Can We Assign an Upper Limit to Skin Permeability?

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INTRODUCTION

The combination of a lipoidal penetration barrier in the stratum corneum and an aqueous diffusion layer in the underlying strata imparts a bilaminate structure to the skin permeability barrier (1). Arguments for (2,3) and against (4) the need to consider the aqueous layer when calculating the overall resistance of the skin have been presented. In the latter work it was shown that by incorporating an appreciable molecular weight dependence into the stratum corneum diffusion coefficient, one does not need an aqueous resistance term to describe the permeability coefficients of many commonly studied compounds (4).

Nevertheless, physical arguments and experimental data suggest that, in the absence of skin metabolism, the permeability, P, of human skin to compounds of pharmaceutical or toxicology interest should not exceed a value of about 0.3 cm/hr. This value may be obtained by considering the depth of the capillary bed and typical values for diffusion coefficients in the dermis and viable epidermis (1,3). Studies of diffusion through delipidized human stratum corneum suggest a slightly lower limit, $P \approx 0.1$–0.2 cm/hr, due to the resistance of the polar regions of the stratum corneum itself (5). An additional limitation to overall skin permeability results from the finite capacity of the skin capillaries to clear a compound from the dermis. This value depends on the capillary permeability–surface area product (which is not rate-limiting) and the capillary blood flow (which may be rate-limiting). As shown below, these limits are important to consider when estimating the penetration rates of highly lipophilic compounds or of all compounds when the stratum corneum is compromised. But first we consider three examples, noted by Flynn (2), of calculated permeability coefficients that apparently contradict the permeability limit: 0.64 cm/hr for styrene (6), 1.0 cm/hr for toluene (6), and 1.2 cm/hr for ethylbenzene (7). These values are almost certainly overestimated, as can be seen from the following argument.

DISCUSSION

Skin absorption, Q, in Refs. 6 and 7 was determined by the concentration drop in an aqueous solution of test compound into which the hand of a human volunteer was immersed for $t = 1$ hr. Absorption rate, J, was calculated as Q/t. P was evidently calculated by other workers by dividing J by the solution concentration C_v, i.e., $P = J/C_v = Q/(tC_v)$, as is commonly done for steady-state measurements.

The oversimplification here (not even considering the question about the relative permeabilities of palmar and nonpalmar stratum corneum) is to assume that the value of J calculated in this fashion corresponds to the steady-state flux. The magnitude of the error incurred may be estimated by using the familiar model for diffusion through a homogeneous membrane of thickness h (1,8). Consider a permeant having fixed concentration C_h at $x = h$ and zero concentration at $x = 0$, with zero initial concentration in the membrane. The solution to this problem is given in Ref. 8. One notes that the initial flux at $x = h$ (given by $DC_h/\sqrt{\pi Dt}$) is much larger than the flux at steady state (given by DC_h/h).

Now consider the experiments conducted by Dutkiewicz and Tyras (6,7). Had these experiments been conducted for a longer period of time, one would have expected to observe a skin lag time, t_L, of at least 1–2 hr, based on studies of other lipophilic compounds. Using the homogeneous membrane approximation we have $t_L = h^2/6D$, so that the dimensionless time parameter Dt/h^2 at $t = 1$ hr (calculated as $t/6t_L$) should be in the range 0.08–0.17. It can be readily seen from the small time approximation given above (which is accurate to within 1.5% for $Dt/h^2 < 0.2$) that the mean flux over this time period is three to four times the steady-state value. Hence, the value of P obtained by this method is likely to be at least three to four times higher than the true value.

This correction means that the actual human skin permeability of these small, lipophilic compounds is no more than 0.2 cm/hr for styrene and 0.4 cm/hr for ethylbenzene, in good agreement with the estimated upper bound of approximately 0.3 cm/hr (2,3).

Having dismissed these apparent violations of the skin permeability limit as non-steady-state results, we turn to the consequences of the skin's bilaminate structure. Consider the pesticide DDT, which has a molecular weight of 354.5 and a log octanol/water partition coefficient ($\log K_{oct}$) of 6.36 (9). The permeability of human stratum corneum to this compound, as estimated by two recent models, lies between 0.41 and 5.2 cm/hr (see Table I). The difference between the estimates is due primarily to a considerably stronger dependence of P on K_{oct} proposed in Ref. 3 compared to Ref. 4. However, when the diffusive resistance of the aqueous layer is taken into account, the estimated values for overall skin permeability P are in the range 0.17–0.28 cm/hr. These values not only are lower than the stratum corneum estimates, but also are in much better agreement with one another. Thus it can be important to include the effect of the aqueous skin layers in order to avoid overestimating the hazard resulting from dermal exposure to highly lipophilic compounds. Furthermore, the inclusion of this term makes the choice of which model to use for stratum corneum permeability less critical to the end result. Conversely, it is probable that the presence of aqueous barriers in experimental *in vitro* penetration studies, combined with the relatively small number of highly lipophilic compounds whose skin permeability has been quantitatively determined, has limited the precision of current models of stratum corneum permeability.

