Final Project Report
Improved Methods for Dermal Exposure Estimation

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List of Terms and Abbreviations

Parameter	Units	Definition
ρ	g/cm^3	Density
σ		Lipid/corneocyte permeability ratio
C_{sat}	g/cm^3	Solubility of permeant in SC
D_{de}	cm^{2}s^{-1}	Dermis diffusivity including binding
de		Dermis
D_{ed}	cm^{2}s^{-1}	Viable epidermis diffusivity
D_{free}		Dermis diffusivity of an unbound permeant
D_{cor}^{free}	cm^{2}s^{-1}	Diffusivity of unbound permeant within a corneocyte
D_{lip}	cm^{2}s^{-1}	Lateral diffusivity in SC lipids
D_{sc}	cm^{2}s^{-1}	Effective diffusivity of permeant in SC
ed		Viable epidermis
f_u	-	Fraction unbound in a 2% albumin solution[b]
h_{de}	cm	Dermis thickness
h_{dep}	cm	Thickness of deposition layer in SC
h_{ed}	cm	Viable epidermis thickness
H_{lat}	-	Hydration effect factor for lateral diffusion in SC lipid bilayers
h_{sc}	cm	Stratum corneum thickness
H_{trans}	-	Hydration effect factor for transverse mass transfer in SC lipid bilayers
k_{de}	s^{-1}	Capillary clearance rate constant including binding
K_{de}[a]	-	Dermis/water partition coefficient including binding
K_{ed}	-	Viable epidermis/water partition coefficient
k_{ed}	s^{-1}	First-order metabolic clearance constant in viable epidermis
k_{evap}	cm/s	Condensed phase mass transfer coefficient for a volatile permeant
K_{free}		Dermis/water partition coefficient for an unbound permeant
K_{cor}^{free}	-	Partition coefficient (with respect to water) of unbound permeant within a corneocyte
k_{free}	s^{-1}	Capillary clearance rate constant for an unbound permeant
k_g	cm/s	Gas phase mass transfer coefficient for a volatile permeant
K_{lip}	-	SC lipid/water partition coefficient
K_{sc}	-	SC/water partition coefficient
k_{trans}	cm·s^{-1}	Transverse mass transfer coefficient in SC lipids
log K_{oct}	-	Octanol/water partition coefficient
M_r		Reduced dose (= Applied Dose/M_{sat})
M_{sat}	μg/cm^2	Saturation dose for permeant applied to SC
MW	Da	Molecular weight
MW$_r$	-	Reduced molecular weight (= MW/100)
pK_a	-	Ionization constant(s)[a]
P_{sc}	cm·s^{-1}	Permeability coefficient for SC
P_{vp}	torr	Vapor pressure
R		Ratio of transverse mass transfer to lateral diffusion in SC lipids
sc		Stratum corneum
S_w	g/cm^3	Water solubility of unionized form

Abstract
A mathematical model that closely mimics percutaneous absorption, tissue concentrations and clearance in human skin in vivo was developed. Unique features of this model include an unprecedented level of detail in relating solute transport to the skin microstructure and the ability to simulate a broad variety of exposure conditions and skin hydration states. Completed components include a microscopic model of transport in human stratum corneum, a dermal vascular model including solute exchange in capillary loops, and a disposition model for arbitrary doses of volatile organic compounds contacting the skin. Experimental refinement of the model parameters in our laboratory has included microscopic analysis of stratum corneum structure and skin disposition studies for fragrance ingredients and pesticides deposited from ethanolic solutions.

Absorption model development was approached in a stepwise fashion involving five specific aims. Aims 1-4 involved development of the specific model components (stratum corneum transport, dermal clearance, volatiles disposition and skin hydration effect) and Aim 5 involved the synthesis of these components into a comprehensive computer model with a user-friendly interface. At each step a systematic analysis of skin literature data combined with experimental measurements to obtain otherwise unavailable information was used to justify and calibrate the selected approach. Mathematical methods were based on finite difference approximations to diffusive transport involving variable-spaced grids and asymptotic solutions to describe transport in complex geometries. Laboratory methods included in vitro human skin penetration and sorption/desorption studies and volatiles trapping studies with test ingredients applied to human skin in vitro and on the volar forearm in vivo.

