A New Method for Estimating Dermal Absorption from Chemical Exposure: 2. Effect of Molecular Weight and Octanol-Water Partitioning

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A new method for estimating dermal absorption including the effects of exposure time and chemistry is described generally in Part 1 of this series. This method accounts for the larger absorption rates during the initial exposure period as well as the hydrophilic barrier which the viable epidermis presents to lipophilic chemicals. A key parameter in this procedure, the ratio of the stratum corneum and epidermis permeabilities (B) depends on molecular weight and octanol-water partitioning. Several approaches for approximating B and its affect on the dermal absorption prediction are discussed here. Generally, the parameter B is only important for highly lipophilic chemicals which also have relatively small molecular weights. When B is important, the recommended prediction for B is based on the Potts and Guy correlation for human stratum corneum permeability.

KEY WORDS: dermal absorption; exposure assessment; percutaneous absorption; mathematical models; stratum corneum; permeability; octanol-water partitioning.

1. BACKGROUND

Estimates of systemic chemical exposure from dermal absorption should be based on the total mass absorbed including chemical that has entered but not yet left the stratum corneum (SC). Chemicals absorb into the SC more rapidly during short exposure times slowing over longer exposure periods to eventually reach a constant absorption rate, characterized by the steady-state permeability. From a given vehicle v, the steady-state permeability (P_v) for intact skin including both the SC and viable epidermis (EPI) depends on permeabilities for each:

$$\frac{1}{P_v} = \frac{1}{P_{cv}} + \frac{1}{P_{ev}} \tag{1}$$

where P_{cv} and P_{ev} represent the individual steady-state permeabilities for the SC and EPI, respectively. Assuming steady-state and local equilibrium between the vehicle and the SC, the SC and the EPI, and the EPI and the receptor fluid, it is easily shown that P_{cv} and P_{ev} defined as:

$$P_{cv} = \frac{K_{cv}D_c}{L_c} \tag{2}$$

$$P_{ev} = \frac{K_{ev}D_e}{L_e} \tag{3}$$

depend on the SC and EPI equilibrium partition coefficients (K_{cv} and K_{ev}), diffusion coefficients (D_c and D_e), and thicknesses (L_c and L_e). The steady-state permeability across the SC-EPI composite is then related to the steady-state SC permeability,

$$P_v = \frac{P_{cv}}{1 + B} \tag{4}$$

where the parameter B, defined as

$$B = \frac{P_{cv}}{P_{ev}} = \frac{D_cL_eK_{ce}}{D_eL_c} \tag{5}$$

measures the relative permeability of the SC to the EPI and is independent of the vehicle provided that the vehicle has not altered the physicochemical properties of either the SC or EPI. Large values of B correspond to highly lipophilic compounds while highly hydrophilic compounds give rise to small values for B. For less lipophilic compounds (i.e., small B), the overall skin permeability (P_v) is represented essentially by the permeability across only the SC (P_{cv}). For more lipophilic compounds (i.e., B values larger than 1), the overall skin permeability (P_v) will be significantly less than the permeability across the SC because the relatively hydrophilic EPI chokes the flux of chemical leaving the SC.

In addition to the SC-EPI permeability ratio B, the ratio of the SC and EPI lag times defined as G,

$$G = \frac{t_{lag,c}}{t_{lag,e}} = \frac{L_c^2}{6D_c}\frac{6D_e}{L_e^2} = \frac{L_c^2D_e}{L_e^2D_c} \tag{6}$$

appears in the exact mathematical description of dermal absorption into the SC-EPI composite membrane. Physically, G represents the time for a chemical to diffuse across the SC relative to the time to diffuse across the EPI. Based on literature values for D_c, D_e, L_c and L_e, G is 10 or larger for skin with undamaged SC (1).

Figure 1 shows the normalized mass of chemical absorbed per unit of exposed area [$M_{in}/(C_v^oK_{cv}AL_c)$] as a function of the dimensionless exposure time ($\tau = t_{exp}D_c/L_c^2$) for the SC-EPI composite membrane, assuming the vehicle concentration remains constant at C_v^o, the initial chemical concentrations in the skin layers were zero, the chemical concentration in the body system remains at zero during the entire exposure event, and G is large. By plotting M_{in} normalized with respect to ($C_v^oK_{cv}AL_c$) against t_{exp} normalized with respect to D_c/L_c^2, we can compare chemicals with different concentrations, exposure areas, or physicochemical parameters (K_{cv}, D_c, and L_c) on an equal basis.

Two distinctly different regions are evident in Figure 1. For short exposure times, the normalized cumulative mass absorbed is independent of B and nonlinear in time. For longer exposure times, the normalized cumulative mass absorbed depends on B and is linear in time. Limiting conditions are reached for either highly lipophilic compounds ($B > 100$) or relatively hydrophilic compounds ($B < 0.01$).

