Does Epidermal Turnover Reduce Percutaneous Penetration?

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Purpose. After its removal from the skin surface, chemical remaining within the skin can become systemically available. The fraction of chemical in the skin that eventually enters the body depends on the relative rates of percutaneous transport and epidermal turnover (i.e., stratum corneum desquamation). Indeed, some investigators have claimed that desquamation is an efficient mechanism for eliminating dermally absorbed chemical from the skin.

Methods. The fate of chemical within the skin following chemical contact was examined using a mathematical model representing turnover of and absorption into the stratum corneum and viable epidermis. The effects of turnover rate, exposure duration, penetrant lipophilicity, and lag time for chemical diffusion were explored.

Results. These calculations show that significant amounts of chemical can be removed from skin by desquamation if epidermal turnover is fast relative to chemical diffusion through the stratum corneum. However, except for highly lipophilic and/or high molecular weight (>350 Da) chemicals, the normal epidermal turnover rate is not fast enough and most of the chemical in the skin at the end of an exposure will enter the body.

Conclusions. Epidermal turnover can significantly reduce subsequent chemical absorption into the systemic circulation only for highly lipophilic or high molecular weight chemicals.

KEY WORDS: viable epidermis; stratum corneum; desquamation; dermal absorption; epidermal turnover; mathematical model.

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INTRODUCTION

The skin can be an important exposure route to chemicals from a variety of pharmaceutical, cosmetic, household, agricultural, or industrial products. For organic chemicals of moderate size, penetration through the skin membrane is a solution–diffusion process (1–4). Once a chemical is removed from the skin's surface, chemicals within the skin can continue to diffuse through the skin and enter the bloodstream. As a result, for brief chemical exposures, much of the systemic chemical absorption can occur after the chemical has been removed from the skin surface.

For many chemicals, the outermost skin layer, the stratum corneum (sc), is the rate-limiting barrier for mass transfer into and through skin. For highly lipophilic chemicals, the underlying viable epidermis (ve) also contributes a significant resistance to mass transfer across the skin. The dermis, located beneath the epidermis (epi = sc + ve), is a highly vascularized tissue that ususally has sufficient blood flow to efficiently clear away all chemicals passing through the epi (5).

Skin is continuously replaced through epidermal turnover, the process by which new cells are generated at the base of the epidermis while the outermost surface flakes off (i.e., desquamates) at the same rate. Chemicals in desquamated skin cannot be absorbed systemically. Some investigators have suggested (6,7) that desquamation will significantly reduce systemic exposure to dermally-absorbed chemicals. The typical time required to completely replace the sc (i.e., the turnover time for the sc, $t_{t,sc}$) is approximately 14 days, but varies with physiological location (8,9) and age (10,11). The turnover time for the ve, $t_{t,ve}$, has been reported as 38–61 days (12), 31 days (13), 33–34 days (14), and 25 days (15). The variations in reported values of $t_{t,ve}$ arise because in each of the references cited, $t_{t,ve}$ was calculated using different methods, models, and assumptions. Turnover times can be shorter for diseased skin (15). While the rate of desquamation can be changed by chemically or mechanically forcing desquamation or by protecting a site, the rate of cell proliferation does not change (9,16).

Although the potential contribution of desquamation to chemical elimination from the skin has been described elsewhere, quantitative mathematical modeling of the process has been limited. The model described by Auton *et al.* (7) did include desquamation and sc turnover. However, their model did not include ve turnover and did not clearly relate sc turnover and chemical loss from the surface layer. Here, a mathematical model describing chemical absorption into the epidermis allowing for epidermal turnover is used to address these issues quantitatively.

ABBREVIATIONS: A, surface area of chemical exposure; B, ratio of the sc and ve permeability coefficients of the absorbing chemical from the same vehicle, $P_{sc,v}/P_{ve,v}$; C_j, concentration of the absorbing chemical in membrane layer j as a function of both position and time; C_v^o, initial concentration of the absorbing chemical in the vehicle; D_j, effective diffusion coefficient of the absorbing chemical in membrane layer j; epi, epidermis; FA, fraction of chemical in the epi at t_{exp} that systemically absorbs, M_{abs}/M_{epi}^o; G, ratio of $t_{lag,sc}$ to $t_{lag,ve}$; j, variable denoting sc or ve; J, flux (i.e., mass/area/time) of absorbing chemical through a position in the epi; J_{ss}, steady-state flux of the absorbing chemical; $J_{ss}(u_{sc} = 0)$, steady-state flux of the absorbing chemical with no epidermal turnover; $K_{j/v}$, equilibrium partition coefficient between membrane layer j and the vehicle for the absorbing chemical; $K_{o/w}$, octanol–water partition coefficient; L_j, apparent thickness of membrane layer j; M_{abs}, total mass of chemical absorbed systemically after an exposure ends; M_{desq}, cumulative mass of chemical removed from the sc by desquamation; M_{epi}, mass of absorbing chemical in the epi; M_{epi}^o, mass of absorbing chemical in the epi at $t = t_{exp}$; MW, molecular weight; N_j, number of nodes in membrane layer j for the finite difference solution; $P_{j,v}$, steady-state permeability coefficient of the absorbing chemical through membrane layer j from the vehicle, $K_{j/v}\,D_j/L_j$; sc, stratum corneum; t, time; t_{exp}, duration of the exposure; $t_{lag,j}$, lag time for chemical penetrating through membrane layer j, $L_j^2/(6D_j)$; $t_{t,j}$ turnover time of membrane layer j; u_j, velocity at which membrane layer j moves, $L_j/t_{t,j}$; ve, viable epidermis; x, position in the sc; Δx_j, distance between finite difference nodes in membrane layer j; γ, ratio of the sc and ve turnover times, $t_{t,sc}/t_{t,ve}$; λ_n, eigenvalues; η_{ve}, ratio of the ve and sc thickness, L_{ve}/L_{sc}.

