet.,* 42, 883-908.

[3] Poet, T. S., Weitz, K. K., Gies, R. A., Edwards, J. A., Thrall, K. D., Corley, R. A., Tanojo, H., Hui, X., Maibach, H. I. & Wester, R. C. (2002). PBPK modeling of the percutaneous absorption of perchloroethylene from a soil matrix in rats and humans. *Toxicol. Sci.,* 67, 17-31.

[4] Poet, T. S., Thrall, K. D., Corley, R. A., Hui, X., Edwards, J. A., Weitz, K. K., Maibach, H. I. & Wester, R. C. (2000). Utility of real time breath analysis and physiologically based pharmacokinetic modeling to determine the percutaneous absorption of methyl chloroform in rats and humans. *Toxicol. Sci.,* 54, 42-51.

[5] Blank, I. H. (1965). Cutaneous barriers. *J. Invest. Dermatol.,* 45, 249–256.

[6] Goyal, A., Mandapuram, S., Michniak, B. & Simon, L. (2007). Application of orthogonal collocation and regression techniques for recovering parameters of a two-pathway transdermal drug-delivery model. *Comput. Chem. Eng.,* 31, 107-120.

[7] Spcar, R. (1997). Large simulation models: calibration, uniqueness and goodness of fit. *Environ. Modell. Softw.,* 12, 219-228.

[8] Bookout, R. L. J., McDaniel, C. R., Quinn, D. W. & McDougal, J. N. (1996). Multilayered dermal subcompartments for modeling chemical absorption. *SAR QSAR Environ Res,* 5, 133-50.

[9] Roy, A., Weisel, C., Lioy, P. & Georgopoulos, P. (1996). A distributed parameter physiologically-based pharmacokinetic model for dermal and inhalation exposure to volatile organic compounds. *Risk Analysis,* 16, 147-160.

[10] Poet, T. S. & McDougal, J. N. (2002). Skin absorption and human risk assessment. *Chem. Biol. Interact.,* 140, 19-34.

[11] Pinheiro, J. & Bates, D. (2000). *Mixed-effects models in S and S-Plus.* New York: Springer.

[12] Liu, X., Smith, B. J., Chen, C., Callegari, E., Becker, S. L., Chen, X., Cianfrogna, J., Doran, A. C., Doran, S. D., Gibbs, J. P., Hosea, N., Liu, J., Nelson, F. R., Szewc, M. A. & Van Deusen, J. (2005). Use of a physiologically based pharmacokinetic model to study the time to reach brain equilibrium: an experimental analysis of the role of blood-brain barrier permeability, plasma protein binding, and brain tissue binding. *J. Pharmacol. Exp. Ther.,* 313, 1254-1262.

[13] Chinery, R. L. & Gleason, A. K. (1993). A compartmental model for the prediction of breath concentration and absorbed dose of chloroform after exposure while showering. *Risk Anal.*, 13, 51–63.

[14] Andersen, M. E. & Keller, W. C. (1984). Toxicokinetic principles in relation to percutaneous absorption and cutaneous toxicity. In V. A. Drill & P. Lazar (Ed.), *Cutaneous Toxicity* (pp. 9-27). New York:Raven Press.

[15] Jepson, G. W. & McDougal, J. N. (1997). Physiologically based modeling of nonsteady state dermal absorption of halogenated methanes from an aqueous solution. *Toxicol. Appl. Pharmacol.*, 144, 315-324.

[16] McKone, T. E. (1993). Linking a PBPK model for chloroform with measured breath concentrations in showers: implications for dermal exposure models. *J. Exp. Anls. & Env. Epi.*, 3, 339-365.

[17] Kalia, Y. & Guy, R. (2001). Modeling transdermal drug release. *Adv. Drug Del. Rev.*, 48, 159–172.

[18] Finlayson, B. A. (1981). *Nonlinear Analysis in Chemical Engineering*. New York: McGraw-Hill.

[19] Srivastava, R. K. & Joseph, B. (1985). Reduced-order models for separation columns — V. Selection of collocation points. *Comput. Chem. Eng.*, 9, 601–613.

[20] Adrover, A., Continillo, G., Crescitelli, S., Giona, M. & Russo, L. (2000). Wavelet-like collocation method for finite-dimensional reduction of distributed systems. *Comp. and Chem. Eng.*, 24, 2687-2703.

[21] Cruz, P., Mendes, A. & Magalhaes, F. D. (2002). Wavelet-based adaptive grid method for the resolution of nonlinear PDEs. *AIChE J.*, 48, 774-785.

[22] Simon, L. (2005). Observing biomass concentration in a fixed-bed bioreactor. *Chem. Eng. Comm.*, 192, 272–285.

[23] Albanese, R. A., Banks, H. T., Evans, M. V. & Potter, L. K. (2002). Physiologically based pharmacokinetic models for the transport of trichloroethylene in adipose tissue. *Bull Math Biol*, 64, 97-131.

[24] Loizou, G., Jones, K., Akrill, P., Dyne, D. & Cocker, J. (1999). Estimation of the dermal absorption of m-xylene vapor in humans using breath sampling and physiologically based pharmacokinetic analysis. *Toxicol. Sci.*, 48, 170-179.

[25] Cleek, R. L. & Bunge, A. L. (1993). A new method for estimating dermal absorption from chemical exposure. 1. General approach. *Pharm Res*, 10, 497-506.

[26] Norman, A. M., Kissel, J. C., Shirai, J. H., Smith, J. A., Stumbaugh, K. L. & Bunge, A. L. (2008). Effect of PBPK model structure on interpretation of in vivo human aqueous dermal exposure trials. *Toxicol Sci*, 104, 210-7.

[27] Collins, R. (1980). The choice of an effective time constant for diffusive processes in finite systems. *J. Phys. D: Appl. Phys.*, 13, 1935-1947.

[28] Simon, L. (2007). Analysis of heat-aided membrane-controlled drug release from a process control perspective. *Int. J. Heat Mass Transfer*, 50, 2425-2433.