In a previous paper (1), a simple method was described for estimating the cumulative mass absorption curves shown in Figure 1. For short exposure times (i.e., $t_{exp} < t^*$),

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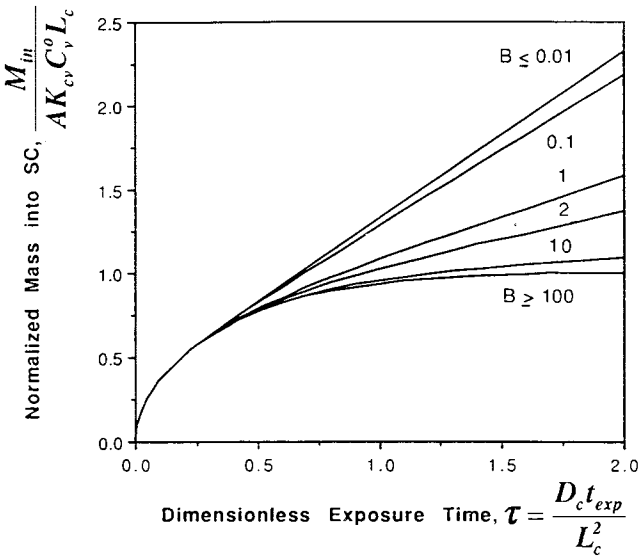

Figure 1. Normalized cumulative mass entering the stratum corneum $[M_{in}/(AL_cK_{cv}C_v^o)]$ as a function of dimensionless t_{exp} when the viable epidermis is present (from (1)).

$$\frac{M_{in}}{A} = 2C_v^o K_{cv}\sqrt{\frac{D_c t_{exp}}{\pi}} \tag{7}$$

the chemical only penetrates the SC and is not affected by the presence of the EPI as indicated by the absence of B in Eqn. (7). For longer exposure times (i.e., $t_{exp} > t^*$), an EPI affected steady-state is reached which is described by (2,3):

$$\frac{M_{in}}{A} = \frac{C_v^o K_{cv} L_c}{1+B}\left[\tau + \frac{G(1+3B)+B(1+3BG)}{3G(1+B)}\right] \tag{8}$$

where τ is the dimensionless exposure time, $t_{exp}D_c/L_c^2$ and t^* is the transition time for changing from Eqn. (7) to Eqn. (8). For large values of G, Eqn. (8) simplifies to give:

$$\frac{M_{in}}{A} = \frac{C_v^o K_{cv} L_c}{1+B}\left[\tau + \frac{1+3B+3B^2}{3(1+B)}\right] \tag{9}$$

which no longer depends on G. We show later that Eqn. (9) accurately represents Eqn. (8) when G is 10 or larger.

The limiting conditions of small and large B are evident in Eqn. (9). When B is less than 0.01, the cumulative mass absorbed is no longer a function of B. As B becomes large, the EPI permeability becomes so small relative to the SC permeability that the transfer of mass from the SC is almost entirely choked. In this situation, chemical is absorbed into the SC until it is almost completely saturated (for $t < t^*$) and then the rate of continued absorption becomes nearly zero (for $t > t^*$). For B values between 0.01 and 100, both the EPI and SC permeabilities affect the cumulative mass absorbed when $t > t^*$.

As expected from Figure 1, recommended values for the transition time t^* depend on B: For $B \leq 0.6$,

$$t^* = \frac{0.4L_c^2}{D_c} \tag{10}$$

For $B > 0.6$,

$$t^* = (b - \sqrt{b^2 - c^2})\frac{L_c^2}{D_c} \tag{11}$$

where b and c are defined as:

$$b = \frac{2}{\pi}(1+B)^2 - c \tag{12}$$

$$c = \frac{1+3B+3B^2}{3(1+B)} \tag{13}$$

Physically, the transition time t^* approximately represents the time required to reach steady state.

Equations (7) and (9) through (13) require that D_c, K_{cv}, L_c and B be known. Generally, experiments on human skin have measured the C or combined SC-EPI (and sometimes dermis) permeability, but not the separate components. Cleek and Bunge (1) proposed dividing the Potts and Guy correlation (4) for steady-state SC permeability from water,

$$\log_{10}P_{cw}\,(\text{cm/s}) = -6.36(\pm 0.18) - 6.0(\pm 0.6)10^{-3}\,(\text{MW}) + 0.74(\pm 0.07)\log_{10}K_{ow} \tag{14}$$

into parts separately representing D_c/L_c and K_{cw} as follows:

$$\log_{10}(D_c/L_c,\ \text{cm/s}) = -6.36 - 0.0060(\text{MW}) \tag{15}$$

$$\log_{10}K_{cw} = 0.74\log_{10}K_{ow} \tag{16}$$

This division is supported by the semi-theoretical development of the Potts and Guy correlation as well as a number of SC-water partition coefficient experiments (5–7) which are compared to Eqn. (16) in Part 1 of this series (1). Specifically, Eqns. (15) and (16) assume that the K_{ow} dependence in the SC permeability is entirely from the SC-water partition coefficient, and that there is no additional MW dependence in the partition coefficient beyond that already reflected in K_{ow} itself. This approach for estimating D_c/L_c and K_{cw} is a reasonable starting place which may need modification based on future evaluations of existing and new experimental data for SC partitioning and diffusivities.

Estimating B presents an even greater challenge since there are almost no data available for EPI permeability. Although experimental protocols exist for removing the EPI leaving an intact SC, techniques for removing the SC without damaging the EPI do not exist. Consequently, the few reported EPI permeability values were estimated by subtracting a measured SC-only permeability (P_{cv}) from the SC-EPI composite permeability (P_v). However, as indicated in Eqn. (4), P_{cv} and P_v are nearly identical except for relatively lipophilic compounds when B is no longer small. Unfortunately, reliable steady-state permeability measurements are difficult for such highly lipophilic compounds. Therefore, the small number of EPI permeabilities which are reported are of questionable quality and certainly far too limited to draw conclusions on the effects of parameters such as K_{ow} or MW. A more thorough discussion of the factors contributing to B and the impact on resulting dermal absorption predictions is presented next.