THEORY

Typically, dermal absorption models account for chemical transport through the skin by passive diffusion alone (17–19). However, cell proliferation at the basal layer of the ve, along with desquamation of the outer surface of the sc, cause the epi to move slowly outward, carrying chemicals dissolved in the sc along with it. Most dermal absorption models neglected this convective transport of absorbed chemicals because cell growth is usually much slower than diffusion. By including the epi turnover velocity in the model presented here, we are able to theoretically examine the effect of desquamation on dermal absorption.

In the ve, cells are released from the basal layer and move upward in a random manner (12). However, many cells in the differentiating layers of the ve move in tandem as a front (15). Once the cells reach the sc, they are tightly attached to each other and travel in unison (12). Consequently, we assume that the sc and ve move at the constant velocities u_{sc} and u_{ve}, respectively. These velocities are estimated as the constant apparent thickness of the sc (L_{sc}) or ve (L_{ve}) divided by the turnover time for each layer (i.e., $u_{sc} = L_{sc}/t_{t,sc}$ and $u_{ve} = L_{ve}/t_{t,ve}$).

We describe dermal absorption as mass transport through two pseudohomogeneous membranes in series representing the sc and ve. The differential mass balance equations describing the one-dimensional chemical transport by passive diffusion and epidermal turnover within the sc and ve are (20):

$$\frac{\partial C_{sc}}{\partial t} = D_{sc}\frac{\partial^2 C_{sc}}{\partial x^2} + u_{sc}\frac{\partial C_{sc}}{\partial x} \quad \text{for } 0 < x < L_{sc} \tag{1}$$

$$\frac{\partial C_{ve}}{\partial t} = D_{ve}\frac{\partial^2 C_{ve}}{\partial x^2} + u_{ve}\frac{\partial C_{ve}}{\partial x} \quad \text{for } L_{sc} < x < L_{sc} + L_{ve} \tag{2}$$

where x is the distance in the epi from the skin surface and t is time. In Eqs. 1 and 2, with j designating either the sc or ve, C_j is the concentration in membrane layer j and D_j is the effective diffusion coefficient of the absorbing chemical through layer j of apparent thickness L_j. Eqs. 1 and 2 are written assuming that the epi moves outward (i.e., the sc and ve velocities are negative). The assumption of one-dimensional transport is reasonable when the width of the exposed area of the skin is much larger than the thickness of the sc.

In the general case, Eqs. 1 and 2 are solved assuming the skin is initially chemical free, and then is exposed to a vehicle at a constant concentration C_v^o for a period of time t_{exp} with sink conditions at the ve–dermis interface. In addition, local equilibrium is assumed between the vehicle and the skin surface and at the sc–ve interface, flux is conserved at the sc–ve interface, and the absorbing chemical is not volatile (i.e., the flux from the outer surface of the sc is zero once the chemical has been removed). Stated mathematically, these conditions are:

$$\text{at } t = 0 \quad C_{sc} = 0 \text{ for } 0 < x < L_{sc} \quad \text{and} \quad C_{ve} = 0 \text{ for } L_{sc} < x < L_{sc} + L_{ve} \tag{3}$$

$$\text{at } x = 0 \quad C_{sc} = K_{sc/v}\,C_v^o \quad \text{for } 0 < t < t_{exp} \tag{4}$$

$$\text{and} \quad \frac{\partial C_{sc}}{\partial x} = 0 \quad \text{for } t > t_{exp} \tag{5}$$

$$\text{at } x = L_{sc} \quad C_{sc} = \frac{K_{sc/v}}{K_{ve/v}}C_{ve} \quad \text{for } t > 0 \tag{6}$$

$$\text{and} \quad D_{ve}\frac{\partial C_{ve}}{\partial x} + u_{ve}C_{ve} = D_{sc}\frac{\partial C_{sc}}{\partial x} + u_{sc}C_{sc} \quad \text{for } t > 0 \tag{7}$$

$$\text{at } x = L_{sc} + L_{ve} \quad C_{ve} = 0 \quad \text{for } t > 0 \tag{8}$$

where $K_{sc/v}$ is the equilibrium partition coefficient of absorbing chemical between the sc and the vehicle and $K_{ve/v}$ is the equilibrium partition coefficient between the ve and the vehicle. Eqs. 1 through 8 must be solved numerically during ($t \le t_{exp}$) and following a chemical exposure ($t > t_{exp}$). Simplifying assumptions representing special physical situations make analytical solutions possible for $t \le t_{exp}$, allowing for algebraic representations of C_{sc} and C_{ve} at $t = t_{exp}$. In these situations, numerical solutions are only required for $t > t_{exp}$. Solutions for two such cases are presented next.