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Table I. Calculated Values for Overall Skin Permeability P (cm/hr) of DDT Based on the Stratum Corneum Models of Potts and Guy (4) and Kasting *et al.* (3), Together with the Effects of an Aqueous Barrier and Flow-Limited Capillary Clearance

	Potts and Guy (4)	Kasting *et al.* (3)
Stratum corneum alone	0.41	5.2
Stratum corneum + aqueous layer	0.18	0.28
Stratum corneum + aqueous layer + capillary clearance	0.15	0.22

The possibility of flow-limitation imposes a similar, though slightly more generous, upper bound to steady-state skin permeability. In the steady state, the skin penetration rate of a compound cannot exceed the rate at which the capillary blood flow can clear the compound from the skin (in the absence of other clearance mechanisms). It is likely that the capillary endothelial cell membrane does not pose a significant permeability barrier, because it consists of only two phospholipid bilayers, compared with perhaps 60–120 bilayers of the less permeable stratum corneum lipids. Furthermore, its surface area is more than an order of magnitude greater than that of the stratum corneum (10). In this case, the clearance parameter λ for entry into the blood for adjacent skin tissue (defined as a third resistance in series with the stratum corneum and aqueous layer as in Ref. 1) reduces to the flow-limited value F/S, where F is the total capillary blood flow and S is the corresponding skin surface area. In this limit, the capillaries carry away compound from the skin at a theoretically maximum venous concentration equal to that in the adjacent skin tissue. For 70-kg male humans, the skin blood flow is approximately 4.64 cm^3/sec or 16,700 cm^3/hr (11), while the skin surface area can be taken as 18,000 cm^2. Thus, $F/S \approx 0.93$ cm/hr. Taking this additional resistance to overall skin penetration rate into account for the DDT example gives even further reduced values of P (Table I). The capillary blood flow effect has recently been observed in an experimental penetration model in which blood flow to the skin can be modulated (12) and in a human pharmacokinetic study with the vasoactive compound, nicotine (13).

To estimate how often the above considerations come into play, we examined a list of compounds of interest in environmental hazard assessment (14). We calculated their skin permeability according to the Potts–Guy stratum corneum model alone (as in Line 1 of Table I), then with the effects of the aqueous layer and capillary clearance incorporated into the model (as in Line 3). We found a greater than 100% difference between the two calculations for 16 of the 213 compounds, or about 8% of the data base. The largest difference was approximately 12-fold for dibenzo(*a*,*h*)anthracene.

From our perspective, however, the greatest value of including sequential resistive barriers in skin penetration models is the perspective this can add to dermal absorption estimates for compromised skin. In the absence of an accepted model for compromised skin, safety assessments for consumer products are often made under the assumption of 100% absorption. By applying a composite membrane permeability model, sans stratum corneum, a more realistic estimate can readily be generated.

An exception to the above permeability limits may be noted for compounds which are extensively metabolized in the upper layers of the skin. For such compounds it is conceivable that effective values of P considerably greater than 0.3 cm/hr could be obtained when estimated from disappearance of the permeant from the skin surface, since the flux of the parent compound is not constrained by either the aqueous barrier or capillary clearance. However, agreement of such a result with a unilaminate model calculation that did not consider metabolism would, in this case, be fortuitous.

REFERENCES

1. R. J. Scheuplein. In A. Jarrett (ed.), *The Physiology and Pathophysiology of the Skin, Vol. 5*, Academic Press, New York, 1978, pp. 1659–1752.
2. G. L. Flynn. Physicochemical determinates of skin absorption. In T. R. Gerrity and C. J. Henry (eds.), *Principles of Route-to-Route Extrapolation for Risk Assessment*, Elsevier, New York, 1990, pp. 93–127.
3. G. B. Kasting, R. L. Smith, and B. D. Anderson. Prodrugs for dermal delivery: Solubility, molecular size, and functional group effects. In K. B. Sloan (ed.), *Prodrugs: Topical and Ocular Drug Delivery*, Marcel Dekker, New York, 1992, pp. 117–161.
4. R. O. Potts and R. H. Guy. Predicting skin permeability. *Pharm. Res.* 9:663–669 (1992).
5. B. D. Anderson, W. I. Higuchi, and P. V. Raykar. Heterogeneity effects on permeability-partition coefficient relationships in human stratum corneum. *Pharm. Res.* 5:566–573 (1988).
6. T. Dutkiewicz and H. Tyras. Skin absorption of toluene, styrene, and xylene in man. *Br. J. Industr. Med.* 25:243 (1968).
7. T. Dutkiewicz and H. Tyras. A study of the skin absorption of ethylbenzene in man. *Br. J. Industr. Med.* 24:330–332 (1967).
8. J. Crank. *The Mathematics of Diffusion*, Oxford University Press, Oxford, 1975, pp. 32, 49–53.
9. Pomona College Medicinal Chemistry Project. *MEDCHEM Software*, Release 3.54, Pomona College, Claremont, CA, Jan. 1989.
10. C. Crone and D. G. Levitt. Capillary permeability to small solutes. In E. M. Renkin and C. C. Michel (eds.), *Handbook of Physiology—The Cardiovascular System IV*, American Physiological Society, Bethesda, MD, 1984, pp. 411–466.
11. S. Lindstedt, Personal communication.
12. J. E. Riviere, B. Sage, and P. L. Williams. Effects of vasoactive drugs on transdermal lidocaine iontophoresis. *J. Pharm. Sci.* 80:615–620 (1991).
13. N. L. Benowitz, P. Jacob III, P. Olsson, and C.-J. Johansson, Intravenous nicotine retards transdermal absorption of nicotine: Evidence of blood flow-limited percutaneous absorption. *Clin. Pharmacol. Ther.* 52:223–230 (1992).
14. K.-C. T. Hoang *et al.* Dermal exposure assessment: Principles and applications. Interim report No. EPA/600/8-91/011B, U.S. Environmental Protection Agency, Office of Research and Development, Washington, DC, Jan. 1992, pp. 5-39–5-47.