2. THEORY

As indicated in Eqn. (5), the parameter B measures the relative magnitude of the SC to EPI permeability which in

turn depend on the SC to EPI partition coefficient (K_{ce}), and the ratios of the SC to EPI diffusivities (D_c/D_e) and thicknesses (L_e/L_c). Tables 1 through 4 summarize four different methods for estimating B following two distinctly different approaches. We can calculate B if P_{cv} and P_{ev} are both known, or if reasonable approximations for all the contributing parameters (D_c, D_e, L_c, L_e, and K_{ce}) are available. Limited literature values do exist for L_e/L_c and D_e/D_c. Scheuplein and Blank (8) suggest that the EPI is usually 5 to 10 times thicker than the SC, and D_e is about and 10^4 times larger than D_c. Tojo and Lee (9) report average values for D_e and D_c for drugs with MW between 170 and 490 were 9.5×10^{-8} cm^2/s and 6.4×10^{-11} cm^2/s, respectively.

Tables 1 and 2 summarize values and assumptions for two methods calculating B using estimates for the individual contributing parameters. From Eqn. (15) we calculate that D_c/L_c is 2.5×10^{-7} cm/s for very small molecules (i.e., MW is zero). In addition, assuming that the EPI is 10^{-2} cm thick and has a diffusivity about one order of magnitude smaller than water (i.e., $D_e = 10^{-6}$ cm^2/s), then $D_e/L_e = 10^{-4}$ cm/s. The ratio of D_c/L_c to D_e/L_e is then 1/230. If we assume that this ratio is constant for all chemicals, we have assumed that the effect of molecular size on diffusivity is the same in both the SC and EPI. The validity of this assumption will be discussed later.

To calculate B, we still need an estimate for the SC-EPI partition coefficient K_{ce}, which is a problem because no direct experimental values for K_{ce} exist, although a relationship between K_{ce} and K_{ow} is reasonable. Based on pharmacokinetic analysis of in vivo percutaneous absorption data, Guy and Hadgraft (10–12) inferred that K_{ce} is approximately $K_{ow}/5$. Combining this with D_c/L_c and D_e/L_e values already given suggest that B should be about $K_{ow}/1{,}150$.

However, this relationship between K_{ce} and K_{ow} is not consistent with the functional form deduced by Potts and Guy (4) and many others for estimating the steady-state SC permeability P_{cv} and the SC-vehicle partition coefficients (K_{cv}) knowing K_{ow}. For example, experimental SC-water partition coefficients K_{cw} for a number of chemicals are reasonably represented by (1,7,13–15):

$$K_{cw} = \alpha_c K_{ow}^{\gamma_c} \tag{17}$$

where α_c and γ_c are constants. Typically, α_c is roughly 1 and γ_c is between about 0.6 and 0.8. Physically, the fact that γ_c is between zero and one means that the SC is more lipophilic than water but less lipophilic than octanol.

If we assume that K_{ew} should be represented by a similar form, then the SC-EPI partition coefficient K_{ce} should depend on K_{ow} raised to the power ($\gamma_c - \gamma_e$) as shown below:

$$K_{ce} = \frac{K_{cw}}{K_{ew}} = \frac{\alpha_c}{\alpha_e} K_{ow}^{\gamma_c - \gamma_e} \tag{18}$$

Equation (18) utilizes the fact that K_{ce} itself does not vary with vehicle (provided the vehicle does not alter the physicochemical character of the SC or EPI), although it is the product of partition coefficients of the SC and EPI with respect to any common vehicle.

If the solvent properties of the EPI behaved exactly as water, γ_e would be exactly zero. In this case, $\gamma_c - \gamma_e$ would equal γ_c. In fact, the EPI is probably somewhat more lipophilic than water and γ_e would then be larger than zero, but certainly smaller than γ_c for the much more lipophilic SC. Guy et al. (16) fit *in vivo* dermal absorption data from 12 chemicals (aspirin, benzoic acid, benzyl nicotinate, caffeine, chloramphenicol, colchicine, dinitrochlorobenzene, diethyltoluamide, malathion, methyl nicotinate, nitrobenzene and salicylic acid) with a pharmacokinetic model from which apparent K_{ce} could be extracted. They showed that these fitted K_{ce} values were reasonably represented by:

$$K_{ce} = K_{ow}^{0.36} \tag{19}$$

which suggests that γ_e is 0.38 if γ_c is 0.74. Although this functional form is consistent with Eqn. (18), we emphasize that Eqn. (19) was inferred indirectly from in vivo data and that the data scatter was not small meaning we must have limited confidence in the magnitude of the power.

In Method Two for estimating B, we have assumed that K_{ce} is described by Eqn. (18), where α_c/α_e is one and γ_e is approximately zero. Taking γ_e as zero is equivalent to assuming that solvency for all chemicals in the EPI is essentially the same as in water.

