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Pharmacokinetics of the Dermal Route of Exposure to Volatile Organic Chemicals in Water: A Computer Simulation Model

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A kinetic model of dermal absorption of nonpolar organic nonelectrolytes in dilute aqueous solutions is described. The model uses systems dynamics STELLA software and is designed for a Macintosh computer. The model assumes the outer stratum corneum layer skin to be the rate-determining barrier to dermal absorption and assumes that both stratum corneum and viable epidermal layers have storage capacity for lipophilic solutes. The model predicts between 30 and 94% of experimental results with humans under the same tions. The degree of departure between experimental and theoretical results is inversely related to the solutes's octanol/water partition coefficient, which is consistent with the most recently hypothesized mechanisms of transport of molecules across the dermal barrier. The model has potentially useful applications for risk assessment if used within its defined limits.

INTRODUCTION

Skin absorption may be a significant pathway of entry into the human body f volatile organic contaminants (VOCs) in tap water, in addition to the inhalation contaminated indoor air and the direct ingestion pathways.

In this paper we describe a kinetic model of transdermal absorption of nonpol organic nonelectrolytes in dilute aqueous solutions. The model is designed to be used on a Macintosh computer and represents a further elaboration on an init model proposed in an earlier paper (Brown and Hattis, 1989). We use the mo to follow the course of absorption and distribution of several VOCs under seve exposure scenarios and suggest a range of its possible applications.

THEORETICAL BASIS

Stratum corneum represents the major bamer to percutaneous absorpti (Scheuplein and Blank, 1973; Elias, 1981; Yardley, 1985). Once believed to hav properties of a homogeneous barrier to physiological water uptake and loss, th stratum corneum has been shown to consist of two distinct layers of very differe properties: stratum disjunctum and stratum compactum. It appears that the dis junctum region acts as a barrier to solute uptake, as demonstrated by Marzulli (1963) and Bettley (1970), whereas the compactum region forms a major wate barrier (Bettley, 1970; Bowser and White, 1985).

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has been generally assumed that transport of aqueous nonelectrolytes ugh skin is governed by Fick's Law of passive diffusion. The underlying ise has been twofold: (1) stratum corneum has minimal storage capacity; and tratum corneum behaves as a relatively uniform, if not homogeneous, diffu- membrane.

lthough Scheuplein *et* al. (1969) questioned the first assumption over 2 de- es ago by showing significant binding of radiolabeled steroids in aqueous so- on to isolated human stratum corneum, the importance of the storage and its ion to lipophilicity was only recently demonstrated experimentally. Thus, an se correlation between lipid content in stratum corneum and the amount of ylic acid crossing that membrane, most likely due to the solute's retention, demonstrated by Elias *et al.* (1981) and Smith *et al.* (1982), whereas Wester (1987) showed that the extent of stratum corneum binding is proportional to ophilicity of a penetrant.

er investigators have questioned the applicability of Fick's Law to describe ovement of nonpolar solutes across stratum corneum on the grounds that it ghly heterogeneous membrane. Raykar et al. (1988), for example, suggested xistence of two distinct pathways for transport of solutes across stratum eum: a lipid pathway for highly lipophilic compounds, and a protein pathway ydrophilic compounds. A combination of the two pathways would apply to pounds with intermediate properties. Only transport via the lipid pathway is istent with the premise of Fick's Law. Anderson et *al.* (1988) further hypoth- d that the assumption of a primarily lipid pathway applies to molecules with ctanol/water partition coefficient greater than approximately 50.

ese findings suggest that the assumption of passive diffusion across stratum eum applies primarily to nonelectrolytes having relatively small molecular hts and octanol/water partition coefficients greater than approximately 50. thermore, the lipid content of stratum corneum and its potential for storage of philic solutes should not be disregarded in the cases where the objective is to tify the transdermal absorption of toxic substances.

our earlier work, we demonstrated how dermal absorption of solutes can be icted using a kinetic computer model designed to be used on a Macintosh puter (Brown and Hattis, 1989). In that work, we treated the stratum corneum barrier alone and disregarded its storage properties. In this paper, we describe etic model of dermal absorption which incorporates the most recent findings he barrier and storage properties of the skin and, specifically, of the stratum rneum layer. At the same time, however, we treat stratum corneum as a single yer rather than distinguish the disjunctum and conjunctum regions. This is for o reasons: (1) theoretical—although the structure of stratum corneum differs between these two regions, Marzulli (1963) and Bettley (1970) have shown that olute diffusion is relatively uniform throughout the stratum corneum; and (2) ractical—measurements of diffusion coefficients and partition coefficients of sol- tes have been reported in the literature for total stratum corneum, not its two sublayers. Furthermore, the very small thickness of the stratum compactum (5–7 µm hydrated) makes its contribution to total storage in stratum corneum insignif- icant

METHODS

Description of the Model

The pharmacokinetic model is shown schematically in Fig. 1. Both a tradition compartmental representation and a scheme designed to represent the physiolo ical significance of the model are shown. We identify three body compartme stratum corneum, viable epidermis, and blood. Molecules diffuse through fu hydrated stratum corneum and viable epidermis in a dissolved state by pur passive means, with the passage through stratum corneum being the rate-limit step. We assume a uniform thickness of 40 μm for stratum corneum, althou adjustments for different parts of the body are also made, as shown later on. T scenario assumed is either hand or full-body immersion into a vessel of solu contaminated water of a known volume. The viable epidermis is assumed to 200 μm thick between stratum corneum and dermal capillary bed, althoug testing the sensitivity of the model we vary that thickness up to 1000 μm on assumption that solute can be stored beyond the capillaries in the epidermal papillary dermal layers.

Blood is represented by the third kinetic compartment in Fig. 1. No distinc is made between a chemical in the dermal blood vessels and a chemical in gen circulation. The rate of transfer of a chemical from the epidermis into bloo proportional to the instantaneous amount in the epidermis, the epidermal bl flow rate, and the relative solubilities of the agent in the two compartments (dermis/blood partition coefficient, K_{eb}). The blood and epidermal compartme are in equilibrium with each other at the boundaries and a chemical can reenter epidermal compartment from the blood. The net rate of change in the amou chemical in the epidermis depends on the rate of entry from, and removal to, stratum corneum; the rate of removal into blood; and the rate of reentry from blood.

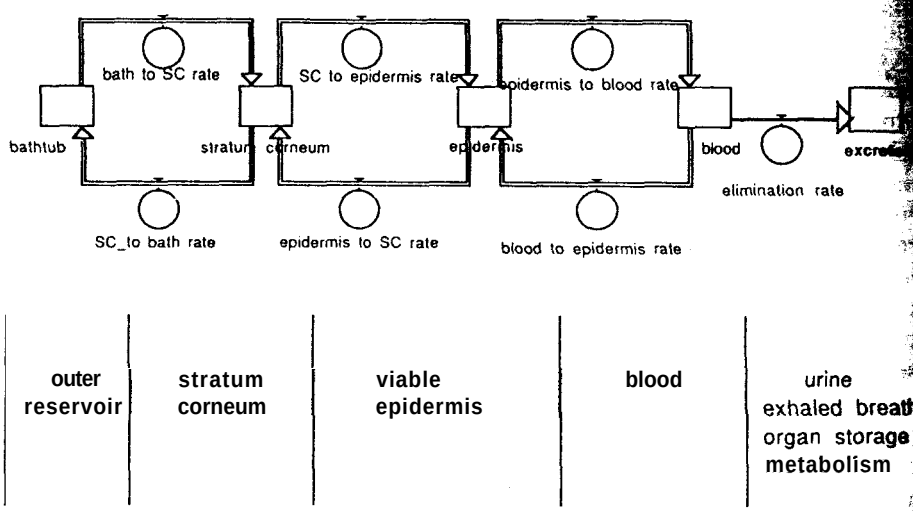

FIG. 1. Schematic representation of the model of dermal absorption.

