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Two-Dimensional Description of Absorption in Humans after Dermal Exposure to Volatile Organic Compounds

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A two-dimensional diffusion model was developed to predict the absorption of chemicals in humans following dermal contact. A first-order evaporation rate equation was applied to the skin surface while a perfect-sink boundary condition was imposed at the stratum corneum/viable epidermis interface. Initially, there was a certain amount of the substance present within the stratum corneum at the end of the exposure period. Laplace transform techniques were implemented to solve the governing equations and to derive an expression for the time elapsed before reaching 90% of the final amount of chemical absorbed by the body. This index was 0.43, 2.67, 6.91, and 36.9 h for ethanol, diphenylamine, *p*-nitroaniline, and benzyl butyl-phthalate, respectively. Simulations show that surface evaporation is important for highly volatile compounds. A large fraction of the amount of poorly volatile compounds, available in the skin after exposure, was absorbed into the bloodstream.

Keywords: Diffusion; Drug delivery; Evaporation; Mathematical modeling; Simulation; Transport phenomena

Introduction

A descriptive system, such as physiologically based pharmacokinetic (PBPK) model, is often developed to predict the distribution of chemicals that come into contact with the skin (Poet et al., 2002). *In vivo* blood levels of benzoic acid were analyzed in hairless guinea pigs after topic exposure (Macpherson et al., 1996). Even though the approach provided useful information on the fate of toxic chemicals in the body, the emphasis was placed on several biological tissues and not solely on the skin. In addition, the well-stirred compartment model, adopted, failed to explain the absorption and penetration of chemicals through the skin layers.

Other researchers turned their attention to the skin and applied a perfect-sink condition at the skin–capillary interface (Kasting, 2001). This narrow focus allows researchers to develop models containing a few parameters that can be calculated from physicochemical properties of the permeant (e.g., molecular weight). Evaporation that occurs at the skin surface is included when studying the dermal absorption of volatile compounds (Frasch, 2012). After writing the diffusion equation in one dimension (1D), it is possible to predict the transport of small and large doses deposited on the upper layer of the stratum corneum (Kasting & Miller, 2006). An important study, recently conducted, discusses a chemical applied to the skin for a finite period before it is completely removed from the skin's surface (Frasch & Bunge, 2015). These researchers obtained expressions for the concentration, flux, and cumulative mass of chemicals absorbed and evaporated in the Laplace domain. A numerical routine was later implemented to invert the results. They also estimated the time elapsed before reaching 90% of the final amount of substance absorbed by the body ($t_{90\%}$) following the exposure. The relationship between $t_{90\%}$ and a dimensionless evaporation rate constant was represented by a fitted exponential decay function. Their approach serves as the basis for this study, which considers a two-dimensional (2D) model for the absorption of a topically applied chemical. Laplace-transform-based procedures are offered to solve the problem and a method is outlined to calculate $t_{90\%}$ directly from the Laplace-domain solution.

Two-dimensional mathematical models have been developed to describe percutaneous absorption of a drug (George, 2005). Permeation studies show that lateral diffusion in lipid bilayer systems may be significant (Johnson et al., 1996). In such cases, it is relevant to consider diffusion in the directions parallel and normal to the skin surface. One-dimensional models only cover the latter case. Current 2-D models do not generally address the diffusion and evaporation of a chemical or a solvent from the skin surface. An *in silico* approach was adopted in Chen et al. (2015) to predict the percutaneous absorption and disposition of chemicals in the skin layers. To the best of our knowledge, no theoretical framework exists for the estimation of $t_{90\%}$ after exposure to VOCs using a two-dimensional transport analysis of

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transdermal absorption. In the case of competitive spreading and lateral diffusion within the stratum corneum, a 2D model may be necessary to predict the absorption and distribution of chemicals in the skin layer.

Materials and Methods

Development of the Mathematical Model

A volatile organic compound (VOC) came into contact with the skin and covered a length h_c(Figure 1). Once inside the stratum corneum, the chemical was allowed to diffuse in the directions parallel and perpendicular to the skin surface. A 1D transport model assumes the concentration only varies in the direction parallel to the skin surface (x_1 direction). When calculating the total delivery rate through the device, the flux is simply multiplied by the area available for diffusion. This is true of a solution in a donor cell that is in contact with a flat membrane of a Franz cell. To include variation along another direction (x_2 direction), a line segment is drawn on the skin surface. Calculation of the flux includes changes in the drug concentration along x_1 (depth) and x_2 (length), and no changes in the direction normal to the x_1-x_2 plane. Just as in a 1D model, the region of interest is defined as a rectangle. Another choice is to outline a circle at that interface, which would lead to a cylindrical coordinate. This contribution examines transport in a Cartesian coordinate. The notion of equivalent areas can be adopted when extrapolating the results to a different geometry.