As already mentioned, Methods 1 and 2 for estimating B assume that the effect of molecular size on diffusivity is the same in both the SC and EPI. That diffusivity varies with molecular size is well established, although the functional

Table 1. Estimating B—Method One

$$B = \frac{K_{ce} D_c L_e}{D_e L_c} = \frac{K_{ow}}{1150}$$

Assumes MW dependence is the same in both SC and EPI

$\frac{D_c}{L_c} = 4.4 \times 10^{-7}$ cm/s	From Potts and Guy correlation for small molecules
$\frac{D_e}{L_e} = 10^{-4}$ cm/s	Assumes $D_e = 10^{-6}$ cm^2/s and $L_e = 10^{-2}$ cm
$K_{ce} = K_{ow}/5$	Guy & Hadgraft, J. Pham. Sci., 74: 1016–1018 (1985)

Table 2. Estimating B—Method Two

$$B = \frac{K_{ce} D_c L_e}{D_e L_c} = \frac{K_{ow}^{0.74}}{230}$$

Assumes MW dependence is the same in both SC and EPI

$\frac{D_c}{L_c} = 4.4 \times 10^{-7}$ cm/s	From Potts and Guy correlation for small molecules
$\frac{D_e}{L_e} = 10^{-4}$ cm/s	Assumes $D_e = 10^{-6}$ cm^2/s and $L_e = 10^{-2}$ cm
$K_{ce} = K_{ow}^{0.74}$	Assumes that partitioning between the SC and EPI is the same as between the SC and water

form varies depending on the size of the diffusing solute molecule and the size and configuration of the solvent molecules. For example, solute diffusion through a more rigid molecular matrix, like a polymeric membrane, which acts as a molecular sieve is reasonably represented by an exponential function of the molecule size (17–20). That is,

$$D = D_o e^{-\beta' V} \cong D_o e^{-\beta(MW)} \quad (20)$$

where V is the molar volume of the solute, $1/\beta'$ physically represents the effective size of the molecular size openings in the membrane matrix, and D_o is the diffusivity of a molecule of size zero. Molecules which are much smaller than $1/\beta'$ diffuse almost unhindered, while molecules with sizes much larger than $1/\beta'$ are almost entirely blocked. The molar volume of the solute will be approximately its molecular weight divided by its density. Since liquid density of most compounds do not vary too greatly, molecular weight (MW) reasonably substitutes for molar volume as indicated in Eqn. (20).

In liquid or liquid-like phases, solute diffusion is inversely proportional to MW raised to a power ω which depends on the relative sizes of the solute and solvent molecules. For example, assuming that the solute is dilute and the solvent is a continuum (i.e., solvent molecules are much smaller than the solute), the semi-theoretical Stokes-Einstein equation predicts $\omega = 1/3$. When solute and solvent molecules have comparable sizes, kinetic energy theory predicts ω should be 1/2. The empirically derived Wilke-Chang correlation assigns 0.6 to ω (21).

The SC and EPI are known to be quite different structurally. An extensive body of research supports the view that SC diffusion is primarily through the multilamellar, intercellular lipid domains which are tightly aggregated pseudocrystalline structures at body temperature (22,23). In contrast, the EPI is comparably hydrous mass with quasi-liquid like properties. Consequently, we might anticipate that diffusivities in the SC and EPI may depend differently on MW. Differences of this sort are not represented by Methods 1 or 2 for estimating B.

The second approach for estimating B is to use values for the SC and EPI permeabilities. For the steady-state SC permeability from water, we use the correlation proposed by Potts and Guy (4), Eqn. (14), which assumes that diffusion through the SC varies exponentially as described by Eqn. (20) with β equal to 0.014. To proceed further, estimates must be made for P_{ew}. If, as for Method 2, we assume that chemical solvency in the EPI is reasonably represented by solvency in water, then $K_{ew} = 1$. Also consistent with Methods 1 and 2, we assume that the EPI is 10^{-2} cm thick and that the EPI diffusivity is one order of magnitude smaller than water (i.e., $D_e = 10^{-6}$ cm^2/s) and does not vary with MW. Table 3 summarizes this case, Method 3, concluding that $B = P_{cw}/(0.36$ cm/h).

Selecting D_e as 10^{-6} is arbitrary, although not unreasonable for a gelatinous aqueous phase. However, the assumption of no molecular weight dependence is not only unreasonable, but also inconsistent with the estimate of P_{cw} which does include a MW dependence. Therefore, based on theory and empirical observations described earlier, Method 4 (Table 4) assumes that D_e decreases with the square root of MW. In this case, we arbitrarily choose that D_e is 10^{-6} cm^2/s for a chemical with a MW of 50. However, this assumption is consistent with Tojo and Lee (9) who report an average D_e of 10^{-7} for drugs with MW between 170 and 490.

Table 3. Estimating B—Method Three

$$B = \frac{P_{cv}}{P_{ev}} = \frac{P_{cw}}{P_{ew}} = \frac{P_{cw}}{0.36 \text{ cm/h}}$$

Assumes MW dependence is $e^{-\beta(MW)}$ for SC and no MW dependence for EPI

$$\log_{10} P_{cw} = -2.8 - 6.0 \times 10^{-3} (MW) + 0.74 \log_{10} K_{ow}, \text{ cm/h}$$

$P_{ew} = K_{ew} D_e / L_e$

$K_{ew} = 1$ — Assumes EPI behaves essentially as water

$L_e = 10^{-2}$ cm

$D_e = 10^{-6}$ cm^2/s — Assumes no molecular weight dependence

Assuming that D_e is proportional to $1/\sqrt{MW}$ predicts that D_e becomes infinitely large for very small molecules (i.e., MW = 0). By contrast, the exponential dependence on MW for D_c predicts that D_c reaches a constant for very small molecules. As a consequence, for small molecules ($0 < MW < 36$), B increases as MW increases to a maximum. For MW larger than 36, B values decrease with further increases in MW because D_c decreases more strongly with MW than does D_e. The MW corresponding to the maximum value of B ($MW_{maxB} = 36$) is easily determined by differentiating the B expression for Method 4 with respect to MW and setting equal to zero (i.e., $MW_{maxB} = 1/2\beta$ where $\beta = 0.014$).