The overall elimination rate includes excretion via exhalation, urinary filtration, metabolism, and deposition in other body compartments. It represents the net rate decline of a chemical in blood and accounts for reentry into the venous circu- from temporary storage in various organs. Exploration of elimination of cals from blood using a full pharmacokinetic model shows that the latter is the most important process in short exposures such as bathing (Hattis et al.,).

We assume first-order kinetic behavior of the chemical between all compart- ts and in all directions, whereby the instantaneous rate of change in the centration is proportional to the concentration in that compartment and to the constant specific to that compartment. In the feedback loops, we assume the ge distance the solute had to travel to exit the compartment is half the ness of the compartment. We also assume that solute travels only within the ied skin area and only in a direction perpendicular to the skin. Solute in the n corneum reservoir at the end of exposure is assumed to be absorbed into dy eventually. Other pathways for transdermal solute uptake, such as the lity of transport via hair follicles, or cuts in the skin, are assumed to be ible.

The model was developed using STELLA systems dynamic software from High mance Systems of New Hampshire. System dynamics is helpful in explor- e complex behavior of any dynamic system governed by feedback mecha- In a STELLA model, all components of the dynamic system can be rep- ed in terms of stocks and flows: stocks represent net accumulation through and flows represent the movement of stock per unit time, or the rate of ge. STELLA allows one to construct a model on a terminal screen as an cit structural diagram, element by element. The conceptual relationships een the elements are entered visually by arrows, while the mathematical ionships between the independent variables (such as skin surface, membrane ness, or solute concentration) are entered explicitly. These are shown in . 2 and 3. The compartments and their mutual relationships shown in Fig. 2 dentical to those shown in Fig. 1 but the variables that determine the rates of sfer between the compartments are shown as well. For example, the rate of nsport across stratum corneum depends on the surface area of the skin, S, the kness of stratum corneum, H_{sc}, the stratum corneum/water partition coeffi- K_m, the solute's diffusion coefficient in stratum corneum, D_{sc}, and the centration of chemical in the bathtub, as indicated by the arrow pointing from bathtub to the rate regulator. Total absorbed in Fig. 2 represents the amount chemical entering the body over time without regard to its fate and includes material removed from the blood by any of the mechanisms discussed above, as well as that stored in the blood and skin. It thus represents the total amount ssing through the flow regulator termed "bath to SC rate" minus the amount ssing through "SC to bath rate" flow regulator. A more detailed description of TELLA applications to pharmacokinetics has been published previously (Bo- en, 1989; Hattis et al., 1986).

The required parameters and validation with experimental data are discussed in the sections below.

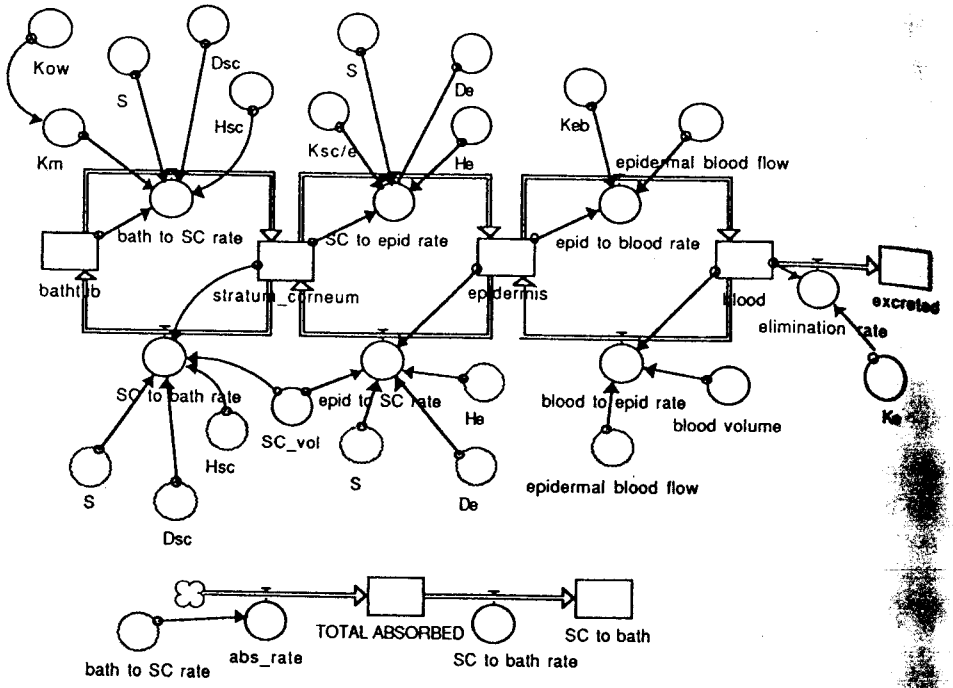

FIG. 2. Full diagram of the model of dermal absorption. Symbols used: H_{sc}, stratum corneum thickness; D_{sc}, stratum corneum diffusion coefficient; K_m, stratum corneum/water partition coefficient; K_{eb}, epidermis/blood partition coefficient; K_{ow}, octanol/water partition coefficient; SC_vol, volume of stratum corneum = $H_{sc}*S$; H_e, epidermis thickness; D_e, epidermis diffusion coefficient; $K_{sc/e}$, stratum corneum/epidermis partition coefficient; S, skin area; K_e, elimination rate constant; SC, stratum corneum.

Parameters for the Model

All parameters used were either taken from published experimental work of others or calculated from previously reported mathematical relationships.

Stratum corneum/water partition coefficient (K_m). This is calculated from the octanol/water partition coefficient, K_{ow}, using the empirical relationship reported by Roberts and colleagues (1975). For nonelectrolytes in dilute aqueous solutions with K_{ow} values ranging between 10 and several thousands, the relationship has the following form:

$$K_m = 1.2771 + 0.1208\ K_{ow}.$$

Stratum corneum diffusion coefficient (D_{sc}). Following Guy and Maibach (1984), the diffusion coefficient for a solute in stratum corneum was calculated from its molecular weight (MW) using the relationship

$$D_{sc} = D_{benz}\left(\frac{\text{MWbenz}}{\text{MWsolute}}\right)^{1/3},$$

STRUCTURAL EQUATIONS
bathtub = bathtub + dt * (−bath to SC rate + SC to bath rate)
corneum = Stratum corneum + dt * (−SC to epidermis rate + bath to SC rate
+ epidermis to SC rate − SC to bath rate)
epidermis = epidermis + dt • (SC to epidermis rate + blood to epidermis rate
− epidermis to blood rate − epideris to SC rate)
blood = blood + dr * (−elimination rate − blood to epidermis rate + epidermis to blood rate)
elimination = elimination + dt * (elimination rate)
to bath = SC to bath + dt * (SC to bath rate)
TOTAL ABSORBED = total absorbed + dt * (bath to SC rate − SC to bath rate)

RATE EQUATIONS
Bath to SC rate = $(D_{sc} * K_m * S *$ bathtub$)/H_{sc} * V_b)$
SC to bath rate = Stratum corneum * S * $D_{sc}/(H_{sc} * 0.5 * V_{sc})$
SC to epidermis rate = $(D_e * S *$ Stratum corneum$)/(K_{sc/e} * V_{sc} * H_e)$
epidermis to blood rate = (epidermis * $F_{eb}/K_{eb} * V_e$)
epidermis to SC = $(S * D_e *$ epidermis$)/(V_e * H_e * 0.5)$
blood to epidermis rate = $F_{eb} *$ blood$/V_b$
elimination rate = $K_e *$ blood

FIG. 3. Structural equations of the model. Symbols used: H_{sc}, Stratum corneum thickness {cm}; D_{sc}, Stratum corneum diffusion coefficient {cm²/min}; K_m, Stratum corneum/water partition coefficient {unitless}; S, Skin surface {cm²}; D_e, Epidermis diffusion coefficient {cm²/min}; H_e, Epidermis thickness {cm}; K_{eb}, Epidermis/blood partition coefficient {unitless}; F_{eb}, Epidermal blood flow {ml/min}; $K_{sc/e}$, Stratum corneum/epidermis partition coefficient {unitless}; V_b, Blood volume {cm³}; V_e, Epidermal volume {cm³}; V_{sc}, SC volume {cm³}; K_e, Elimination rate constant {min⁻¹}.

where D_{sc} and D_{benz} are diffusion coefficients in stratum corneum. The diffusion coefficient of benzene in stratum comeum was experimentally estimated by Blank and McAuliffe (1985) to be 4.1×10^{-9} cm²/sec.