In the first case, $C_{ve} = 0$ for $t \le t_{exp}$. This case is relevant for chemicals with low to moderate lipophilicity for which the sc alone contributes a significant barrier or for exposures that are short enough that chemical has not reached the ve. Eq. 1 was solved for the conditions specified by Eqs. 3, 4, and 6 to produce the following algebraic expression for C_{sc} at $t = t_{exp}$:

$$\frac{C_{sc}}{K_{sc/v}\,C_v^o} = \frac{\exp\left(-\frac{6t_{lag,sc}}{t_{t,sc}}\frac{x}{L_{sc}}\right) - \exp\left(-\frac{6t_{lag,sc}}{t_{t,sc}}\right)}{1 - \exp\left(-\frac{6t_{lag,sc}}{t_{t,sc}}\right)} - 2\pi\sum_{n=1}^{\infty}\frac{n}{\lambda_n^2}\exp\left(-\frac{3t_{lag,sc}}{t_{t,sc}}\frac{x}{L_{sc}} - \frac{\lambda_n^2 t_{exp}}{t_{lag,sc}}\right)\sin\left(\frac{n\pi x}{L_{sc}}\right) \tag{9}$$

in which λ_n are eigenvalues satisfying Eq. 10:

$$\lambda_n^2 = n^2\pi^2 + 9\left(\frac{t_{lag,sc}}{t_{t,sc}}\right)^2 \tag{10}$$

and $t_{lag,sc}$ is the lag time for a chemical to cross the sc, defined as $L_{sc}^2/(6D_{sc})$. As indicated in Eq. 9, C_{sc} depends on t_{exp} and $t_{t,sc}$ relative to $t_{lag,sc}$. When only the sc contributes a resistance to mass transport across the epi and $u_{sc} \approx 0$, the mass of chemical in the sc will be within 95% of its steady-state value when $t_{exp} \approx 1.7\,t_{lag,sc}$. When $u_{sc} \neq 0$, even less time is required.

In the second case, dermal absorption through the epi has reached steady state during the exposure (i.e., $\partial C_{sc}/\partial t = \partial C_{ve}/\partial t = 0$). Eqs. 1 and 2 were solved for the conditions specified in Eqs. 4 and 6 through 8 to obtain the following algebraic equations for C_{sc} and C_{ve} at $t = t_{exp}$:

$$\frac{C_{sc}}{K_{sc/v}C_v^o} = \left\{\exp\left(-\frac{6t_{lag,sc}}{t_{t,sc}}\frac{x}{L_{sc}}\right)\left[\frac{\gamma}{BG} - 1 + \exp\left(\frac{\gamma}{G}\frac{6t_{lag,sc}}{t_{t,sc}}\right)\right] - \frac{\gamma}{BG}\exp\left(-\frac{6t_{lag,sc}}{t_{t,sc}}\right)\right\} \Big/ \left\{\frac{\gamma}{BG}\left(1 - \exp\left(-\frac{6t_{lag,sc}}{t_{t,sc}}\right)\right) + \exp\left(\frac{\gamma}{G}\frac{6t_{lag,sc}}{t_{t,sc}}\right) - 1\right\} \tag{11}$$

$$\frac{C_{ve}}{K_{ve/v}C_v^o} = \frac{\exp\left[\frac{\gamma}{\eta_{ve}G}\frac{6t_{lag,sc}}{t_{t,sc}}\left(1 + \eta_{ve} - \frac{x}{L_{sc}}\right)\right] - 1}{\frac{\gamma}{BG}\left[\exp\left(\frac{6t_{lag,sc}}{t_{t,sc}}\right) - 1\right] + \exp\left(\frac{6t_{lag,sc}}{t_{t,sc}}\right)\left[\exp\left(\frac{\gamma}{G}\frac{6t_{lag,sc}}{t_{t,sc}}\right) - 1\right]} \tag{12}$$

Eqs. 11 and 12 include five dimensionless quantities: (1) $t_{t,sc}/t_{lag,sc}$; (2) $\gamma = t_{t,sc}/t_{t,ve}$, the ratio of the sc and ve turnover times; (3) $\eta_{ve} = L_{ve}/L_{sc}$, the ratio of the ve and sc thicknesses; (4) B, the ratio of permeability coefficients of the absorbing chemical in the sc, $P_{sc,v}$, to the ve, $P_{ve,v}$, from the same vehicle,

$$B = \frac{P_{sc,v}}{P_{ve,v}} = \frac{K_{sc/v}D_{sc}/L_{sc}}{K_{ve/v}D_{ve}/L_{ve}} \quad (13)$$

and (5) G, the ratio of the lag time through the sc, $t_{lag,sc}$, to the lag time through the ve, $t_{lag,ve}$,

$$G = \frac{t_{lag,\,sc}}{t_{lag,ve}} = \frac{L_{sc}^2/(6D_{sc})}{L_{ve}^2/(6D_{ve})} \quad (14)$$

The parameters γ and η_{ve} are properties of the skin alone, while $t_{t,sc}/t_{lag,se}$, B, and G will vary with the properties of the absorbing chemical.