3. RESULTS AND DISCUSSION

Tables 1 through 4 summarize the four different methods for estimating B, all of which have a reasonable basis in experiments or theory. Figure 2 illustrates how B varies with $\log_{10} K_{ow}$ for MW of 300. Figure 3 shows the effect of MW as predicted by Methods 3 and 4 for K_{ow} of 1500.

Clearly, quite different values for B are obtained for a given K_{ow} depending on which method is chosen. When MW

Table 4. Estimating B—Method Four

$$B = \frac{P_{cv}}{P_{ev}} = \frac{P_{cw}}{P_{ew}} = \frac{P_{cw}\sqrt{MW}}{2.6 \text{ cm/h}}$$

Assumes MW dependence is $e^{-\beta(MW)}$ for SC and $1/\sqrt{MW}$ for EPI

$$\log_{10} P_{cw} = -2.8 - 6.0 \times 10^{-3} (MW) + 0.74 \log_{10} K_{ow}, \text{ cm/h}$$

$P_{ew} = K_{ew} D_e / L_e$

$K_{ew} = 1$ — Assumes EPI behaves essentially as water

$L_e = 10^{-2}$ cm

$D_e = 7.1 \times 10^{-6}/\sqrt{MW}$ cm^2/s — Assumes $D_e = 10^{-6}$ cm^2/s when MW = 50

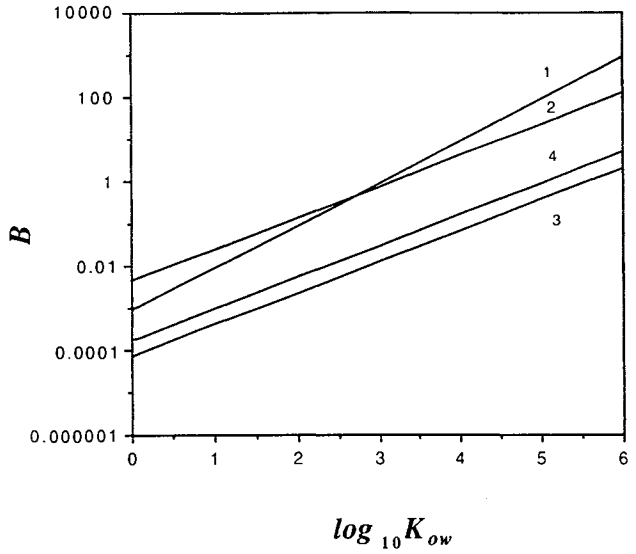

Figure 2. Comparison of the four methods for calculating B as a function of K_{ow} for a MW of 300.

is 50, Methods 2, 3 and 4 all predict similar B values, because all three methods were based on consistent values for the ratio of D_c/L_c to D_e/L_e at a MW of 50. For small K_{ow}, Method 1 predicts smaller B values than does the other methods. However, as K_{ow} increases, the B value predicted by Method 1 increases much more rapidly than does the other methods. This is because Method 1 assumes that the lipophilic-hydrophilic balance between the SC and EPI varies directly with K_{ow}. Based on the correlation for steady-state SC permeability showing that K_{ow} is best modeled as $K_{ow}^{0.74}$, we would expect that the K_{ow} effect assumed in Model 1 is probably too strong.

Models 1 and 2 predict that B does not change with MW, whereas Models 3 and 4 predict that B decreases as MW increases from 50 as illustrated in Figure 3. Models 3 and 4 predict the same B at MW of 50 because this was the chosen reference condition for specifying D_e. As already described, Model 4 predicts a maximum in B at MW of 36. Below this MW the EPI permeability approaches infinity as MW decreases to zero compared to the SC permeability which is approaching a constant. Model 3 always predicts a more rapid decrease with MW, because it assumes that EPI permeability is unaffected by MW while the SC permeability decreases exponentially. Except for small molecules, Model 4 probably represents the more realistic situation that the EPI permeability decreases with MW but more moderately than does the SC permeability.

Only when B is larger than 0.1 does it significantly affect the estimate of dermal absorption. Figure 4 plots, as a function of MW, the $\log_{10}K_{ow}$ value which corresponds to a B of 0.1 as predicted by the four methods. If a chemical with a given MW has a $\log_{10}K_{ow}$ below that indicated, then that chemical is not lipophilic enough for its permeability to be affected by the EPI. Methods 1 and 2 do not depend on MW and predict that the EPI permeability will begin to be a factor for chemicals with $\log_{10}K_{ow}$ above around 2.

For Methods 3 and 4 which assume a MW dependence, the K_{ow} value corresponding to B = 0.1 increases as MW increases for MW larger than 36. That is, a larger MW chemical must be more lipophilic for the EPI to proportionally restrict flux from the SC. This situation reflects the assumption that the SC acts as a molecular sieve producing larger increases in resistance as MW increases than the more fluid like EPI. This seems reasonable intuitively and consistent qualitatively with experimental observations. However, the MW dependence of Method 3 seems too strong. For a chemical with MW of 400 to produce a B of 0.1, $\log_{10}K_{ow}$ must be larger than 5 according to Method 3 compared to 4.5 for Method 4.