Skin surface (S). Experimental values of 320 cm² for adult hands and forearms were used to validate the model (Dutkiewicz and Tyras, 1967, 1968), except for the phenol data where 347 cm² was used (Baranowska-Dutkiewicz, 1981). Otherwise, the data of Guy and Maibach (1977) were used. We also assume that the chemical is stored only in the surface area of the skin that is immersed in the reservoir and that no diffusion into nonimmersed skin occurs.

The skin area of a 9-kg infant was calculated from the published data for a 3-kg infant, 1900 cm² (Guy and Maibach, 1977), assuming that the surface-to-volume ratio increases to a ⅔ power with increasing volume. Thus, the surface of a 9-kg infant is $1900 \times (3)^{2/3} = 3800$ cm². In the bathtub scenarios we assumed that 91 and 81% of the body is immersed for adult and infant, respectively, which includes the torso, legs, arms, and, for adults only, the upper chest region.

Epidermis diffusion coefficient (D_e). As estimated by Scheuplein (1959, 1976) the value of 3.6×10^{-4} cm²/min was used for all solutes.

Stratum corneum thickness (H_{sc}). An average of 0.004 cm for fully hydrated stratum corneum was used (Blank and Scheuplein, 1969).

Epidermis thickness (H_e). Blank and McAuliffe (1985), Blank and Scheuplein (1969), and Guy et *al.* (1982) used a value of 0.02 cm for transport of molecules across viable epidermis between stratum corneum and blood vessels. Values ranging from 0.02 to 0.1 cm were used in the model to account for the possibility of Storage in lower dermal layers.

Epidermal blood flow (F_{eb}). A flow rate of 280 ml/min-m^2 in the skin of average adult at rest was used (Wade *et al.*, 1962). Under heavy exercise, as in swimming scenario, the rate is assumed to be 4000 ml/min-m^2 (Rowell, 1986).

Epidermis/blood partition coefficient (K_{eb}). This parameter was estimated from K_{ow}, the octanol/water partition coefficient, assuming certain values for lipid content in epidermis and blood compartments. For 2% fat in skin and 0.07% in blood, K_{eb} was calculated as

$$K_{eb} = \frac{0.98 + 0.02 * K_{ow}}{0.993 + 0.007 * K_{ow}} = 2.75.$$

Stratum corneum/epidermis partition coefficient ($K_{sc/e}$). $K_{sc/e}$ was calculated similarly to K_{eb}.

Blood volume (V_b). The volume of blood was 5000 ml for adults and 693 ml for infants.

Fat in blood. The amount of fat in the blood was 0.7–0.9% (Brown and Hall, 1989).

Fat in stratum corneum. The fat content of stratum corneum varies between individuals and anatomical sites. An average value was estimated by Elias (1983) to be approximately 5%. Raykar *et al.* (1988) measured stratum corneum lipid content for 35 skin samples and found that lipid content for dry stratum corneum ranged from 3 to 46%. With an approximate factor of 4 to convert dry stratum corneum lipid content to hydrated stratum corneum, these values become approximately 1–10%. Based on the distribution of Raykar's values, we assumed that mean stratum corneum fat content was to fall in the range of 3 to 6%.

Fat in epidermis. The amount of fat in the epidermis was 2.0–2.5% (Scheuplein, 1976).

Elimination rate constant (K_e). For alkylbenzenes, the elimination rate constants were calculated from published elimination half lives as

$$K_e = \frac{0.693}{T_{1/2}}.$$

Elimination rate (K_e) *values.*

Ethylbenzene	approx 0.1 min^{-1} (Hagemann, 1979)
Toluene	approx 0.05 min^{-1} (Veulemans and Masschlein, 1978)
Styrene	approx 0.1 min^{-1} (Lof *et al.*, 1986)
Phenol	approx 0.1 min^{-1} (analogous to the other compounds)

The K_e values calculated from these experimental results are likely to be underestimated, because in all the experimental studies human subjects were exposed for up to 4 hr to the agent and the elimination half-lives were determined by measuring a decline in the concentration of the compounds in venous blood over time. During the exposure a considerable amount of material was probably deposited in various body tissues, to be partly released into blood circulation at

later time. The rate of decline in the concentration of the chemical in the blood during the postexposure period was therefore slower in these experiments than it would have been in the absence of substantial earlier exposure. To account for the underestimation, values ranging from 0.05 to 1 min^{-1} were therefore used in the model. As shown later, the value of K_e has little effect on the results of the model.

In the case of trichloroethylene and tetrachloroethylene, a full pharmacokinetic model (Hattis *et* al., 1986) was used to estimate time-dependent elimination constants under the conditions of the first 20 min of bathing. These are:

Tetrachloroethylene	5 (1–0.03 * Time)
Trichloroethylene	6 (1–0.035 * Time).

Octanol/water partition coefficient (K_{ow}). The following published values were used:

Ethylbenzene	2230
Styrene	932
Toluene	669
Tetrachloroethylene	339
Trichloroethylene	263
Chloroform	93
Phenol	29

RESULTS AND DISCUSSION

The model prediction of the time course of absorption and distribution of ethylbenzene from aqueous solution is shown in Fig. 4. The skin compartments achieve steady state much before the blood compartment. Storage capacity of stratum corneum compared to epidermis is small due to the size of the reservoir, while, as expected, the blood is the main reservoir among the three compartments. Increasing the epidermal thickness (not shown here) significantly increases the storage capacity of that compartment, resulting in a smaller proportion of solute absorbed in the blood compartment. These changes affect primarily the lag time to achieving steady state by the skin compartments, because with either epidermal thickness the total absorbed is almost identical.