Highlights/Signficant Findings

The salient findings of the study include the following: For most permeants, solute permeation through stratum corneum involves a combination of intercellular and transcellular transport with the balance determined by solute size and lipophilicity. Conventional models restricting transport to intercellular lipids fail to quantitatively describe lag times or solute holdup within the stratum corneum; hence, they are limited in their ability to describe the transient skin exposures common to occupational settings. Solute transport in the dermis can be described by a diffusivity and partitioning model incorporating binding to albumin and insoluble skin components combined with a distributed model for capillary clearance. Significant correlations of absorption and evaporation rates of fragrance ingredients with their physicochemical properties (vapor pressure, molecular weight and lipid solubility) were obtained and justified on the basis of the diffusive transport model. Validation of the approach for pesticides and organic solvents is underway in the related continuation project. The first quantitative microscopic model for hydration effects in human stratum corneum has been proposed. The model components have been combined into a user-friendly format as a Visual Basic add-in operating under Microsoft Excel®.

Translation of Findings

At the project completion date in 2007 (4 years of NIOSH support + one year no-cost extension) a prototype spreadsheet skin absorption model was up and running and available – in principle – to interested users. However, it was not widely publicized and several of the key articles summarizing the work had not yet appeared. Progress was sufficient to support a continuation proposal to NIOSH that was accepted after one revision (5 R01 OH007529, 09/01/2007 – 08/31/2012). A substantial portion of the continuation project is being conducted by Dr. John Kissel at the University of Washington's School of Public Health. John is an environmental

engineer in the Department of Environmental and Occupational Health Sciences. A component of his job is to use the skin absorption model to critically assess clinical and field data on pesticides, and to subsequently publicize this work. We furthermore generated interest from a Brussels-based industrial consortium, COLIPA, to create a related model for epidermal bioavailability in conjunction with animal-free risk assessment methods for putative contact allergens. This aspect of our work has resulted in two rounds of support from COLIPA.

As of this writing (late 2008) use of the computer model is moving forward on several fronts. Dr. Kissel is analyzing in vitro and clinical data on chlorpyrifos and will present this work at OEESC 2009 in Edinburgh. We are working with industrial toxicologists from three COLIPA companies to analyze skin concentration data associated with topical application of cosmetic ingredients. We recently published research articles in *Environmental Science and Technology* and the *Journal of Occupational and Environmental Hygiene* giving details of the Excel-based skin absorption model and advertising its availability to government and industrial toxicologists.

Longer term plans involve validation of the model as an animal alternative method through the European toxicology group ECVAM. We furthermore plan to make the model available in a to-be-determined public format. This may involve licensing or selling the rights to the computer model to a toxicology software firm, or it may involve putting a streamlined version on a toxicology website.

Outcomes/Relevance/Impact

The estimation of skin penetration rates and systemic absorption of compounds following intentional or incidental application to the skin is an important aspect of dermal risk assessment in occupational safety and hygiene. The number of chemicals to which the population is exposed on a daily basis is so high that only a small fraction can be studied experimentally. For the remaining compounds judicious application of well-conceived mathematical models can make the difference between a plausible and defensible risk analyses and the lack thereof. This, in turn, can aid in early identification and elimination of workplace or consumer hazards.

Our research is distinguished primarily by the attention to which skin physiology, physical chemistry and microstructure are built into the developed mathematical models. Published work to date concerns microtransport processes within the stratum corneum (Aim 1, three papers); solute diffusivity, partitioning and clearance in the dermis (Aim 2, five papers); the disposition of finite doses of (potentially) volatile chemicals following application to the skin (Aim 3, seven papers); water sorption and mobility in skin (Aim 4, two papers), and a Visual Basic™ add-in and Excel™ spreadsheet interface implementing the calculations (Aim 5, two book chapters). The stratum corneum and dermis models are fundamentally new treatments of solute transport within these skin layers. The finite dose model incorporates new concepts of a solute deposition depth within the stratum corneum and a calibrated evaporative mass transfer coefficient. The skin hydration papers present a new analysis of equilibrium water content in human stratum corneum as a function of water activity and a detailed analysis of water transport in the stratum corneum that challenges entrenched beliefs regarding solute permeation pathways in this tissue. We anticipate that the work will lead to a re-examining of the disposition of topically-applied compounds and, ultimately, to an improved understanding of chemical absorption through the skin.