Differences in the four methods are more apparent if we examine the P_{ew} which each predicts when we divide P_{cw}, calculated from Eqn. (14), by B as calculated by each method. Figure 5 compares these calculated P_{ew} for the four methods as a function of MW. Of the four methods, only Method 1 (dashed lines) predicts that P_{ew} depends on K_{ow}, with P_{ew} decreasing as K_{ow} increases. Methods 1 and 2 assume the same exponential MW dependence for both the EPI and SC. Consequently, a semi-logarithmic plot of P_{ew} as a function of MW produces parallel lines for Methods 1 and 2. Method 1 predicts that P_{ew} becomes small (less than 0.1 cm/h) when MW is larger than 250 for $\log_{10}K_{ow} \geq 1$. Method

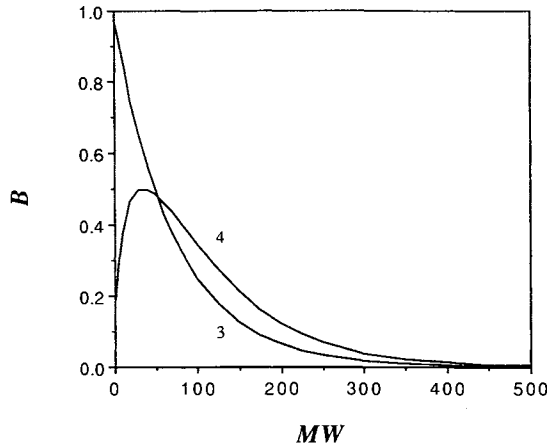

Figure 3. Comparison of Methods 3 and 4 for calculating B as a function of MW for K_{ow} of 1500.

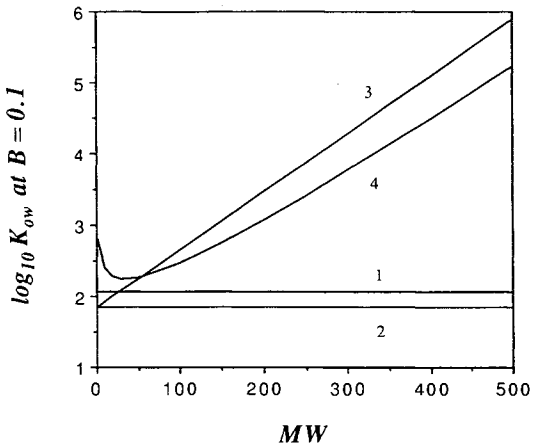

Figure 4. Comparison of K_{ow} which gives B = 0.1 as predicted by the four methods as functions of MW.

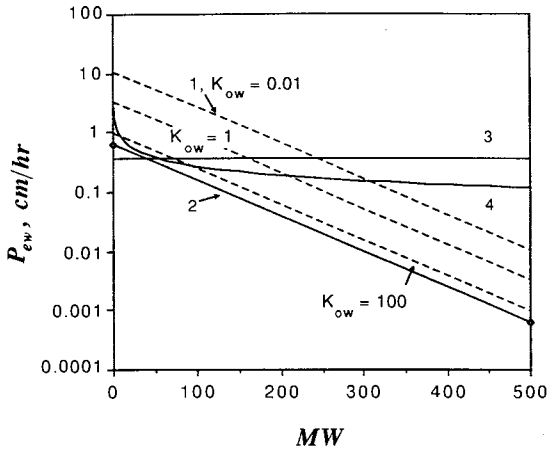

Figure 5. Comparison of P_{ew} calculated from the four methods (1 - dashed; 2,3,4 - solid) for estimating P_{cw}.

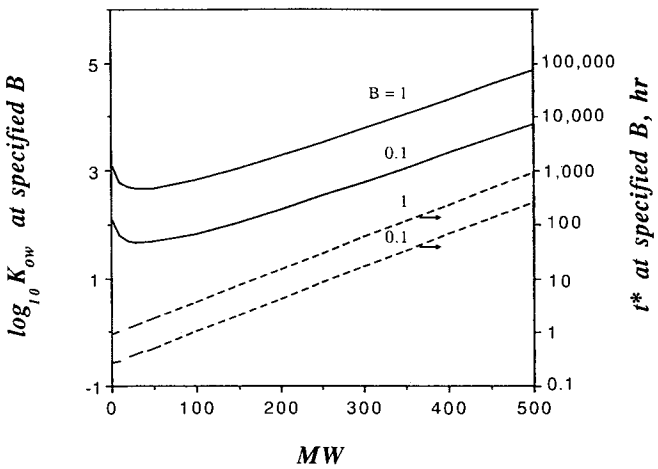

Figure 6. t* (dashed) and K_{ow} (solid) values which give B of 0.1 and 1 as predicted by Method 4 as functions of MW.

2 predicts that P_{ew} becomes less than 0.1 cm/h for MW larger than 250 and, less than 0.001 for MW larger than 500.

Although no thorough investigation of MW on EPI permeabilities exist, such dramatic decreases in P_{ew} have never been reported. In contrast, Method 3 assumes that the EPI permeability does not depend on MW at all. This seems equally unreasonable. All fluids present an increasing resistance to molecules of larger size. By assuming a square root dependence on MW, Method 4 shows a decrease in P_{ew} which seems more consistent with observations. Consequently, given that Method 4 is based on an experimentally derived correlation for P_{cw}, reasonably approximates P_{ew} including a plausible description of the effect of MW, and produces logical values for B, we adopt it as the recommended method. Later we discuss the sensitivity of the dermal absorption prediction to estimates for B.