The mass of chemical in the epi, M_{epi}, at any time t is calculated by integrating the concentration of absorbing chemical in the sc and ve as follows:

$$M_{epi} = A\int_0^{L_{sc}} C_{sc}\,dx + A\int_{L_{sc}}^{L_{sc}+L_{ve}} C_{ve}dx \quad (15)$$

where A is the surface area exposed to the absorbing chemical. The mass of chemical in the skin at the end of an exposure, M^o_{epi}, is defined as M_{epi} at $t = t_{exp}$. The flux, J, through any position x in the epi (j denotes either the sc or the ve) due to convection and diffusion is calculated as (20):

$$J = -D\frac{\partial C_j}{\partial x} - u_j C_j \quad (16)$$

For nonvolatile chemicals, the mass of chemical removed from the sc by desquamation after an exposure ends, M_{desq}, is calculated by integrating the convective term in Eq. 16 at the outer edge of the sc with respect to time, to yield

$$M_{desq} = u_{sc}A\int_{t_{exp}}^{\infty} C_{scl_{x=0}}\,dt \quad (17)$$

The total mass of chemical absorbed systemically after an exposure ends, M_{abs}, is calculated by integrating the diffusive term in Eq. 16 at the inner edge of the ve with respect to time as follows:

$$M_{abs} = -AD_{ve}\int_{t_{exp}}^{\infty} \left.\frac{\partial C_{ve}}{\partial x}\right|_{x=L_{sc}+L_{ve}} dt \quad (18)$$

When the ve contributes little resistance to mass transport compared to the sc,

$$\left.\frac{\partial C_{ve}}{\partial x}\right|_{x=L_{sc}+L_{ve}} \approx D_{sc}\left.\frac{\partial C_{sc}}{\partial x}\right|_{x=L_{sc}} \quad (19)$$

Chemical in the skin at $t = t_{exp}$, is either systemically absorbed or removed from the skin by desquamation, and thus,

$$M^o_{epi} = M_{abs} + M_{desq} \quad (20)$$

For convenience, we define

$$FA = M_{abs}/M^o_{epi} \quad (21)$$

which is the fraction of chemical in the skin at the end of an exposure that systemically absorbs.

METHODS

The mathematical model described in Eqs. 1–8 was used to quantitatively examine the effect of exposure time, chemical lipophilicity, and epidermal turnover rate on chemical elimination from the skin by desquamation. Eqs. 1 and 2 were solved numerically for $t > t_{exp}$ using the finite difference scheme described in the Appendix. To simplify the computational strategy, the effect of varying t_{exp} was examined when the sc limits the rate of mass transport through the skin (i.e., B is small). Under these circumstances, the ve is an infinite sink (i.e., $C_{ve} = 0$) and model results do not depend on lipophilicity of the absorbing chemical. For this calculation, Eqs. 9 and 10 were used to describe C_{sc} at $t = t_{exp}$.

Since the ve can present a significant barrier to highly lipophilic chemicals, both the sc and ve were included in the general form of the model. The resulting increase in computational complexity was partially reduced by assuming the chemical penetration rate had reached steady state before the exposure ended, allowing Eqs. 11 and 12 to describe C_{sc} and C_{ve} at $t = t_{exp}$. For these calculations, we assumed $\gamma = t_{t,sc}/t_{t,ve} = 0.5$, $\eta_{ve} = L_{ve}/L_{sc} = 10$, and $G = t_{lag,sc}/t_{lag,ve} > 10$, which are all based on typical values for normal human skin (i.e., L_{sc} ~ 10–40 μm, L_{ve} ~ 100–200 μm and $D_{sc}/D_{ve} < 10^{-3}$) (21). When $G > 10$, C_{sc} and C_{ve} are insensitive to changes in G (22). The amount of chemical removed by desquamation was calculated as a function of B and $t_{t,sc}/t_{lag,sc}$.

RESULTS AND DISCUSSION

Figure 1 shows FA as a function of the sc turnover time for small and large values of t_{exp} (i.e., relative to the time required to reach steady state) assuming the sc alone limits dermal absorption (i.e., B < about 0.1). The upper axis of Fig. 1 specifies values of $t_{lag,sc}$ for $t_{t,sc} = 14$ days (i.e., typical for healthy human skin). As $t_{lag,sc}$ increases relative to $t_{t,sc}$, desquamation reduces the amount of dermal absorption (i.e., FA approaches 0). If $t_{lag,sc} < 0.05\ t_{t,sc}$, FA > 0.8. This corresponds to $t_{lag,sc}$ < about 17 hours for $t_{t,sc} = 14$ days. Many chemicals penetrate the sc with lag times less than 17 hours. For example, $t_{lag,sc}$ for benzoic acid and 4-cyanophenol (with molecular weight, MW, of 122.1 and 119.4, respectively) are less than 1 hour (23,24). Lag times are affected by molecular size and larger molecules will have longer $t_{lag,sc}$ values. One would expect that for nonvolatile chemicals that are not highly lipophilic (i.e., with an octanol–water partition coefficient, $K_{o/w}$, < about 4) or large (i.e., MW < about 350 Da), almost all of the chemical in the sc at the end of an exposure would eventually be absorbed systemically.