After 60 min the amount of solute taken up from solution (total absorbed) is much greater than can be accounted for by storage in the three compartments. This is due to elimination of the penetrant, because the elimination rates of the compounds under consideration were very high. The significance of this cannot be assessed in a quantitative way. Since our definition of elimination is simply removal of the solute from the blood, without regard to its subsequent fate, a significant fraction of "eliminated" material may be stored in other body compartments rather than be removed from the body. If so, "total absorbed" is a more appropriate parameter for describing the toxicologically significant dose. On the other hand, if little storage in the body takes place then the total amount in blood and the skin compartments is of toxicological significance. Short of study-& a full-body pharmacokinetic model, and due to the fact that we studied li-

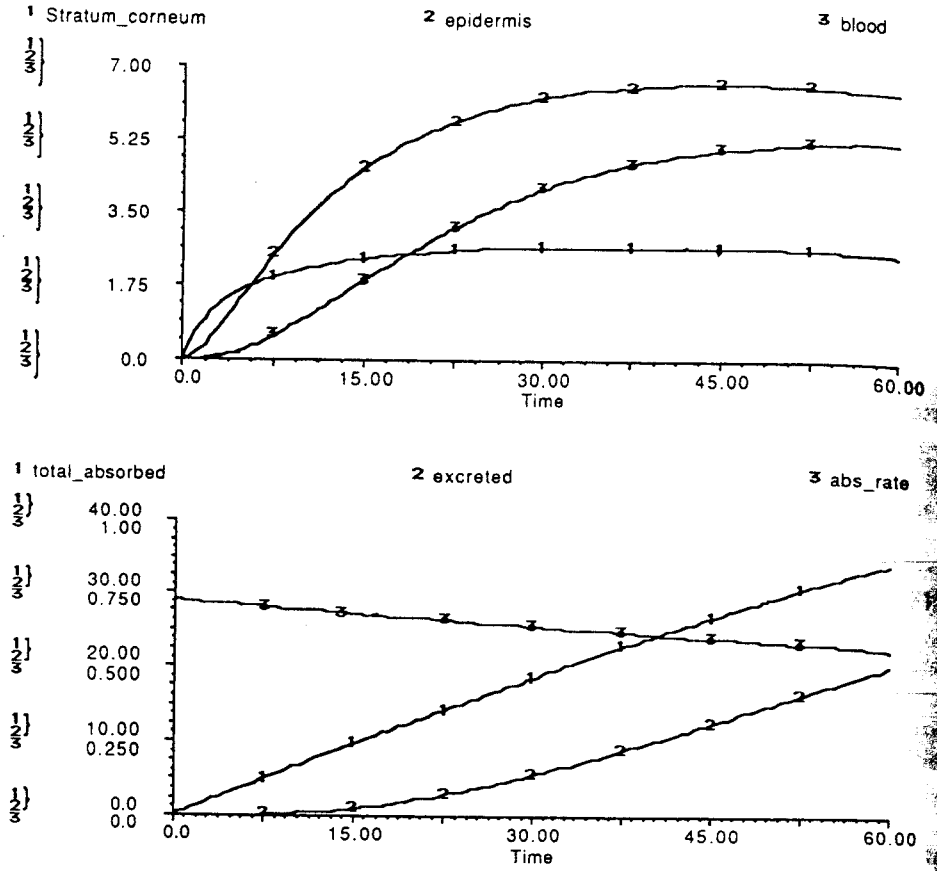

FIG. 4. Time course of absorption and distribution of ethylbenzene from aqueous solution. Simulation was run under the following conditions: Concentration of ethylbenzene, 151 mg/1000 cm^3; skin thickness, 0.1 cm; fat content, 6% stratum corneum, 2.5% epidermis, 0.7% blood; skin area, 320 cm^2; blood flow, 0.028 ml/cm^2-min.

pophilic compounds, we chose to equate the bodily dose with "total absorbed" although we recognize that it may lead to the overestimation of the toxicologically significant dose.

The total absorbed is dependent on the values of all the parameters in the model, as well as their unique combination. The estimated values of these parameters are associated with varying degrees of uncertainty. To evaluate the effects of the uncertainty on the overall transdermal dose, we ran the model for several sets of parameters, which, in our view, were most uncertain. The results are shown graphically in Fig. 5.

According to Fig. 5, the total amount of chemical entering the body is most sensitive to changes in the epidermal blood flow rate, which, when changed from 0.028 to 0.4 ml/min-cm^2, resulted in an increase in total absorbed of +4%. The next greatest change resulted from increasing the epidermal thickness from 0.02 to 0.1 cm, decreasing total absorbed by 3%. An increase in stratum corneum fat by

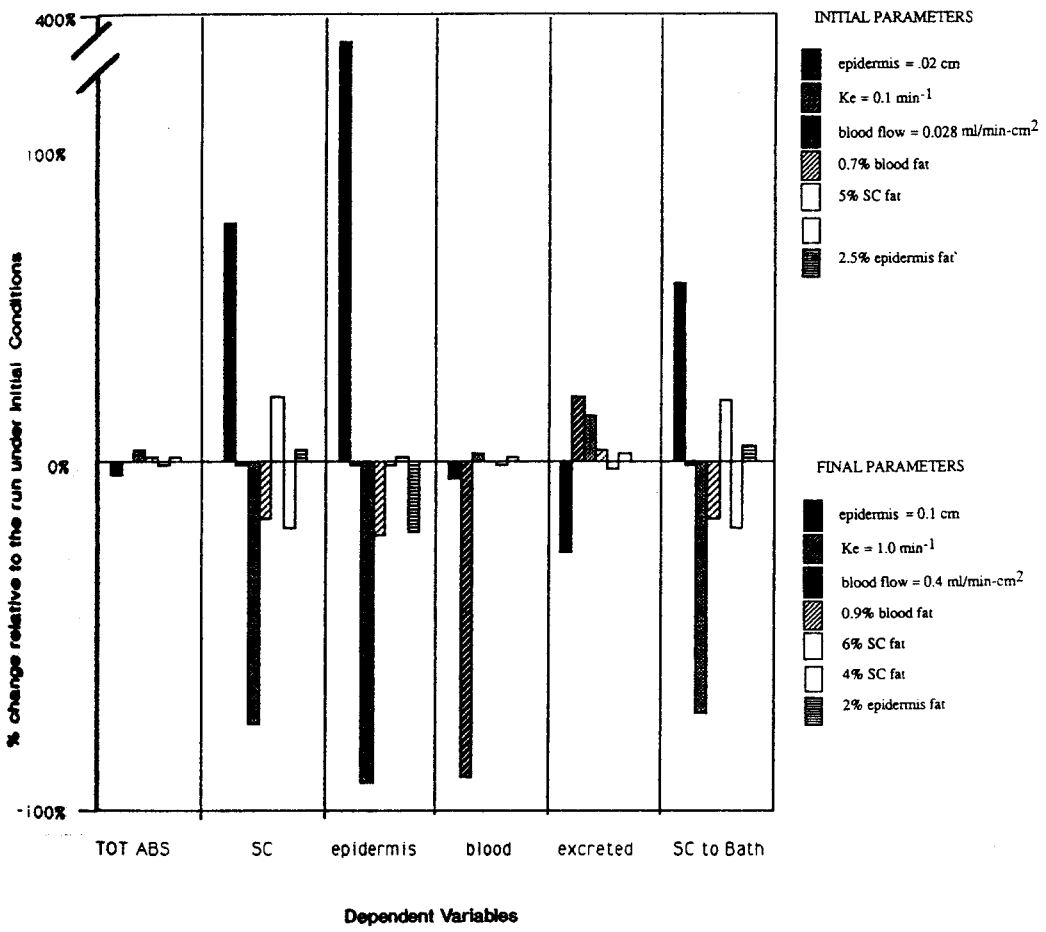

FIG. 5. Effect of changing the model parameters on total and compartment-specific absorption of ethylbenzene. The values of individual parameters were changed one at a time from the "initial conditions." The bars indicate the percentage change in the amount of chemical in each compartment as a result of that parameter change. Conditions were as in Dutkiewicz and Tyras' experiments: 320-cm^2 skin area, 1-hr skin exposure, 151 mg/liter ethylbenzene.

1% decreased total absorbed by 1%, while increasing the blood fat from 0.7 to 0.9% resulted in an increase in total absorbed of 0.5%. Increasing the elimination rate from 0.1 to 1.0 min^{-1} had no effect on the total absorbed.