Even when a chemical is lipophilic enough so that $B \geq 0.1$, B is still only important when exposures are long enough that the steady-state region is reached (i.e., when $t_{exp} > t^*$; see Figure 1). Based on Eqn. (10) combined with Eqn. (15), t* depends on MW. Assuming an SC thickness of 10^{-3} and $B \leq 0.1$, t* is more than 20 minutes for chemicals with MW larger than 20. Consequently, B affects the amount absorbed only if the exposure time is longer than 20 minutes. For MW of 100 or larger, t* is 1 hour. For exposure times of 24 hours or less, predicted diffusion coefficients indicate that B will not affect dermal absorption estimates if MW is 330 or larger. If the SC is thicker than 10^{-3} cm or the chemical is more lipophilic, then the time to reach steady state will be even longer.

Figure 6 plots the K_{ow} producing a B of 0.1 and 1 as calculated from Method 4 along with the corresponding t*. When estimating dermal absorption from exposure to a chemical of a given MW, B is needed in the calculation only if the chemical's K_{ow} causes B to exceed 0.1 and the exposure time is greater than t*. Since chemicals with larger K_{ow} tend to have larger MW, this causes t* to increase while also decreasing B, meaning that the importance of B in the dermal absorption calculation is reduced. This may explain why permeability measurements on SC-EPI samples are almost always equivalent to SC only samples. It is likely that most experiments on more lipophilic compounds have involved chemicals with large enough MW that the experimental times did not exceed t* and the SC still controlled dermal absorption.

Figure 6 provides the necessary information for identifying chemicals with steady-state permeabilities affected by the presence of the EPI. To observe a measurable effect, B must be 1 or larger and the chemical exposure must continue for a period exceeding t*. Clearly, we would choose a low MW chemical with a large K_{ow}. However, the difficulties of conducting permeability experiments with highly lipophilic chemicals in water have been discussed extensively by many authors and should be mentioned here. Stated simply, the SC capacity for a highly lipophilic chemical is so large that an extremely large aqueous vehicle reservoir is required to maintain the experimentally required slowly changing vehicle concentration. In addition, the rate of absorption into the SC, which is proportional to K_{cw}, is so large that water phase diffusion limitations begin to contribute. The only way to avoid these two complications is to measure dermal absorption from a nonaqueous vehicle with a much larger chemical solubility than water, but which also does not alter the SC or EPI.

Since data from which we can obtain experimental B values do not exist presently, we cannot experimentally identify which, if any, of the four methods described in Tables 1 through 4 best approximates the true B. However, we have established that the exact B value will only be important when the exposure times is larger than t* and B is larger than 0.1. For many chemical exposure situations, one or both of these criteria will not be met and consequently, knowing the exact value of B is unnecessary.

In those other situations when t_{exp} and K_{ow} are both large enough that B effects would probably arise, how sensitive will the dermal absorption estimate be to the parameter B? This question is answered by Figure 1. The largest possible error in the estimate of dermal absorption would occur when the actual and estimated values for B were 100 and 0.01. Although this 10,000-fold difference in estimated and actual B values is highly unlikely, Figure 7 shows this worst possible situation. The maximum percent error plotted in Figure 7 was calculated by subtracting the cumulative

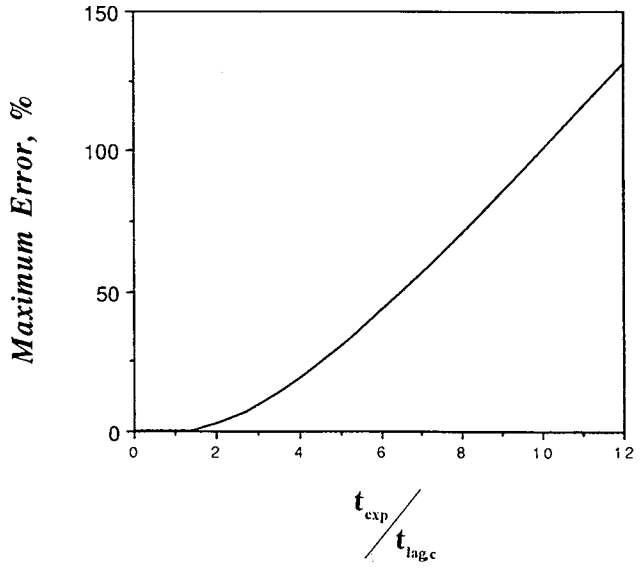

Figure 7. Maximum possible error in calculations of the cumulative mass absorbed arising from errors in estimates of the parameter B.

mass absorbed when B is 100 from the value when B is 0.01 and then normalizing by the value at B equal to 100. The magnitude of the error depends on both the exposure time and lag time of the absorbing chemical. Prior to $t_{exp}/t_{lag,c}$ of about 2, the difference in estimates made using B of 100 and 0.01 are zero. For longer t_{exp}, the EPI restricts absorption when B is large and the normalized cumulative mass absorbed increases only slowly. Consequently, for larger values of $t_{exp}/t_{lag,c}$ the difference between the B equals 0.01 and 100 estimates grows linearly with time.