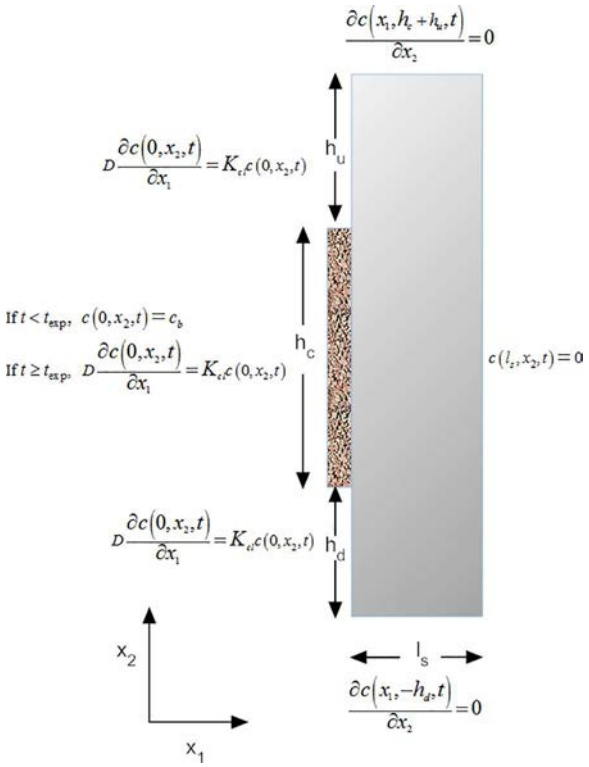

Fig. 1. Schematic of the two-dimensional absorption model. A volatile organic compound (VOC) came into contact with the skin at $x_1 = 0$ and covered a length h_c. A perfect sink condition is assumed at the corneum/viable epidermis interface $x_1 = l_s$.

The constant surface concentration of the VOC c_b is defined as

$$c_b = K_{sv}c_v \tag{1}$$

where K_{sv} is the skin–vehicle partition coefficient, and c_v is the concentration in the vehicle. Two sections perpendicular to the skin surface, h_u and h_d, are chosen. The main equations for the absorption and pre-absorption processes are (George et al., 2004; Simon & Ospina, 2013)

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial x_1^2} + \frac{\partial^2 c}{\partial x_2^2}\right) \tag{2}$$

$$D\frac{\partial c(0,x_2,t)}{\partial x_1} = K_{cl}c(0,x_2,t),\ -h_d \leq x_2 < 0 \tag{3}$$

$$\text{If } t < t_{exp},\ c(0,x_2,t) = c_b,\ 0 \leq x_2 \leq h_c \tag{4}$$

$$\text{If } t \geq t_{exp},\ D\frac{\partial c(0,x_2,t)}{\partial x_1} = K_{cl}c(0,x_2,t),\ 0 \leq x_2 \leq h_c \tag{5}$$

$$D\frac{\partial c(0,x_2,t)}{\partial x_1} = K_{cl}c(0,x_2,t),\ h_c < x_2 \leq h_c + h_u \tag{6}$$

$$\frac{\partial c(x_1,-h_d,t)}{\partial x_2} = 0,\ 0 \leq x_1 \leq l_s \tag{7}$$

$$\frac{\partial c(x_1,h_c+h_u,t)}{\partial x_2} = 0,\ 0 \leq x_1 \leq l_s \tag{8}$$

$$c(l_s,x_2,t) = 0,\ -h_d \leq x_2 \leq h_c + h_u \tag{9}$$

where D and K_{cl} are the diffusivity and evaporation rate constant, respectively, and l_s is the thickness of the stratum corneum. One-dimensional forms of Equations (5), (6), and (9) were given in Frasch and Bunge (2015). Degradation of the chemical, or its binding to the skin, is omitted in the present model. If these effects become significant for a particular compound, first-order terms can be added to Equation (2). Initially, no organic compound is found in the skin:

$$c(x_1,x_2,0) = 0 \tag{10}$$

After an exposure time t_{exp}, the VOC starts to evaporate from the skin (Equation (5)). The parameter t_{exp} is defined as the period elapsed from the initial contact time with the chemical to its removal from the skin. The exposure duration is set by the particular scenario, for example, environmental conditions. A zero-flux condition is imposed at $x_2 = -h_d$ (Equation (7)) and $x_2 = h_c + h_u$ (Equation (8)). Evaporation occurs during and after the exposure period at skin locations close to the affected areas (Equations (3) and (6)). The perfect-sink condition is described by Equation (9). The assumption is that all drug reaching the viable epidermis at l_s is immediately absorbed into the bloodstream. A coupled vehicle–skin model is not applied to describe the VOC dynamics during the first and second time periods because a concentration gradient is not present in the device. Accordingly, Equation (4) implies that the surface concentration remains constant, while Equation (5) describes elimination of the VOC from a homogeneous source.

The following dimensionless variables are defined:

$$x=\frac{x_1}{l_s},\ y=\frac{x_2}{l_s},\ \tau=\frac{tD}{l_s^2},\ C=\frac{c}{c_b},\ w=\frac{l_s K_{cl}}{D},\ L_d=\frac{h_d}{l_s}$$
$$L_c=\frac{h_c}{l_s},\ L_u=\frac{h_c+h_u}{l_s} \tag{11}$$

As a result, Equations (2)–(10) become

$$\frac{\partial C}{\partial \tau}=\frac{\partial^2 C}{\partial x^2}+\frac{\partial^2 C}{\partial y^2} \tag{12}$$

$$\frac{\partial C(0,y,\tau)}{\partial x}-wC(0,y,\tau)=0,\ -L_d\le y<0 \tag{13}$$

$$\text{If } \tau<\tau_{exp},\ C(0,y,\tau)=1,\ 0\le y\le L_c \tag{14}$$

$$\text{If } \tau\ge\tau_{exp},\ \frac{\partial C(0,y,\tau)}{\partial x}-wC(0,y,\tau)=0,\ 0\le y\le L_c \tag{15}$$

$$\frac{\partial C(0,y,\tau)}{\partial x}-wC(0,y,\tau)=0,\ L_c<y\le L_u \tag{16}$$

$$\frac{\partial C(x,-L_d,\tau)}{\partial y}=0,\ 0\le x\le 1 \tag{17}$$

$$\frac{\partial C(x,L_u,\tau)}{\partial y}=0,\ 0\le x\le 1 \tag{18}$$

$$C(1,y,\tau)=0,\ -L_d\le y\le L_u \tag{19}$$

$$C(x,y,0)=0 \tag{20}$$

Analytical Solution

The problem is split into two parts: a period before and a time after the absorption of the volatile compound. The first model is solved with a method similar to the one described in Simon and Ospina (2013). The Laplace transform of Equation (12) is

$$s\overline{C}(x,y,s)-C(x,y,0)=\frac{\partial^2\overline{C}(x,y,s)}{\partial x^2}+\frac{\partial^2\overline{C}(x,y,s)}{\partial y^2} \tag{21}$$

or

$$s\overline{C}_2(x,y,s)=\frac{\partial^2\overline{C}_2(x,y,s)}{\partial x^2}+\frac{\partial^2\overline{C}_2(x,y,s)}{\partial y^2} \tag{22}$$

after using Equation (20). The solution to Equation (22) is

$$\overline{C}_2(x,y,s)=\left(C_1e^{x\sqrt{c_1}}+C_2e^{-x\sqrt{c_1}}\right)\left(C_3\sin\left(y\sqrt{-s+c_1}\right)+C_4\cos\left(y\sqrt{-s+c_1}\right)\right) \tag{23}$$

We apply the boundary conditions (17), (18), and (19) to Equation (23) and obtain

$$\overline{C}(x,y,s)=-A_0e^{\sqrt{s}x}+A_0e^{-\sqrt{s}x}e^{2\sqrt{s}}-\sum_{n=1}^{\infty}\cos\left(\frac{\pi n(y+L_d)}{L_d+L_u}\right)\left(A_ne^{G_nx}-A_ne^{-G_nx}e^{2G_n}\right) \tag{24}$$

with

$$G_n=\sqrt{\frac{n^2\pi^2}{(L_u+L_d)^2}+s} \tag{25}$$

A first-order approximation is

$$\overline{C}(x,y,s)=-A_0e^{\sqrt{s}x}+A_0e^{-\sqrt{s}x}e^{2\sqrt{s}}-\cos\left(\frac{\pi(y+L_d)}{L_d+L_u}\right)\left(A_1e^{G_1x}-A_1e^{-G_1x}e^{2G_1}\right) \tag{26}$$