Increasing the epidermal blood flow had a dramatic effect on the amount of chemical taken up by the stratum corneum and epidermal compartments, although the total absorbed was not significantly affected. This is because of the increased rate at which the blood removes the solute from the skin (the "epidermis to blood rate"). Increasing the elimination rate similarly decreased uptake by the skin compartments. Because of elevated storage capacity, uptake by stratum corneum was greater with increasing stratum corneum fat content. The model predicts that increasing stratum corneum fat content by 1% increases the amount of solute

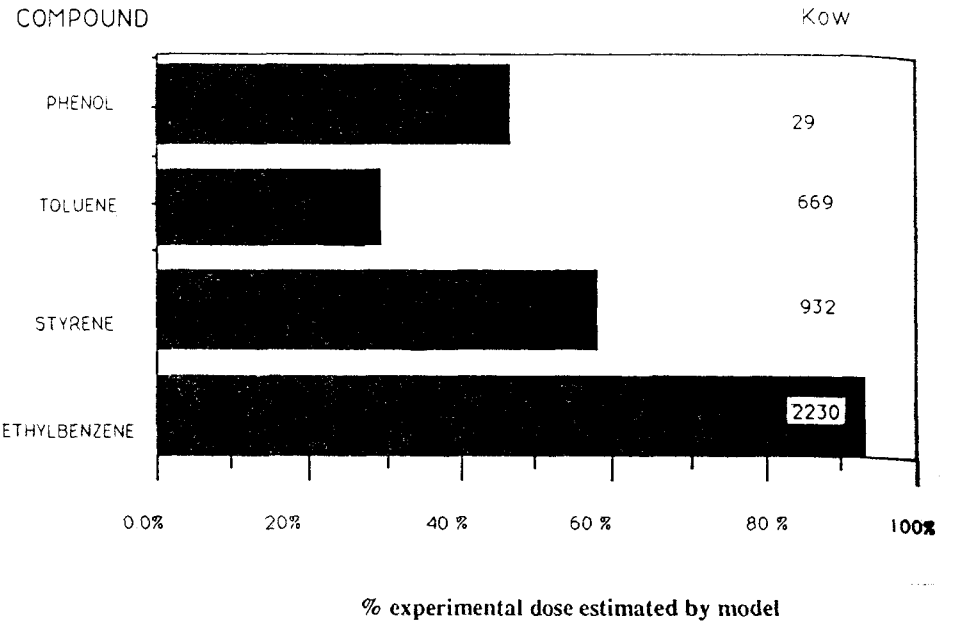

FIG. 6. Percentage of experimental dose predicted by the model in relation to the octano/water partition coefficients for four solutes. Values are from Table 1.

stored in the stratum corneum by 20% (Table 1). This is because the partition coefficient between the stratum corneum and epidermis ($K_{sc/e}$) is based on the relative lipid content of the two compartments, and as stratum corneum lipid content increases, so does $K_{sc/e}$. This effectively decreases the amount crossing from stratum corneum to skin (because $K_{sc/e}$ is in the denominator) and increases the amount returning to the bath in the feedback loop from the stratum corneum. This finding is consistent with findings of Elias *et al.* (1981), and Anderson *et al.*,

TABLE 1

COMPARISON OF CALCULATED VS EXPERIMENTAL DOSES OF ETHYLBENZENE, STYRENE, TOLUENE, AND PHENOL ABSORBED DERMALLY VIA THE HAND

Compound	Concn (mg/liter)	Model predictions		Experimental dose (mg)	% Dose predicted
		Minimum	Maximum		
Ethylbenzene	0.151	34.26	36.72	39.2	94
Styrene	0.167	6.96	7.48	12.8	58
Toluene	0.180	14.21	15.31	51.2	30
Phenol[a]	2.5	6.75	7.06	15.1	47
Parameter		Minimum	Maximum		
SC Fat %		6	3		
Blood fat %		0.7	0.9		
Epidermal thickness (cm)		0.1	0.02		

[a] 30-min exposure instead of 1 hr.

(1988). Overall, the model predicts that thicker and fattier skin would provide better barriers to dermal exposure of chemicals, because greater storage of compounds by the skin compartments results in a decreased absorption rate, and also that a rapid blood flow rate would increase absorption.

Figure 5 indicates that, although the distribution of the solute between the three compartments of the model can be significantly affected by varying epidermal thickness, blood flow, and stratum corneum fat, total absorbed changes little. Thus, the total amount of ethylbenzene absorbed ranged between 34.26 and 37.43 mg under two sets of extreme conditions (minimum and maximum). This is not surprising since the passage across stratum corneum, primarily determined by the solute diffusion coefficient, is the rate-limiting step. This means that as long as we assume that all the material stored in stratum corneum and viable epidermis is eventually taken up by the blood stream, the overall uncertainty in the model is relatively small. In order to put quantitative bounds on that uncertainty, the follow-up runs were set for *minimum* and *maximum* conditions.

In order to validate the model, we compared the experimental results of Dutkiewicz and Tyras (1967, 1968) and Baranowska-Dutkiewicz (1981) with the results of simulations conducted under the same conditions as in the experimental studies. In these studies, absorption of ethylbenzene, toluene, and styrene was calculated as the difference in solute concentration before and after a 1-hr immersion of hands in aqueous solutions of known concentration ("direct method"). Loss of the compound was prevented by a polyethylene bag. This method proved effective in control experiments in which a solution protected in this manner did not change concentration in 2 hr. The authors conducted 14 experiments with seven male subjects. The results were checked against a second set of experiments using excretion of major metabolites to measure absorption ("indirect method"). In this case, 5 experiments were carried out with five male subjects in which hands were exposed for a period of 2 hr. Urine samples were collected every 2 hr for the 14 hr beginning with exposure and again 10 hr later. Measurements of the compound were also taken from expired air. For phenol the method was similar to that for alkylbenzenes except that duration of exposure was 30 min. We used the results of the "direct methods" to evaluate our model because there the amount of chemical absorbed transdermally was more accurately estimated by the authors. The results are shown in Table 1.

According to Table 1, the doses predicted by the model under maximum conditions are all within a factor of 3 or less of the experimental values. All modeled values are underpredicted, as compared with the experimental results. Furthermore, as shown in Fig. 6, it appears that the predictive capacity of the model is higher for more lipophilic compounds with higher values of octanol/water partition coefficient.

Without more data with which to validate the model, we can only speculate on the sources of the observed differences. In addition to the obvious possibility of measurement error in the experiments, several factors could have increased the absorption rate in these studies: in the course of a 1-hr exposure to the moderately concentrated solutions of ethylbenzenes and 0.5 hr to phenol, the barrier properties of the skin could have changed in favor of greater permeability, either because

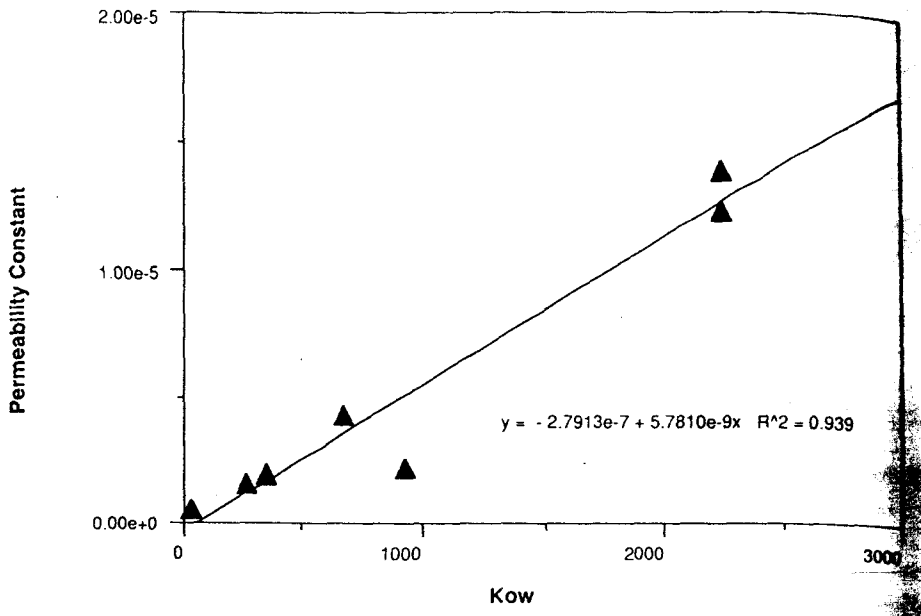

FIG. 7. Correlation between permeability constant and K_{ow} of solute.

of facilitated transport due to solvent accumulated in stratum corneum or because of the increased role of "holes" or "artificial" shunts created in stratum corneum. Rapid metabolism in the epidermal layer, not accounted for by the model, would reduce the concentration of penetrants and shift the equilibrium toward greater absorption. If that were the case, for highly dilute solutions there should be a better consistency between experimental and calculated doses. On the other hand, our model may underestimate the absorption by underestimating any one of several parameters, such as K_m and D_{sc}.