If the purpose of the cumulative mass calculation is to estimate health risks, then the most conservative estimate, (i.e., the highest predicted absorption) is obtained using the smallest B value. However, if the purpose of the absorption calculation is to estimate drug delivery, then the more conservative estimate may be the lowest amount absorbed, in which case it is better to error in the direction of a larger B value.

When G is large enough, Eqn. (8) becomes independent of G resulting in Eqn. (9). Comparing Eqns. (8) and (9), we observe that G affects only the zero-time intercept. Therefore, the relative error in the absorption estimate made using Eqn. (9) is always less than the relative difference in the zero-time intercepts, Δ, from Eqns. (8) and (9) where Δ is defined as

$$\Delta = 1 - \frac{G(1 + 3B + 3B^2)}{G(1 + 3B) + B(1 + 3BG)} \qquad (21)$$

which further simplifies to,

$$\Delta = \frac{B}{G(1 + 3B) + B(1 + 3BG)} \qquad (22)$$

Although Δ depends on both B and G, it is easily shown that for any G, Δ is a maximum when B equals $\sqrt{1/3}$. Based on Eqn. (22), we calculate that differences between Eqns. (8) and (9) are less than 2% when G is 10 decreasing as 1/G when G increases further. For chemicals with MW between about 100 and 400, literature values for D_e/D_c and L_e/L_c are between 10^3–10^4 and between 5–10, respectively (8,9). Consequently, G is between 10 and 400. Furthermore, as MW increases we expect D_c to decrease more dramatically than D_e, meaning G would be larger still. We conclude that Eqn. (9) is appropriate when the SC is not compromised relative to the EPI by damage or the SC diffusivity is not greatly increased by enhancers.

4. CONCLUSIONS

A predictive method has been developed for estimating the cumulative mass absorbed during a dermal exposure including the faster rates during short exposures and the EPI resistance presented to lipophilic chemicals. This procedure requires estimates for D_c, L_c, K_{cv}, and the ratio of the stratum corneum and epidermis permeabilities, B. In a previous paper, expressions based on correlations for K_{cw} and P_{cw} were recommended for estimating K_{cw} and D_c/L_c as functions of K_{ow} and MW, respectively. In this paper, several possible methods for calculating B using K_{ow} and MW were described and evaluated. We recommend approximating B as $P_{cw}\sqrt{MW}/(2.6$ cm/h) where P_{cw} is calculated from the Potts and Guy correlation.

For short exposure times or B values less than about 0.1, B will not be required to estimate dermal absorption. Errors in absorption estimates associated with inaccuracies in estimates of B will be largest for highly lipophilic chemicals with exposures times much larger than its lag time. A worst case situation was presented.

NOMENCLATURE

- A = surface area of chemical exposure.
- b = parameter in t* calculation, Eqns. (11) and (12).
- B = parameter for the SC-EPI composite measuring the relative size of the SC permeability to the EPI permeability.
- c = parameter in t* calculation, Eqns. (11) through (13).
- C_v^o = concentration of the absorbing chemical in the vehicle. Assumed to remain constant during the exposure period, t_{exp}.
- D = diffusivity.
- D_c = effective diffusivity of the absorbing chemical in the SC.
- D_e = effective diffusivity of the absorbing chemical in the EPI.
- D_o = diffusivity of a molecule of size zero.
- EPI = viable epidermis.
- K_{ce} = equilibrium partition coefficient between the SC and the EPI for the absorbing chemical.
- K_{cv} = equilibrium partition coefficient between the SC and vehicle for the absorbing chemical.
- K_{cw} = equilibrium partition coefficient between the SC and water for the absorbing chemical.
- K_{ev} = equilibrium partition coefficient between the EPI and the vehicle for the absorbing chemical.
- K_{ew} = equilibrium partition coefficient between the EPI and water for the absorbing chemical.
- K_{ow} = octanol-water partition coefficient.
- L_c = effective thickness of the SC.
- L_e = effective thickness of the EPI.

M_{in} = cumulative mass absorbed into the SC during an exposure period, t_{exp}.
MW = molecular weight of the absorbing chemical.
P_{cv} = steady-state permeability of the SC from a specified vehicle.
P_{cw} = steady-state permeability of the SC from water.
P_{ev} = steady-state permeability of the EPI from a specified vehicle.
P_v = steady-state permeability of the SC-EPI composite membrane from a specified vehicle.
SC = stratum corneum.
t^* = time to approximately reach steady-state. Expressions for estimating are given in Eqns. (10) through (13).
t_{exp} = time period of exposure event.
$t_{lag,c}$ = lag time across the SC alone, equals $D_c/(6L_c^2)$.
$t_{lag,c}$ = lag time across the EPI alone, equals $D_e/(6L_c^2)$.
V = molar volume.

Greek

α_c = parameter in the equation relating K_{cw} and K_{ow}, Eqn. (17).
α_e = parameter in the relationship between K_{ew} and K_{ow}, Eqn. (18).
β = parameter in the function relating solute diffusivity to its MW, Eqn. (20).
β' = parameter in the function relating solute diffusivity to its molar volume, Eqn. (20).
γ_c = parameter in the equation relating K_{cw} and K_{ow}, Eqn. (17).
γ_e = parameter in the relationship between K_{ew} and K_{ow}, Eqn. (18).
ω = parameter relating solute diffusion to its MW.
τ = dimensionless exposure time, $= t_{exp}D_c/L_c^2$.

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