Discussions with industrial hygienists and consumer product toxicologists confirm that a significant weakness in the current methodology for dermal risk assessment involves the extrapolation from steady state absorption models to transient absorption estimates for

incidental exposures to aerosolized ingredients (e.g., field workers applying pesticides) or intentional application of consumer products (e.g., skin creams or hair sprays). The approaches developed in this project and the related continuation project will allow vastly improved absorption estimates for these scenarios, improving the quality of the risk assessment process. A corollary to this benefit is the potential for increased mechanistic understanding of dermal toxicities such as contact allergy due to the ability of the developed model(s) to accurately predict concentration-time profiles of allergens at immunologically responsive sites in the skin (Langerhans cells). This possibility has already attracted the interest of the European consumer products consortium COLIPA and has resulted (by 2008) in two additional projects related to allergic contact dermatitis, another NORA priority area. The objective of these projects is to construct an *in silico* epidermal bioavailability component of an animal-free risk assessment model for putative contact allergens.

Scientific Report:
Improved Methods for Dermal Exposure Estimation

SPECIFIC AIMS

Both dermal exposure estimation and the mechanistic understanding of allergic and irritant dermatitis can be significantly advanced through the development of improved models for percutaneous penetration and absorption of hazardous chemicals under conditions relevant to occupational exposure. This can be accomplished through the construction and experimental verification of physiological and physical properties-based models for skin penetration, tissue concentrations and dermal clearance incorporating features not found in the steady state penetration models presently used to estimate dermal exposure. These include a three-dimensional skin architecture with follicles and sweat glands, a spatially distributed dermal microvasculature, dose and time-dependent absorption rates, and hydration effects on skin permeability. Consequently, the investigators hypothesize as follows:

> "A sophisticated, yet accessible mathematical model that closely mimics percutaneous penetration, tissue concentrations and clearance in human skin in vivo can be developed. The inputs needed for this next-generation approach will come from a program of experiments specifically targeting microscopic thermodynamic and transport properties, rather than just conventional overall penetration rates, the latter representing the convoluted, aggregate outcome of many such parameters unsuitable for fully dissecting the underlying physics. This development will significantly advance the mechanistic and predictive understanding of allergic and irritant dermatitis and the mechanics of dermal exposure assessment."

This hypothesis will be advanced and tested by addressing the following specific aims:

Aim 1: To extend the development of microscopic models of transport in human skin, addressing both structure below the stratum corneum (sc) (by determining microscopic solubility and transport properties of individual tissue layers, and incorporating further skin appendages additional to follicles – initially, the eccrine sweat gland), and the sc itself (by measuring relevant microstructural and microtransport properties – corneocyte arrangement, corneocyte permeability and lipid pathway tortuosity). These results will be incorporated into a working mathematical model under construction in our laboratories.

Aim 2: To develop a dermal vascular model which allows accurate prediction of permeant concentrations and clearance in the viable skin layers following penetration through the sc. The model will consider spatial variations in capillary density and permeability both perpendicularly to the skin surface and radially with respect to skin appendages. Realism will be ensured via calibration of the model against dermal microdialysis and other data reported in the literature or developed independently of this proposal.

Aim 3: To establish the relationship between the physical properties of topically applied compounds and their dose and time-dependent penetration rates through human skin, using finite dose diffusion models to establish the correlation. For volatile compounds, the evaporation rate will be simultaneously predicted as a function of physical properties, skin temperature, and surface airflow.

Aim 4: To incorporate the effect of skin permeability changes subsequent to partial or full occlusion into the mathematical models developed in Aims 1 and 3. This development will link

these models with existing steady state skin permeability models representing fully hydrated skin.