Laplace transforms of Equations (13), (14), and (16) are combined to give:

$$\begin{aligned}&\left[\frac{\partial\overline{C}(x,y,s)}{\partial x}-w\overline{C}(x,y,s)\right]_{x=0}[\text{Heaviside}(y+L_d)\\&-\text{Heaviside}(y)]+\left[\frac{\partial\overline{C}(x,y,s)}{\partial x}-w\overline{C}(x,y,s)\right]_{x=0}\times\\&[\text{Heaviside}(y-L_c)-\text{Heaviside}(y-L_u)]\\&-\left[\overline{C}(x,y,s)-\frac{1}{s}\right]_{x=0}[\text{Heaviside}(y)\\&-\text{Heaviside}(y-L_c)]=0\end{aligned} \tag{27}$$

which incorporates two constants: A_0 and A_1. Analytical expressions for A_0 and A_1 are determined by solving the following two equations:

$$\int_{-L_d}^{L_u}\psi(y,s)dy=0 \tag{28}$$

and

$$\int_{-L_d}^{L_u}\left[\psi(y,s)\cos\left(\pi\left(\frac{y+L_d}{L_u+L_d}\right)\right)\right]dy=0 \tag{29}$$

with

$$\begin{aligned}\psi(y,s)=&\left[\frac{\partial\overline{C}(x,y,s)}{\partial x}-w\overline{C}(x,y,s)\right]_{x=0}\times\\&[\text{Heaviside}(y+L_d)-\text{Heaviside}(y)]\\&+\left[\frac{\partial\overline{C}(x,y,s)}{\partial x}-w\overline{C}(x,y,s)\right]_{x=0}[\text{Heaviside}(y-L_c)\\&-\text{Heaviside}(y-L_u)]-\left[\overline{C}(x,y,s)-\frac{1}{s}\right]_{x=0}\times\\&[\text{Heaviside}(y)-\text{Heaviside}(y-L_c)]\end{aligned} \tag{30}$$

Unique solutions are obtained for A_0 and A_1 because Equations (28) and (29) are linearly independent. A closed-form expression is obtained for the VOC concentration at $\tau=\tau_{exp}$ by using the residue theorem (Rice & Do, 1995):

$$C(x,y,\tau_{exp})=C_{eq}(x,y)+\sum_{p=1}^{\infty}\left[f\left(\alpha_p^2,x,y\right)e^{-\alpha_p^2\tau_{exp}}\right] \tag{31}$$

where $-\alpha_p^2$ are the poles of the concentration in the Laplace domain $\overline{C}(x,y,s)$, $C_{eq}(x,y)$ is the steady-state (or equilibrium) concentration and $f(.)$ is a function of the poles. For simplicity, only the first pole is used. This means that the solution is valid for $\tau_{exp}>\tau_{lag}$ (i.e., lag time). The lag time is indicative of the

time required to reach a steady-state flux (Twizell & Kubota, 1994).

The same technique is applied for the period following absorption of the volatile compound. In this case, Equation (21) becomes

$$s\overline{C}(x,y,s) - C(x,y,\tau_{\text{exp}}) = \frac{\partial^2\overline{C}(x,y,s)}{\partial x^2} + \frac{\partial^2\overline{C}(x,y,s)}{\partial y^2} \quad (32)$$

and $\psi(y, s)$, defined in Equation (30), is reduced to

$$\psi(y,s) = \left[\frac{\partial\overline{C}(x,y,s)}{\partial x} - w\overline{C}(x,y,s)\right]_{x=0} \quad (33)$$

The concentration $C(x, y, \tau)$ is found by inverting $\overline{C}(x,y,s)$ numerically (Durbin, 1974).