These considerations notwithstanding, we believe that the primary reason for model underestimation is a theoretical one; the model's fundamental assumption of an entirely lipophilic pathway of transport holds well only for highly lipophilic solutes. For less lipophilic solutes only part of the uptake observed in the experiments can be attributed to the lipophilic path; the rest occurs through the protein path, as suggested previously by Anderson *et al.* (1988), and is not accounted for by our model. This is further supported by the strong correlation between permeability constant and Kow, as shown in Figure 7.

In a household environment, exposure to a solute in tap water can occur by three major routes: ingestion, inhalation of solute volatilizing from household water surfaces (shower, sink, toilet, etc.), and dermal contact during bathing. The relative contribution of each route to the total daily dose received by an adult and an infant is shown in Table 2 for ethylbenzene, trichloroethylene, and tetrachloroethylene.

According Table 2, the dermal dose to an infant, when expressed in milligrams per kilogram of body weight, is approximately two times greater than the adult

TABLE 2

COMPARISON OF ADULT AND INFANT DAILY DOSE LEVELS FROM 0.1 MG/LITER IN TAP WATER BY DERMAL, ORAL, AND RESPIRATORY ROUTES (MG/DAY)

Compound	Type	Oral[a]	Respiratory[b]	Dermal[c] Minimum	Dermal[c] Maximum
Ethylbenzene	Adult	0.200	0.287	0.470	0.499
	Infant	0.100	0.136	0.043	0.045
Trichloroethylene	Adult	0.200	0.273	0.055	0.058
	Infant	0.100	0.138	0.0049	0.0052
Tetrachloroethylene	Adult	0.200	0.287	0.065	0.069
	Infant	0.100	0.136	0.0059	0.0062
Chloroform[d]	Adult	NC[e]	NC	0.802	0.849

Body parameters	Minimum	Maximum
SC fat %	6%	3%
Blood fat	0.7%	0.9%
Epidermal thickness (cm)	0.1	0.002
Epidermal fat %	2.5	2.5
Blood flow rate (ml/min/cm^2)	0.028	0.4

[a] Assumes 2 liters of water per day for adult, 1 liter for infant, and body weights of 70 and 9 kg, respectively. Concentration of ethylbenzene, trichloroethylene, and tetrachloroethylene, 0.1 mg/liter; concentration of chloroform; 0.134 mg/liter.

[b] According to McKone (1987).

[c] For adult, 91% of an average 19,000-cm^2 adult is immersed 20 min in 150 liters of bathwater; for infant, 81% of 3800 cm^2 for 10 min in 50 liters of water.

[d] Assumes swimming pool concentration of 0.134 mg/liter in 1.36×10^5 liters of water, 91% immersion of 19,000-cm^2 adult (Beech, 1980).

[e] Not calculated.

dose. This is not surprising and can be attributed to the difference in body surface-to-weight ratios. Table 2 also shows that for ethylbenzene the modeled dermal dose is somewhat greater than either the oral or the inhaled dose, while for tetrachloroethylene and trichloroethylene the dermal dose is significantly smaller than the other two. The relatively small predicted dermal dose for the chlorinated ethylenes may be attributable to the behavior of the model in relation to compounds with low octanol/water partition coefficients, such as these two, rather than to a realistic representation of the uptake. If so, our experience with other compounds (Fig. 6) indicates that the model may be underpredicting the dermal uptake of the compounds by a factor of 2 to 3.

All foregoing predictions made by the model for the full body have been based on parameters determined in experiments with forearm skin. Maibach *et al.* (1971) and others have shown, however, that forearm absorption rates can underpredict dermal absorption in other regions of the body. Working with several pesticides and steroids, Guy and Maibach (1984) experimentally determined absorption factors to relate absorption in other body regions to that of the forearm. We used their so-called "penetration indices" to calculate a corrected full-body dose. Table 3 shows that when the correction is made the predicted total-body dose is

TABLE 3
CORRECTED BODY DOSE OF ETHYLBENZENE ABSORBED DERMALLY

Skin region	Skin area (cm^2)	Penetration index[a]	mg Absorbed[b] per cm^2	Forearm (model) prediction[c]	Corrected dose[d]
Genitals	190	12	2.325×10^{-5}	0.005	0.066
Arms	3,420	1	2.325×10^{-5}	0.079	0.079
Legs	6,840	1	2.325×10^{-5}	0.159	0.159
Trunk	6,840	3	2.325×10^{-5}	0.159	0.477
Head[e]	1,710	4	0	0.000	0
Total	19,000			0.402	0.781

Note. Ratio corrected/model = 1.942.

[a] Ratio of absorption (mg/cm^2) at body site relative to forearm prediction from Guy and Ma... (1984).

[b] Total absorbed/total immersed skin area (91% of 19,000 cm^2 = 17,290 cm^2), 20 min in 150-liter ... with 0.1 mg/liter ethylbenzene.

[c] Skin area * (mg absorbed/cm^2).

[d] Area * penetration index * (mg absorbed/cm^2)

[e] Head not immersed, no absorption.

increased by almost a factor of 2. Thus, the dermal doses listed in Table 2 ... require such a correction.

As a final exercise, we calculated the dermal dose of chloroform to a swim... during a 20-min immersion, using the data of Beech (1980) on the concentratio... trihalomethanes in outdoor pools. The results (in Table 3) indicate that roughly ... mg is absorbed in 20 min. If we correct this total dose by a factor of 3 to accou... for the model's possible underpredictions in this low-K_{ow} region and by anot... factor of 2 to account for absorption by body regions with a higher penetrati... rate, then the total dose to a swimmer may be as high as 4.8 mg, significan... greater than the oral daily dose implicitly allowed by the current EPA drinki... water standard of 0.1 mg/liter for trihalomethanes (0.1 mg/liter × 2 liter/day = ... mg/day).

In order to compare these results with those experimentally estimated by Jo... *al.* (1990) for dermal absorption during showering, we also calculated the derm... absorption of a bather at 0.0245 mg/liter chloroform for 10 minutes, the exper... mental conditions used by Jo *et al.* The resulting theoretical dose of 0.003 mg, ... shown in Table 3, is within a factor of 5 of the experimentally found dose. This ... a close correlation considering that the process of dermal absorption is differen... for a bath versus a shower because of volatilization and skin immersion. Again... the low value of the octanol/water partition coefficient for chloroform (K_{ow} = 9... may be the cause of the underprediction.