Aim 5: To combine the components arising from Aims 1-4 into a single, predictive dermal absorption model having both an attractive ease of use and a broad range of applicability. The model will be structured and made available in a form that ultimately outputs the comprehensive calculations involved as an EXCEL™ spreadsheet.

BACKGROUND AND SIGNIFICANCE

The estimation of skin penetration rates and systemic absorption of compounds following intentional or incidental application to the skin is an important aspect of exposure assessment. For compounds having high exposure levels and/or high potential toxicity extensive experimental studies of dermal absorption, metabolism, and toxicity can be justified. Yet the number of chemicals to which the population is exposed on a daily basis is so high that only a small fraction can be studied experimentally [1-3]. For the remaining compounds judicious application of well-conceived mathematical models can make the difference between a plausible and defensible risk analyses and the lack thereof. This, in turn, can aid in early identification and elimination of workplace or consumer hazards. Consequently, such an approach is widely used in many industries [2,4,5]. Even those with serious reservations about the predictions of mathematical models often agree they can be used to prioritize experimental studies [6].

The above comments apply to the occupational health and safety area. Industrial hygienists and government personnel in the U.S. and elsewhere use the best available modeling approaches to identify workplace hazards, guide chemical labeling, recommend protective equipment and prioritize research [7]. Therefore, advances in the modeling process carry with them the prospect of making better decisions in these important areas.

Within the US NIOSH organization extensive use has been made of a skin penetration model identified as the "modified Robinson model" by Wilschut and coworkers in a 1995 study comparing various modeling approaches [8,9]. This is a steady state absorption model derived in part from work of one of the investigators (GBK) [10,11]. The model utilizes the physical properties of the permeant (octanol/water partition coefficient and molecular weight) in conjunction with a composite membrane model for skin (lipid and polar pathways through the sc plus an aqueous skin layer) to derive skin permeability coefficients, k_p, for compounds applied to skin from a large volume of aqueous solution. In combination with water solubility estimates, S_w, the model can be used to predict the maximum flux, $J_m = k_p S_w$, of the compound from an arbitrary, non-damaging solvent [10]. This is the manner in which the model is most often applied [8]. The limitations of this approach are well known and will be discussed in some detail below. Nevertheless, Wilschut [9] considered it to be the best available approach in 1995, a situation that, to the investigators' knowledge, has not changed within the past five years. The time appears ripe to incorporate new data and concepts into this model that can remove some of the limitations and broaden the range of applicability. In particular, the specific aims of this proposal are designed to accomplish the following:

- Provide a physiological basis for the "polar pathway" and "aqueous skin layer" described in the Robinson model based on quantitative estimates of corneocyte, desmosomal, appendageal, and deeper tissue permeabilities (Aim 1).

- Replace the artificially restrictive capillary permeability term in the Robinson model with a distributed vascular clearance and dispersion model incorporating physiological theories of

capillary permeability and transport, and validated against microdialysis and tissue sectioning studies reported in the literature. This is expected to strongly influence calculated dermal and hypodermal concentration profiles, particularly in the vicinity of a hair follicle (Aim 2).

- Provide vastly improved estimates for skin concentrations and systemic absorption following transient exposures to small doses of potentially volatile compounds applied to non-hydrated skin (Aim 3).

- Establish the connection between steady state (infinite dose) and transient (finite dose) models by appropriate incorporation of the effect of hydration on skin permeability into the latter model (Aim 4).

- Make the model easily accessible for use in exposure assessments by implementation in a spreadsheet format (Aim 5).