The cumulative amount of VOC absorbed by the body and evaporated from the surface of the skin are

$$M_{\text{abs}}(\tau) = \int_0^{\tau}\left[-\int_{-L_{\text{d}}}^{L_{\text{u}}}\frac{\partial}{\partial x}C(x,y,\sigma)\Big|_{x=1}dy\right]d\sigma \quad (34)$$

and

$$M_{\text{evap}}(\tau) = \int_0^{\tau}\left[\int_{-L_{\text{d}}}^{L_{\text{u}}}\frac{\partial}{\partial x}C(x,y,\sigma)\Big|_{x=0}dy\right]d\sigma \quad (35)$$

The initial mass of VOC in the skin at the end of the exposure is

$$M_0 = \int_{-L_{\text{d}}}^{L_{\text{u}}}\left[\int_0^1 C(x,y,0)dx\right]dy \quad (36)$$

As a result, the normalized absorption by the body and evaporation from the skin are given by

$$\frac{M_{\text{abs}}(\tau)}{M_0} = \frac{\int_0^{\tau}\left[-\int_{-L_{\text{d}}}^{L_{\text{u}}}\frac{\partial}{\partial x}C(x,y,\sigma)\big|_{x=1}dy\right]d\sigma}{\int_{-L_{\text{d}}}^{L_{\text{u}}}\left[\int_0^1 C(x,y,0)dx\right]dy} \quad (37)$$

and

$$\frac{M_{\text{evap}}(\tau)}{M_0} = \frac{\int_0^{\tau}\left[\int_{-L_{\text{d}}}^{L_{\text{u}}}\frac{\partial}{\partial x}C(x,y,\sigma)\big|_{x=0}dy\right]d\sigma}{\int_{-L_{\text{d}}}^{L_{\text{u}}}\left[\int_0^1 C(x,y,0)dx\right]dy} \quad (38)$$

respectively. At the end of the exposure, the time to reach 98% of the amount absorbed by the body is estimated by using the notion of a time constant of a first-order system. The effective relaxation time (or time constant) is defined by (Collins, 1980; Simon, 2009)

$$\tau_{\text{eff}} = \int_0^{\infty}\tau\Omega(\tau)d\tau \quad (39)$$

where $\Omega(\tau)$ is a probability density function:

$$\Omega(\tau) = \frac{(M_{\text{abs}}(\infty) - M_{\text{abs}}(\tau))}{\int_0^{\infty}(M_{\text{abs}}(\infty) - M_{\text{abs}}(\tau))d\tau} \quad (40)$$

Equation (39) can also be written as

$$\tau_{\text{eff}} = \lim_{s\to 0}\left(\frac{M_{\text{abs}}(\infty)}{s^2} + \frac{d\overline{M}_{\text{abs}}(s)}{ds}\right)\times \left[\lim_{s\to 0}\left(\frac{M_{\text{abs}}(\infty)}{s} - \overline{M}_{\text{abs}}(s)\right)\right]^{-1} \quad (41)$$

where $\overline{M}_{\text{abs}}$ is the Laplace transform of M_{abs}. The amount absorbed is at 98% (or 90%) of the steady-state value when $\tau = 4\tau_{\text{eff}}$ or $2.3\tau_{\text{eff}}$ (LeBlanc & Coughanowr, 2009). The response time is accurate for a first-order system and is a reliable estimate for diffusive processes (Simon, 2009). Moreover, it is not necessary to derive the Laplace inverse of the absorbed mass in order to apply Equation (41).

Results and Discussion

The four chemicals used in this study (Table I) are taken from Frasch and Bunge (2015). To carry out the simulation in 2D, values of L_{c}, L_{d}, and L_{u}, corresponding to those reported by George et al. (2004), were used. Their research focused on the permeation of a drug applied as an ointment on the skin surface. The dimensionless region of contact was defined as $0 \le y \le L_{\text{c}}$. The data were estimated by assuming the skin was exposed to the air and that $t_{\text{exp}}/t_{\text{lag}} = 10$. The last two rows, containing $t_{90\%}$ values, calculated from the models developed in this investigation ($t_{90\%}$) and by Frasch and Bunge (2015) ($t^*_{90\%}$), will be discussed later. Figures 2–5 show the absorption of the chemicals into the body and their evaporation from the skin surface. The amount of ethanol evaporated from the surface of the skin was higher than the amount absorbed (Figure 2). This observation is in line with published studies where evaporation was substantial for highly volatile compounds (Frasch & Bunge, 2015). As the permeant becomes less volatile, more of it is absorbed into the body. Nearly all the *p*-nitroaniline that remained in the skin after an exposure of 12.9 h was absorbed by the body (Figure 5).