CONCLUSIONS

As is the case with most pharmacokinetic models, this one has numerous u... certainties. Some originate from the oversimplification of the complex biologic... system, such as presumption of only the lipid pathway of transdermal transpor...

ply not knowing the system well enough (for example, the theoretical quan-
e foundation of the transport via protein pathway). Other uncertainties arise
roduction of numerous parameters, some experimentally determined in sim-
t not identical systems, such as stratum corneum/water partition coefficient
kness of dermal layers, and others estimated using simplifying assumptions
s the diffusion coefficient in stratum corneum or epidermis/blood partition
cients. Uncertainty also arises from our definition of total absorbed, as
sed earlier.

pite these acknowledged uncertainties, whose effect on the model is largely
wn, the kinetic model presented here is a remarkably good predictor of
absorption of nonelectrolytes in dilute aqueous solutions. Although the
f experimental data available to validate it is admittedly modest, based on
data the theoretical predictions are between 30 and 94% of the experimental
.

on the premise that solutes passively diffuse across stratum corneum
via a lipid path, the model predicts, not surprisingly, that the total uptake
es is proportional to their lipophilicity. Thus, under the same conditions of
re, the dose of ethylbenzene (K_{ow} = 2230) is almost an order of magnitude
than that of trichloroethylene (K_{ow} = 263). Comparison of the model's
on with experimental data also indicates that the above premise may not
compounds with low values of octanol/water partition coefficient and that
repancy between the predicted and experimental dose may be as large as
of 3. Thus, the model should be applied cautiously.

lying the model to bath and swimming pool scenarios we found that the
dose of some VOCs of tap water absorbed during a 20-minute bath may be
in magnitude to either ingested or indoor inhalation dose of that chemical.
per unit of body weight, the dermal dose of an infant is approximately
larger than the adult dose. Furthermore, our estimate of dermal dose of
form absorbed by a swimmer in a typical outdoor pool may exceed the
ermitted oral dose.

en together, these results indicate that dermal uptake of some, although not
OCs in tap water may be significant and deserves attention, on a case-by-
sis, from the regulatory agencies.

REFERENCES

n, B. D., Higuchi, W. I., and Raykar, P. V. (1988). Heterogeneity effects on permeability-
tition coefficient relationships in human stratum corneum. *Pharmacol. Res.* 5(9), 566–573.

on, D. J., and Rook, A. (1986). The newborn. *In* "The Textbook of Dermatology" (A. Rook,
S. Wilkinson, F. J. G. Ebling, R. H. Ebling, and J. L. Burton, Eds.), 4th ed. Vol. 1. Blackwell,
mbridge.

owska-Dutkiewicz, B. (1981). Skin absorption of phenol from aqueous solutions in man. *Int.*
ch. Occup. Health Environ. 49, 99–104.

J. A. (1980). Estimated worst case trihalomethane body burden of a child using a swimming
ol. *Med. Hypothesis.* 6, 303–307.

B., Juang, R. H., and Mazzenga, G. C. (1989). Ethanol and water sorption into stratum
rneum and model systems. *J. Pharmacol. Sci.* 78(6), 472–476.

Bettley, F. R. (1970). The epidermal barrier and percutaneous absorption. *In* "An Introduction
Biology of the Skin" (R. C. Champion, T. Gillman, A. J. Rook, and R. T. Sims, Eds.).
Philadelphia.

Blank, I. H., and McAuliffe, D. J. (1985). Penetration of benzene through human skin. *J.*
Dermatol. **85**, 522–526.

Blank, I. H., and Scheuplein, R. J. (1969). Transport into and within the skin. *Br. J. Der*
81(Suppl. 4), 4–10.

Bogen, D. K. (1989). Simulation software for Macintosh. *Science* **246**, 138–142.

Bowser, P. A., Nugteren, D. H., White, R. J., Houtsmuller, U. M., and Prottey, C. (1985).
cation, isolation, and characterization of epidermal lipids containing linoleic acid. *Biochim*
phys. Acta. **834**, 419–420.

Bowser, P. A., and White, R. J. (1985). Isolation, barrier properties and lipid analysis of
compactum: A discrete region of the stratum corneum. *Br. J. Dermatol.* **112**, 1–14.

Bronaugh, R. L., Stewart, R. F., Congdon, E. R., and Giles, A. L., Jr. (1982). Methods for
percutaneous absorption studies. I. Comparison with *in vivo* results. *Toxicol. Appl. Phar*
62, 474–480.

Brown, H. S., Bishop, D. R., and Rowan, C. A. (1984). The role of skin absorption as a
exposure for volatile organic compounds (VOCs) in drinking water. *Am. J. Public Heal*
479–484.

Brown, H. S., and Hattis, D. (1989). The role of skin absorption as a route of exposure for
organic compounds (VOC's) in household tap water: A simulated kinetic approach. *J. Am*
Toxicol. **8**(5), 839–851.

Davis N. R., and Mapleson, W. W. (1981). Structure and quantification of a physiological mod
distribution of injected agents and inhaled anaesthetics. *Br. J. Anaesth.* **53**, 399–405.

Dugard, P. H. (1977). Skin permeability theory in relation to measurements of percutaneous
tion in toxicology. *In* "Advances in Modern Toxicology: Dermatology and Pharmacology"
Marzulli and H. I. Maibach, Eds.), Vol. 4, Chap. 22. Wiley, New York.

Dutkiewicz, T., and Tyras, H. (1967). A study of the skin absorption of ethylbenzene in man
Ind. Med. **24**, 330–332.

Dutkiewicz, T., and Tyras, H. (1968). Skin absorption of toluene, styrene, and xylene by man
Ind. Med. **25**, 243.

Elias, P. M., Cooper, E. R., Icorc, A., and Brown, B. E. (1981). Percutaneous transport in rela
stratum corneum structure and lipid composition. *J. Invest. Dermatol.* **76**, 297–301.

Elias, P. M. (1981). Lipids and the epidermal barrier layer. *Arch. Dermatol. Res.* **270**, 95–11

Elias, P. M. (1983). Epidermal lipids, barrier function and desquamation. *J. Invest. Dermatol*
448–495.

Flynn, G. L., Durrheim, H., and Higuchi, W. I. (1981). Permeation of hairless mouse skin. II
brane sectioning techniques and influence on alkanol permeabilities. *J. Pharmacol. Sci.*
52–56.

Friberg, S. E., and Kalayi, I. (1989). Water evaporation rates from a model of stratum corneum
J. Pharmacol. Sci. **78**(8), 639–643.

Grayson, S., and Elias, P M. (1988). Human epidermal proteolipids: Isolation characterizatio
subcellular localization. *J. Invest. Dermatol.* **90**, 185–192.

Grubauer, G., Feingold, K. R., Harris, R. M., and Elias, P. M. (1989). Lipid content and lipid ty
determinants of the epidermal permeability barrier. *J. Lipid Res.* **30**, 84–96.

Guy, R. H., Hadgraft, J., and Maibach, H. I. (1985). Percutaneous absorption in man: A ki
approach. *Toxicol. Appl. Pharmacol.* **78**, 123–129.

Guy, R. H., Hadgraft, J., and Maibach, H. I. (1985). Transdermal absorbtion kinetics, a phy
chemical approach. *In* "Dermal Exposure Related to Pesticide Use" (R. C. Honeycutt *et*
Eds.), pp. 19–31. American Chemical Soc., San Diego.

Guy, R H., and Maibach, H. I. (1984). Correction factors for determining body exposure from fore
percutaneous absorption data. *J. Appl. Toxicol.* **4**(1), 26–28.

Hagemann, J. (1979). Cancer risks at work. *In* "Colloquium on Occupational Medicine," 19th An
Conference of German Occupational Medicine Society.

Harpin, V. A., and Rutter, N. (1983). Barrier properties of the newborn infant's skin. *J. Pediatr.* **102**, 419–424.