Although FA increased with increasing $t_{exp}/t_{lag,sc}$, the effect is relatively minor (Fig. 1). This is because at short exposure times, a chemical has penetrated only a short distance into the sc. Consequently, the concentration gradient (i.e., the driving force for mass transfer) is larger than at longer exposure times. As a result, the concentration of the absorbing chemical in the outer layers of the sc is reduced more quickly by diffusion into the sc following a short exposure compared to a longer exposure.

Figure 1 was developed assuming that the sc is the only significant resistance to mass transfer across skin. However, the conclusion that the duration of the exposure affects FA minimally should apply even when the ve contributes signifi-

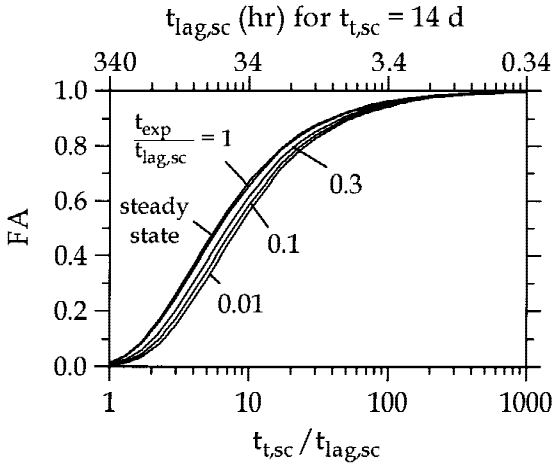

Fig. 1. FA as a function of $t_{t,sc}/t_{lag,sc}$ for varying exposure times calculated assuming the ve adds no significant resistance to dermal absorption.

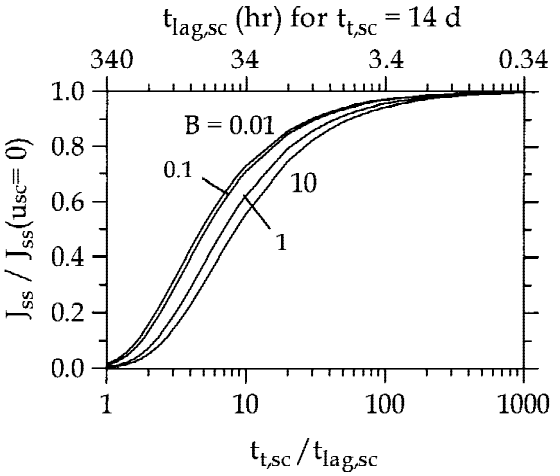

Fig. 2. Steady-state flux through the epi as a function of $t_{t,sc}/t_{lag,sc}$ for varying values of B.

cantly to the skin's barrier (i.e., when B is not small). At exposure times less than the time required to reach steady state, the absorbing chemical has not penetrated far enough into the sc to be affected by the resistance from the ve (i.e., M^o_{epi} is not affected by B when $t_{exp} < t_{lag,sc}$). Furthermore, M_{abs} is less sensitive to t_{exp} when B is large because the fraction of m_{epi} available for elimination by desquamation (i.e., in the inside layer of the scl decreases with increasing B. Consequently, we examined the effect of B assuming that the exposure time was long enough to establish steady-state concentration profiles, recognizing that these steady-state results will represent approximately unsteady-state conditions.

Figure 2 shows the effect of epidermal turnover on steady-state flux through the epi, J_{ss}, for B values varying from 0.01 (i.e., the sc entirely controls the rate of dermal penetration) to 10 (i.e., the ve entirely controls the rate of dermal penetration). In Fig. 2, J_{ss} is normalized by the steady-state flux that would occur if there were no epidermal turnover:

$$J_{ss}\,(u_{sc} = 0) = P_{sc,v}C^o_v/(B + 1) \qquad (22)$$

which was derived by substituting Eq. 11 into Eq. 16 and assuming that $u_{sc} = 0$. It is clear from Fig. 2 that epi turnover does reduce steady-state flux. However, the B parameter does not significantly affect the role of epi turnover in reducing J_{ss} compared to J_{ss} for $u_{sc} = 0$, as indicated by the narrow spread between curves for B = 0.01 to 10.

Once the exposure ends, the B parameter plays a larger role as illustrated in Fig. 3, which shows FA plotted as a function of $t_{t,sc}/t_{lag,sc}$ for varying values of B. As B increases, the ve becomes a more significant mass transfer barrier, preventing chemical entrance to systemic circulation from the sc. Thus, the effect of epi turnover on percutaneous penetration is greater when the ve is a significant barrier (i.e., when B is large). For example, if the barrier contributions of the sc and the ve are the same (i.e., B = 1), 60% of the chemical in the skin systemically absorbs when $t_{lag,sc}$ is about 5% of $t_{t,sc}$. For the same situation, only about 20% systemically absorbs if the ve permeability coefficient is one-tenth of the sc permeability coefficient (i.e., B = 10). The heavy dashed curve in Fig. 3 is the steady-state curve from Fig. 1, which was calculated assuming the sc was the only barrier to dermal absorption (i.e., $C_{ve} \sim 0$). As expected, this curve coincides with curves calculated assuming B < 0.1.