The normalized time constant (τ_{eff}) decreased with an increase in the volatility of the chemical (Table I). Once the normalized exposure time and the diffusion area are specified, τ_{eff} becomes only a decaying function of w and can be used to estimate the time it takes for the body to absorb residual amounts of a chemical that remain in the skin after the exposure. By analogy to a first-order process, the absorbed quantity reaches 90% of the steady state at $2.3\tau_{\text{eff}}$ (LeBlanc & Coughanowr, 2009). At a fixed w, the time constant (t_{eff}) and $t_{90\%}$ are inversely proportional to the compound diffusion coefficient in the skin because $\tau = tD/l_{\text{s}}^2$. Note that τ_{eff} is related to t_{eff} by $\tau_{\text{eff}} = t_{\text{eff}}D/l_{\text{s}}^2$. Similar to the lag time, t_{eff} increases with the diffusional path length l_{s}. The lowest value of $t_{90\%}$is obtained for ethanol (0.43 h). This observation can be explained by the relatively high diffusion coefficient. The effect of w on τ_{eff} is not pronounced for larger values of w. For example, computed values of τ_{eff} are 0.107, 0.106, 0.106 when w is equal to 155, 620, and 1550, respectively. As a result, differences in the time

Table I. Model parameters and calculation of $t_{90\%}$ for four chemicals

Chemicals		Ethanol	Diphenylamine	Benzyl butyl-phthalate	*p*-Nitroaniline
l_s	cm	0.0015	0.0015	0.0015	0.0015
c_v	mg/cm^3	789	789	789	789
t_{lag}	h	0.29	1.34	8.86	1.29
D	cm^2/h	1.29E–06	2.80E–07	4.23E–08	2.91E–07
w		155	5.3	0.48	0.06
K_{cl}	cm/h	1.34E–01	9.89E–04	1.35E–05	1.16E–05
h_c	cm	7.50E–04	7.50E–04	7.50E–04	7.50E–04
h_d	cm	0.00375	0.00375	0.00375	0.00375
h_u	cm	0.00375	0.00375	0.00375	0.00375
L_c		0.5	0.5	0.5	0.5
L_d		2.5	2.5	2.5	2.5
L_u		3.0	3.0	3.0	3.0
k_p	cm/h	8.00E–04	7.70E–03	3.70E–02	8.44E–03
K_{sv}		0.93	41.27	1311.28	43.55
t_{exp}	h	2.9	13.4	88.6	12.9
τ_{exp}		1.67	1.67	1.67	1.67
τ_{eff}		0.11	0.14	0.30	0.39
$\boldsymbol{t_{90\%}}$	h	**0.43**	**2.67**	**36.9**	**6.91**
$t^*_{90\%}$	h	0.55	2.68	41.6	7.22

$t^*_{90\%}$ Values were obtained by Frasch and Bunge (2015).l_s, thickness of the stratum corneum; c_v, drug concentration in the vehicle; t_{lag}, time lag; D, drug diffusivity in the stratum corneum; τ, L_c, L_d, L_u, w, as defined in Equation (11); K_{cl}, evaporation rate constant from the stratum corneum into the surrounding air; k_p, permeability coefficient defined by $k_p = K_{sv}D/l_s$; K_{sv}, skin–vehicle partition coefficient; t_{exp}, period elapsed from the initial contact time with the chemical to its removal from the skin; h_c, h_d, h_u, as defined in Figure 1. Bold values indicate the results calculated using the proposed 2-D model.

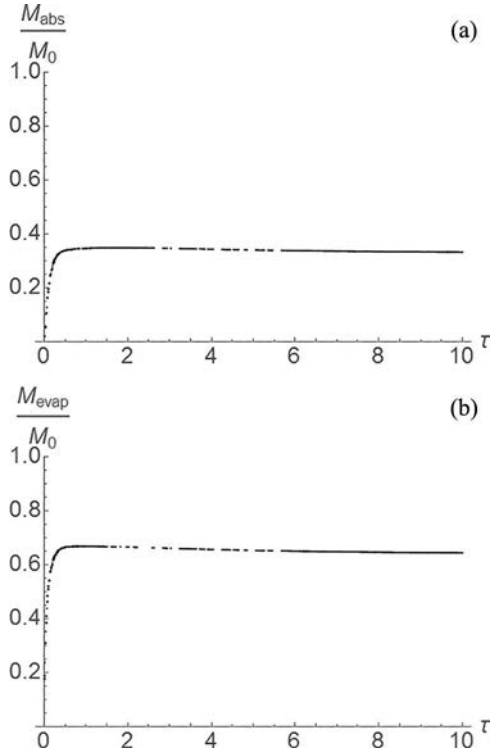

Fig. 2. Ethanol absorption into the body (a) and evaporation from the skin surface (b) after an exposure of 2.9 h to air. The evaporation rate constant is $K_{cl} = 0.13\text{cm}/h$; τ is the dimensionless time.