Hattis, D., Tuler, S., Finkelstein, L., and Luo, Z. (1986). "A Pharmacokinetic/Mechanism-Based Analysis of Carcinogenic Risk of Perchloroethylene," CTPID Publication 86-7. Massachusetts Institute of Technology, Cambridge.

Higuchi, T. (1960). Physical chemical analysis of percutaneous absorption process from creams and ointments. *J. Soc. Cosmet. Chem.* **11**(2), 85–97.

Huq, A. S., Ho, N. F. H., Husari, N., Flynn, G. L., Jetzer, W. E., and Condie, L., Jr. (1986). Permeation of water contaminated phenols through hairless mouse skin. *Arch. Environ. Contam. Toxicol.* **15**, 557–566.

Imokawa, G., Akasiki, S., Minematsu, Y., and Kawai, M. (1989). Importance of intercellular lipids in water retention properties of the stratum corneum: Induction and recovery study of surfactant dry skin. *Arch. Dermatol. Res.* **281**, 45–51.

Jo, W. K., Weisel, C. P., and Lioy, P. J. (1990). Routes of chloroform exposure and body burden from showering with chlorinated tap water. *Risk Anal.* **10**, 581–585.

King, C. S., Barton, S. P., Nicholls, S., and Marks, R. (1979). The change in properties of the stratum corneum as a function of depth. *Br. J. Dermatol.* **100**, 165–172.

Kurihawa-Bergstrom, J., Flynn, G. L., and Higuchi, W. I. (1986). Physicochemical study of percutaneous absorption enhancement by DMSO: Kinetic and thermodynamic determinants of dimethyl sulfoxide mediated transfer of alkanols. *J. Pharmacol. Sci.* **75**(5), 479–486.

Leo, A., Hansch, C., and Elkins, D. (1971). Partition coefficients and their uses. *Chem. Rev.* **71**(6), 555–613.

Lof, A., Lundgren, E., and Byfault Nordquist, M. (1986). Kinetics of styrene in workers from plastics industry after controlled exposure: A comparison with subjects not previously exposed. *Br. J. Ind. Med.* **43**, 537–543.

Maibach, H. I., Feldmann, R. J., Milby, T. H., and Serat, W. F. (1971). Regional variation in percutaneous penetration in man: Pesticides. *Arch. Environ. Health.* **23**, 208–211.

Malkinson, F. D., and Gehlmann, L. (1977). Factors in percutaneous absorption. *In* "Cutaneous Toxicity" (V. A. Drill and P. Lazar, Eds.). Academic Press, New York.

Marzulli, F. N. (1963). Barriers to skin penetration. *J. Invest. Dermatol.* **21**, 387–393.

Mathias, G. G. T., Hinz, R. S., Guy, R. H., and Maibach, H. I. (1985). Percutaneous absorption: Interpretation of *in vitro* data and risk assessment. *In* "Dermal Exposure Related to Pesticide Use" (R. C. Honeycut *et al.*, Eds.), pp. 3–17. American Chemical Society Publishers, San Diego.

McKone, T. E. (1987). Human exposure to volatile organic compounds in household tap water: The indoor inhalation pathway. *Environ. Sci. Technol.* **21**, 1194–1201.

Middleton, J. D. (1968). The mechanism of water binding in stratum corneum. *Br. J. Dermatol.* **80**, 437–450.

Ranasinghe, A. W., Wertz, P. W., Downing, D. T., and MacKenzie, I. C. (1986). Lipid composition of cohesive and desquamated corneocytes from mouse ear skin, *J. Invest. Dermatol.* **86**, 187–190.

Raykar, P. V., Fung, M. C., and Anderson, B. D. (1988). The role of protein and lipid domains in the uptake of solutes by human stratum corneum. *Pharmacol. Res.* **5**(3), 140–150.

Riihhimaki, V., and Pfaffli, P. (1978). Percutaneous absorption of solvent vapors in man. *Scand. J. Work Health.* **4**, 73–85.

Roberts, M. S., Triggs, E. J., and Anderson, R. A. (1975) Permeability of solutes through biological membranes measured by a desorption technique. *Nature* **257**, 225–227.

Rowell, L. B. (1986). "Human Circulation, Regulation During Physical Stress." Oxford Univ. Press, New York.

Ryser, G., and Jequier, E. (1972). Study by direct calorimetry of thermal balance on the first day of life. *Eur. J. Clin. Invest.* **2**, 176–187.

Scheuplein, R. J., Blank. I. H., Brauner, G. J., and MacFarlane, D. J. (1969). Percutaneous absorption of steroids. *J. Invest. Dermatol.* **52**(1), 63–70.

Scheuplein, R. J., and Blank. I. H. (1973). Mechanisms of percutaneous absorption. IV. Penetration of nonelectrolytes (alcohols) from aqueous solutions and from pure liquids. *J. Invest. Dermatol.* **60**, 286–296.

Scheuplein, R. J. (1976). Permeability of the skin: A review of some major concepts. *J. Invest. Dermatol.* **67**, 672–676.

Shehata, A. T. (1985). A multiroute exposure assessment of chemically contaminated drinking water. *Toxicol. Ind. Health* **1**(4), 277–298.

Smith, C. A., and Nelson, N. M., Eds. (1976). "The Physiology of the Newborn Infant," 4th ed., pp. 52, 177–179. Thomas, Springfield, IL.

Smith, W. P., Christensen, M. S., Nacht, S., and Gans, E. H. (1982). Effect of lipids on the aggregation and permeability of human stratum corneum. *J. Invest. Dermatol.* **78**, 7–11.

Sweeney, T. M., and Downing, D. T. (1970). The role of lipids in the epidermal barrier to water diffusion. *J. Invest. Dermatol.* **55**(2), 135–140.

Swyer, P. R. (1978). Heat loss after birth. *In* "Temperature Regulation and Energy Metabolism in the Newborn" (J. C. Sinclair, Ed.). Grune & Stratton, Orlando, FL.

Targett, R. C., Shay, G. F., Heldt, G. P., and McIlroy, M. B. (1986). Doppler blood velocity measurements in the great vessels of newborn infants. *In* "Neonatal Physiological Measurements" (Peter Rolfe, Ed.). Butterworth, Stoneham, MA.

Veulemans, H., and Masschlein, R. (1978). Experimental human exposure to toluene. *Int. Arch. Occup. Health* **42**, 105–117.

Wade, O. L., Bishop, J. M., and Donald, K. W. (1962). "Cardiac Output and Regional Blood Flow," Chaps. 5 and 6. Davis, Philadelphia.

Wertz, P. W., Madison, K. C., and Downing, D. T. (1989). Covalently bound lipids of human stratum corneum. *J. Invest. Dermatol.* **92**(1), 109–111.

West, D. P., Worobec, S., and Solomon, M. (1981). Pharmacology and toxicology of infant skin. *J. Invest. Dermatol.* **76**, 147–150.

Wester, R. C., and Maibach, H. I. (1985). *In vivo* percutaneous absorption and decontamination of pesticides in humans. *J. Toxicol. Environ. Health.* **16**(1), 25–37.

Wester, R. C., Mobayen, M., and Maibach, H. I. (1987). *In vivo* and *in vitro* absorption and binding to powdered stratum corneum as methods to evaluate skin absorption of environmental chemical contaminants from ground and surface water. *J. Toxicol. Environ. Health* **21**, 367–374.

Weston, W. L. (1985). "Practical Pediatric Dermatology," 2nd ed. Little, Brown, Boston.

Yardley, H. J. (1987). Epidermal lipids. *Int. J. Cosmet.* **59**, 13–19.

Yates, J. R. (1971). Mechanisms of water uptake by skin. *In* "Biophysical Properties of the Skin" (H. R. Elden, Ed.), Vol. I. Wiley, New York.

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