It is evident from both Figs. 1 and 3 that significant amounts of chemical can be removed from the skin by desquamation if $t_{t,sc}$ is short relative to $t_{lag,sc}$. This suggests that chemical removal by desquamation could be more significant in diseased skin involving hyperproliferation (e.g., psoriasis). However, this might not be the case if the barrier function of the sc is reduced as this would simultaneously decrease $t_{lag,sc}$.

Figure 4, showing combinations of B and $t_{lag,sc}$ that produce various values of FA, can be used to identify those situations in which desquamation may be an important mechanism for eliminating chemical from the skin after an exposure ends. However, to apply the results in Figs. 1 through 4 to a specific chemical requires an estimate for B and $t_{lag,sc}$, which is considered next.

Permeability coefficients in both the sc and ve have been measured for only a few chemicals, and there are only a few experimental values for B (2). Based on differences in the physical characteristics of the sc and the ve, B should vary with a chemical's lipophilic character, which can be repre-

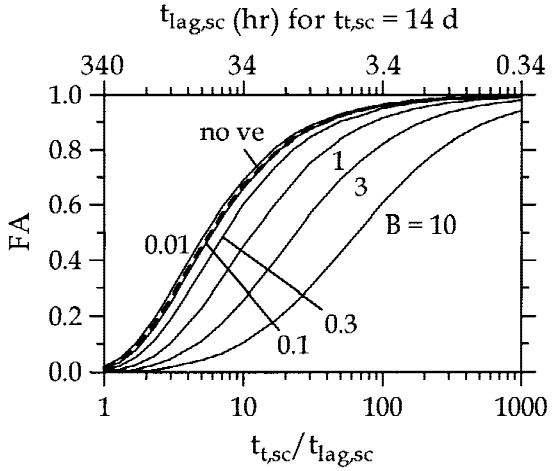

Fig. 3. FA as a function of $t_{t,sc}/t_{lag,sc}$ for varying values of B calculated assuming that the exposure ended after steady state was achieved.

sented approximately by $K_{o/w}$. In addition, the effect of molecular size is likely to be different in the sc and ve, causing B to depend on molecular size as well. Bunge and Cleek (25) proposed that B could be estimated as follows:

$$B = 0.00061\sqrt{MW}10^{-0.006MW}\,K_{o/w}^{0.74} \quad (23)$$

This equation was developed by estimating $P_{sc,v}$ using the correlation proposed by Potts and Guy (3) as reported by Bunge *et al.* (26) and by estimating $P_{ve,v}$ from the following assumptions: (1) $L_{ve} = 100$ μm, (2) $D_{ve} = 10^{-6}$ cm^2/s for a chemical with MW = 50 Da and decreases as $1/\sqrt{MW}$, and (3) the chemical's solubility in the ve is the same as in water (i.e., $K_{ve/w} = 1$). Although Eq. 23 was derived for a water vehicle, the B parameter should be independent of the vehicle if it does not alter skin properties.

While experimental values for lag times are reported for many chemicals, these must be used cautiously for assessing the effect of epidermal turnover. Experimentally determined values of lag time, usually derived from *in vitro* diffusion cell measurements, are notoriously variable. In addition, skin samples used in diffusion cell experiments often include the ve and part or all of the dermis. The difference between the experimental lag time and $t_{lag,sc}$ could be relatively small if there was no dermis in the experiment, but could be larger than $t_{lag,sc}$, the quantity required to use Figs. 1 through 4, if the entire dermis was present. Lacking experimental data, the following equation can be used to provide a preliminary estimate for $t_{lag,sc}$.

$$t_{lag,sc}[\text{hrs}] = 0.17(10^{0.006\ MW}) \quad (24)$$

which was developed using (25):

$$\log(D_{sc}/L_{sc},\text{cm/hr}) = -2.80 - 0.0060\ (MW) \quad (25)$$

and assuming L_{sc} is 16 μm, which is consistent with reported measurements (27) for the human forearm.

Figure 5 presents $t_{lag,sc}$ estimated using Eq. 24. Figure 5 also shows the effects of MW and $\log K_{o/w}$ on B when calculated using Eq. 23. The $\log K_{o/w}$ for absorbing chemicals must be > about 3.5 (and > about 4 for chemicals with MW > 200 Da) to produce B values of 1 or larger. Because $t_{lag,sc}$ varies exponetially with MW, it increases dramatically when MW > about 350 Da. By combining the information in Figs. 4 and 5, we estimate that desquamation might significantly affect FA

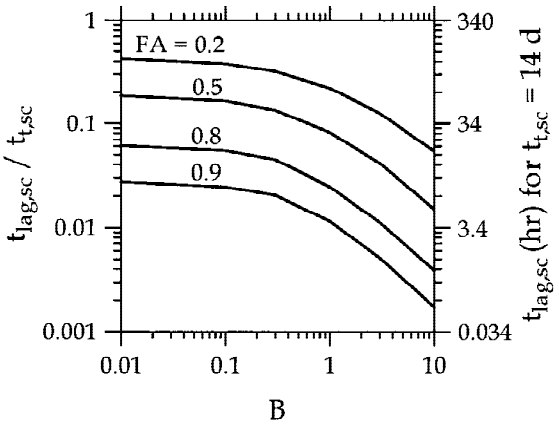

Fig. 4. Values of FA corresponding to specific combinations of $t_{lag,sc}/t_{t,sc}$ and B.