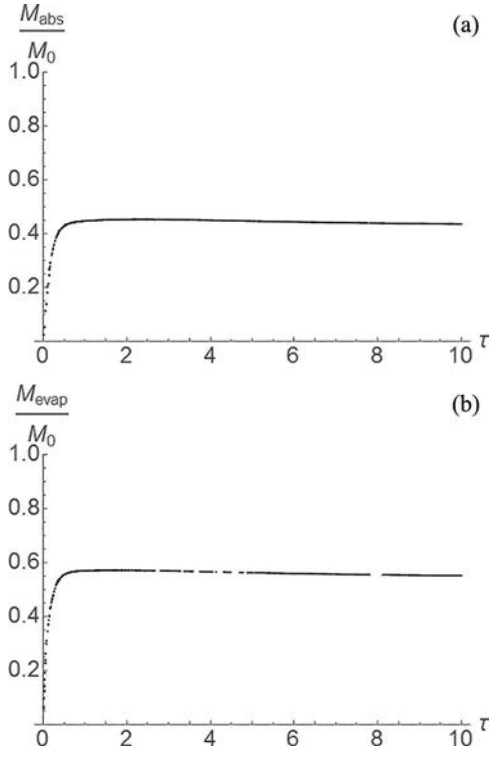

Fig. 3. Diphenylamine absorption into the body (a) and evaporation from the skin surface (b) after an exposure of 13.4 h to air. The evaporation rate constant is $K_{cl} = 1.0 \times 10^{-3}\text{cm}/h$; τ is the dimensionless time.

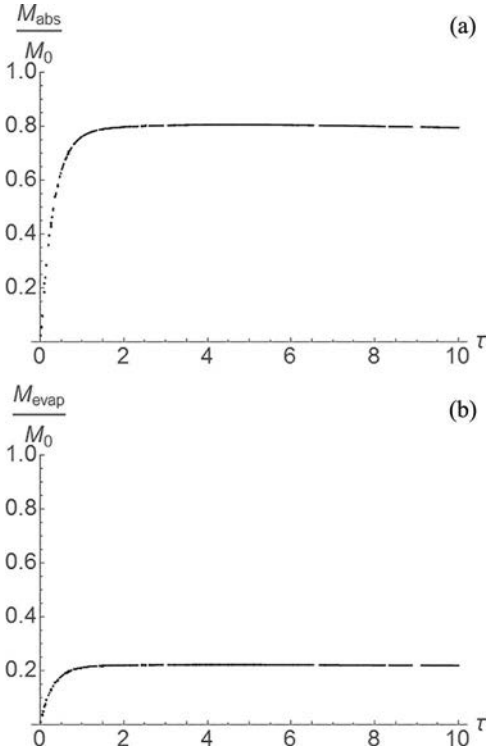

Fig. 4. Benzylbutyl-phthalate absorption into the body (a) and evaporation from the skin surface (b) after an exposure of 88.6 h to air. The evaporation rate constant is $K_{cl} = 1.4 \times 10^{-5}$cm/$h$; τ is the dimensionless time.

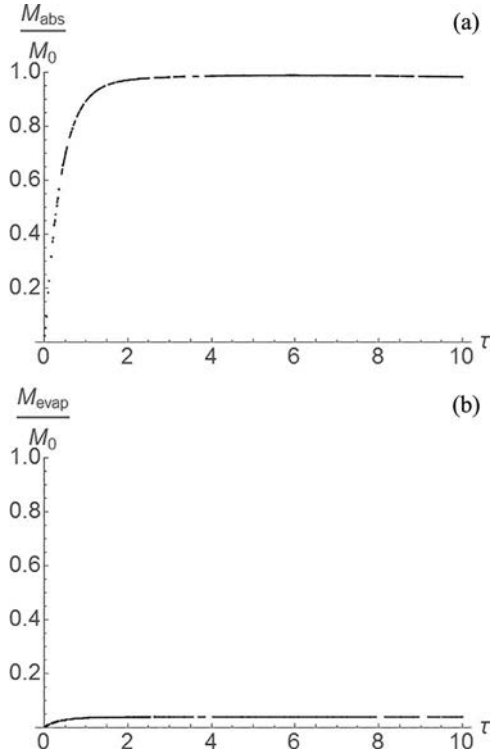

Fig. 5. *p*-Nitroaniline absorption into the body (a) and evaporation from the skin surface (b) after an exposure of 12.9 h to air. The evaporation rate constant is $K_{cl} = 1.2 \times 10^{-5}$cm/$h$; τ is the dimensionless time.