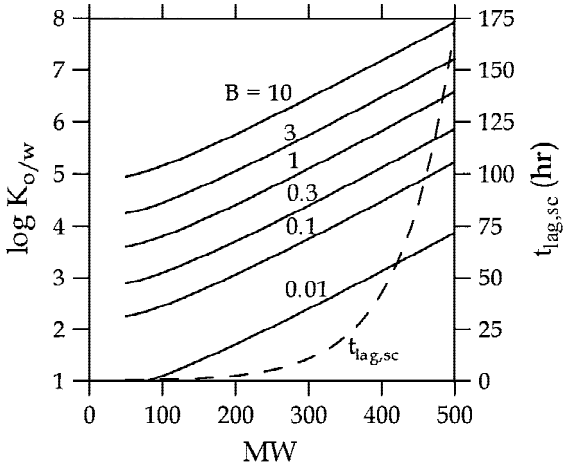

Fig. 5. B parameter as function of MW and $\log K_{o/w}$ (solid curves) and $t_{lag,sc}$ as a function of MW (dashed curve).

when $\log K_{o/w}$ > about 4 or MW > about 350 Da. Chemicals meeting these criteria include several steroids and retinoids as well as highly lipophilic environmental contaminants like benzo[a]pyrene. There is some evidence that *in vivo* values of $t_{lag,sc}$ are shorter than reported *in vitro* (28). Consequently, MW may need to be 400 Da or more for desquamation to reduce FA. However, because the models derived here neglect diffusion through appendages (e.g., sweat ducts and hair follicles), the computed results should not be applied to extremely large compounds (MW > approximately 500 Da), for which absorption through the sc is likely to be small relative to absorption through the appendages.

CONCLUSIONS

Except for highly lipophilic or large MW chemicals, nearly all of the chemical in the epi at the end of an exposure will systemically absorb (i.e., FA ~ 1), regardless of the length of time the skin was exposed to the chemical. Only for chemicals with large values of MW (>about 350 Da) or $\log K_{o/w}$ (> approximately 4 for most chemicals) will epidermal turnover reduce FA significantly.

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REFERENCES

1. R. J. Scheuplein. Permeability of the skin: A review of major concepts. *Curr. Probl. Dermatol* **7**:172–186 (1978).
2. B. Vecchia. *Estimating the Dermally Absorbed Dose from Chemical Exposure: Data Analysis, Parameter Estimation, and Sensitivity to Parameter Uncertainties.* M.S. Thesis, Colorado School of Mines, Golden, CO (1997).
3. R. O. Potts and R. H. Guy. Predicting skin permeability. *Pharm. Res.* **9:**663–669 (1992).
4. US EPA. *Dermal Exposure Assessment: Principles and Applica-*