it takes the body to absorb 90% of semi- and highly volatile compounds should be attributed to the diffusion coefficient instead of the evaporation rate. The influence of the vapor pressure on t_{eff} is more significant at low w values. Frasch and Bunge (2015) stated that the absorption of 90% of diphenylamine took four times longer than ethanol because the lag time ($l_s^2/6D$) of ethanol (0.29 h) is shorter than that of diphenylamine (1.34 h).

An analytical expression, which did not require an inversion of $\overline{M}_{abs}(s)$, was obtained for τ_{eff} (Equation (41)). After a numerical inversion of $\overline{M}_{abs}(s)$, researchers are able to simulate two-dimensional diffusion of a chemical into the skin. The effects of volatility and exposure time can be addressed in the current platform. A similar problem was solved in one dimension (Frasch & Bunge, 2015). After fitting a three-parameter exponential decay function to a set of data, the authors developed a relationship between w and $t_{90\%}/t_{lag}$. Their findings, listed in the last column of Table I, are mostly comparable to the results shown in this work.

Small differences were observed in the $t_{90\%}$values obtained for the two models. The discrepancy may be attributed to several factors. It is possible that normal and lateral diffusions contribute to the observed transport. This would not be revealed in an analysis based on 1D diffusion. In addition, the method outlined in this paper is based on a single diffusion coefficient. Because of the highly anisotropic nature of the stratum corneum lipids (Wang et al., 2006), the diffusivities are likely to be distinct for some compounds. Researchers need to compare the predictions with the experimental data. If skin absorption data are described adequately by a 1D transport equation, metrics such as $t_{90\%}$ and $t_{lag}$are to be calculated from the 1D results. In cases where a significant mismatch exists between the predictions and laboratory data, the 2D approach is recommended. *In vitro* experiments should be performed to validate the results.

The equations can be extended to the case of an anisotropic diffusion in the stratum corneum. In this case, Equation (12) becomes

$$\frac{\partial C}{\partial \tau} = \frac{\partial^2 C}{\partial x^2} + \eta \frac{\partial^2 C}{\partial y^2} \tag{42}$$

where $\eta = D_{x2}/D_{x1}$. The parameters D_{x1} and D_{x2} are the diffusion coefficients in the transversal and lateral directions, respectively. The dimensionless time and parameter w are defined as: $\tau = \frac{tD_{x1}}{l_s^2}$ and $w = \frac{l_s K_{cl}}{D_{x1}}$.

Conclusions

This effort analyzes the absorption of volatile organic compounds into the body and their evaporation from the skin surface using a two-dimensional transport equation. The study is restricted to cases where penetration and lateral diffusion take place simultaneously within the skin bilayers. To conduct the analysis, the amount of chemical in the skin at the end of the exposure period was obtained from an earlier publication. The current application considers scenarios in which the exposure time is

larger than the lag time. Implementation of Laplace transform–based techniques led to analytical expressions for solute concentration in the skin, the effective time constant (t_{eff}) and the time it took to reach 90% of the final amount of chemical absorbed by the body ($t_{90\%}$). Several simulations were conducted to show the absorption of chemicals into the body and their evaporation from the skin surface. Calculations show good agreement with published results based on 1D analyses. For example, after applying the approach to four chemicals, the amount of ethanol absorbed by the body was found to be less than the amount evaporated from the skin's surface and into the air. Compared with their absorption into the body, evaporation was significant for highly volatile compounds. Poorly volatile compounds, such as *p*-nitroaniline that remained in the skin after a finite exposure period, were nearly all absorbed by the body. If the volatility is kept constant, the relaxation time (t_{eff}) and $t_{90\%}$ are inversely proportional to the diffusion coefficient in the skin. In addition to predicting these trends, the proposed scheme can be used to estimate concentration gradients in the directions perpendicular and parallel to the skin surface. The theoretical framework presented in this contribution should be validated with a number of experiments to test its applicability and performance.

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