tions, EPA/600/8-91/011B, Exposure Assessment Group, Office of Health and Environmental Assessment, Washington, DC, (1992).
5. R. J. Scheuplein and R. L. Bronaugh. Percutaneous absorption. In L. A. Goldsmith (ed.) *Biochemistry and Physiology of the Skin,* Vol. II, Oxford University Press, New York, 1983, pp. 1255–1295.
6. H. Schaefer, A. Zesch, and G. Stuttgen, *Skin Permeability,* Springer-Verlag, Berlin, 1982.
7. T. R. Auton, D. R. Westhead, B. H. Woolen, R. C. Scott, and M. F. Wilks. A physiologically based mathematical model of dermal absorption in man. *Hum. Exp. Toxicol.* **13:**51–60 (1994).
8. A. Y. Finlay, R. J. Marshall, and R. Marks. A fluorescence photographic photometric technique to assess stratum corneum turnover rate and barrier function *in vivo. Br. J. Dermatol.* **107:**35–42 (1982).
9. D. Roberts and R. Marks. The determination of regional and age variations in the rate of desquamation: A comparison of four techniques. *J. Invest. Dermatol.* **74:**13–16 (1980).
10. G. L. Grove. Physiologic changes in older skin. *Dermatol. Clin.* **4:**425–432 (1986).
11. M. Takahashi, Y. Machida, and R. Marks. Measurement of turnover time of stratum corneum using dansyl chloride fluorescence. *J. Soc. Cosmet. Chem.* **38:**321–331 (1987).
12. K. M. Halprin. Epidermal "turnover time"—a re-examination. *Br. J. Dermatol.* **86:**14–19 (1972).
13. P. R. Bergstresser and J. R. Taylor. Epidermal 'turnover time'—a new examination. *Br. J. Dermatol.* **96:**503–509 (1977).
14. H. Iizuka. Epidermal turnover time. *J. Dermatol. Sci.* **8:**215–217 (1994).
15. G. D. Weinstein, J. L. McCullough, and P. Ross. Cell proliferation in normal epidermis. *J. Invest. Dermatol.* **82:**623–628 (1984).
16. A. M. Kligman. The biology of the stratum corneum. In W. Montagna and W. C. Lobitz (eds.), *The Epidermis,* Academic Press, New York and London, 1964, pp. 387–433.
17. G. D. Silcox, G. E. Parry, A. L. Bunge, L. K. Pershing, and D. W. Pershing. Percutaneous absorption of benzoic acid across human skin. 2. Prediction of an in vivo, skin-flap system using in vitro parameters. *Pharm. Res.* **7:**352–358 (1990).
18. M. B. Reddy, K. D. McCarley, and A. L. Bunge. Physiologically relevant one-compartment pharmacokinetic models for skin. 2. Comparison of models when combined with a systemic pharmacokinetic model. *J. Pharm. Sci.* **87:**482–490 (1998).
19. R. L. Cleek and A. L. Bunge. A new method for estimating dermal absorption from chemical exposure. 1. General approach. *Pharm. Res.* **10:**497–506 (1993).
20. E. L. Cussler. *Diffusion-Mass Transfer in Fluid Systems,* Cambridge University Press, Cambridge (1997).
21. R. J. Scheuplein. Properties of the skin as a membrane. *Adv. Biol. Skin.* **12:** 125–152 (1972).
22. R. J. Scheuplein. Permeability of the skin: A review of major concepts and some new developments. *J. Invest. Dermatol.* **67:**672–676 (1976).
23. G. E. Parry, A. L. Bunge, G. D. Silcox, L. K. Pershing, and D. W. Pershing. Percutaneous absorption across human skin. I. *In vitro* experiments and mathematical modeling. *Pharm. Res.* **7:**230–236 (1990).
24. F. Pirot, Y. N. Kalia, A. L. Stinchcomb, G. Keating, A. L. Bunge, and R. H. Guy. Characterization of the permeability barrier of human skin *in vivo. Proc. Natl. Acad. Sci. USA* **94:**1562–1567 (1997).
25. A. L. Bunge and R. L. Cleek. A new method for estimating dermal absorption from chemical exposure. 2. Effect of molecular weight and octanol-water partitioning. *Pharm. Res.* **12:**88–95 (1995).
26. A. L. Bunge, G. L. Flynn, and R. H. Guy. Predictive model for dermal exposure assessment. In R. Wang (ed.) *Water Contamination and Health: Integration of Exposure Assessment Toxicology, and Risk Assessment,* Marcel Dekker, New York, 1994, pp. 347–373.
27. Y. N. Kalia, F. Pirot, and R. H. Guy. Homogenous transport in a heterogeneous membrane: Water diffusion across human stratum corneum *in vivo. Biophys. J.* **71:**2692–2700 (1996).
28. T. S. Poet, K. D. Thrall, R. A. Corley, X. Hui, J. A. Edwards, K. K. Weitz, H. I. Maibach, and R. C. Wester. 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 (2000).

APPENDIX

The sc and ve were split into N_{sc} and N_{ve} nodes, respectively. The spatial derivatives were represented by the following finite difference formulas that are second-order accurate in x:

$$\left.\frac{\partial^2 C_j}{\partial x^2}\right|_i = \frac{C_{j,i-1} - 2C_{j,i} + C_{j,i+1}}{(\Delta x_j)^2} \quad \text{(A1)}$$

$$\left.\frac{\partial C_j}{\partial x}\right|_i = \frac{C_{j,i+1} - C_{j,i-1}}{2\Delta x_j} \quad \text{(A2)}$$

$$\left.\frac{\partial C_j}{\partial x}\right|_i = \frac{-3C_{j,i} + 4C_{j,i+1} - C_{j,i+2}}{2\Delta x_j} \quad \text{(A3)}$$

$$\left.\frac{\partial C_j}{\partial x}\right|_i = \frac{C_{j,i-2} - 4C_{j,i-1} + 3C_{j,i}}{2\Delta x_j} \quad \text{(A4)}$$

$$\Delta x_j = L_j/(N_j - 1) \quad \text{(A5)}$$

where i designates a node and j designates either the sc or ve. Eqs. A1 and A2 were used with Eqs. 1 and 2, Eq. A3 was used with Eq. 5 and Eq. 7 in the sc, and Eq. A4 was used with Eq. 7 in the ve. The resulting system of ordinary differential equations were solved using a FORTRAN computer program with the IVPAG routine from the IMSL library, which uses Adams–Moulton's method to solve initial-value ordinary differential equation problems.

The accuracy of the numerical solution was checked by demonstrating that results were unchanged with increases in the number of nodes. Also, the sum of the calculated mass of chemical in the epi, removed by desquamation, and absorbed systemically was within 0.3% of the mass of chemical in the epi at $t = t_{exp}$ (i.e., $|1 - (M_{epi} + M_{abs} + M_{desq})/M^{o}_{epi}| < 0.003$).