These objectives align closely with NORA research priorities in the areas of Exposure Assessment Methods and Allergic and Irritant Dermatitis. In both areas, for exposures involving skin contact, percutaneous absorption estimates provide a crucial link between exposure characterization and biological response. The NORA Allergic and Irritant Dermatitis Team has identified research into the physiology of percutaneous absorption as a key component for understanding the basic pathophysiology of both irritant contact dermatitis and allergic contact dermatitis [7]. The latter is one of six high priority research areas in the basic biomedical sciences. The proposed research represents a radical departure from the correlation-based absorption models presently in use in that skin structure and physiology are built into the new approach in considerable detail. Relative to previous analyses having this more mechanistic character [4,12-14], it represents a major step forward in that appendageal structures will be incorporated at a level of realism heretofore unseen, and microscopic thermodynamic and transport properties will be assigned realistic values on the basis of new microscopically-targeted experiments instead of being left as esoteric adjustable, unassigned or undetermined parameters.

The investigators believe the preceding approach will not only result in more accurate predictive models, but also advance scientific understanding of percutaneous absorption mechanisms. The proposed emphasis on local in-tissue permeant concentrations is key to such mechanistic understanding, and these concentrations are inaccessible by conventional research methods targeting steady state permeability or gross uptake. The proposed work will thus be pivotal in establishing the relationship between local tissue concentrations and skin response, and thereby be directly applicable to the concept of threshold-based contact allergy risk assessment [2,15,16]. It is the investigators' intention to work closely with members of the NORA AID team and others involved in contact dermatitis research and in vivo measurement of permeant concentrations in skin to ensure the applicability of the theoretical developments to skin biology and pathophysiology. Consultants in the project include Dr. Frank Gerberick, a NORA AID team member, Dr. Torkil Menné, a dermatologist with extensive clinical experience in contact allergy, and Dr. Eva Benfeldt, a dermatologist with expertise in dermal microdialysis.

REPORT FORMAT

We take a recent summary of the developed model [62] and annotate it with respect to the specific aims of the project. The aims are highlighted in a **bold blue** font.

MODEL FRAMEWORK (AIM 1)

The disposition of (potentially) volatile products following application to the skin plays a role in both their safety and efficacy. The absorption rate determines systemic levels and skin concentrations, both of which must be factored into risk assessments. The evaporation rate determines efficacy for certain products, e.g., a fine fragrance or an insect repellant. These two factors are interdependent, as both depend on and, in turn, affect the residual concentration of the compound in or on the skin.

We have investigated two general approaches to this problem – a well-stirred compartment or pharmacokinetic model [17-22] and a diffusion model [23,24]. The former is simpler and has merit for interpolation within a closely related set of compounds and exposure conditions. Its application to risk assessment for perfume raw materials (PRMs or fragrance ingredients) has been discussed [22]. The pharmacokinetic approach will not be further considered here; the focus of the research project and this report is how to make predictions using the diffusion model.

A suitable starting point for a skin diffusion model for volatile chemicals is shown in Figure 1. This is a one-dimensional model comprised of four layers – a vehicle layer or donor solution (ds), stratum corneum (sc), viable epidermis (ed) and dermis (de). The upper two layers correspond to the diffusion model described in [23]. If only systemic absorption estimates are required and the compound is not highly lipophilic [25], then solution of the diffusion equation in these two layers with sink conditions at the base of the stratum corneum provides an adequate description of the problem. Analytical solutions to this problem for a number of exposure conditions may be found [23,26,27]. If, on the other hand, skin and underlying tissue concentrations are of interest, it is necessary to include an explicit representation of the skin layers and (perhaps) the underlying fat and muscle. We will not consider the sub dermal layers here; for a useful discussion, see [28]. A distributed model for partitioning, diffusion and clearance in the dermis has recently been described by workers from our laboratories [29,30]. This model forms the basis for the viable skin model presented here. It is noteworthy that less is known about the transport properties of viable epidermis than dermis. Our working approach, discussed later, is to treat viable epidermis as unperfused dermis. Because the diffusive resistance of viable epidermis appears to be low, this assumption has a minimal impact on systemic absorption estimates. However, it does affect the tissue concentration calculation in that layer. For problems such as allergic contact dermatitis, where the putative site of action is the Langerhans cell surface in the mid epidermis, a physiologically accurate representation of the epidermis is desirable. The cellular nature of this tissue, in contrast to the largely acellular (but fibrous) dermis, in all probability imparts to it different selectivity for transport of chemical permeants.

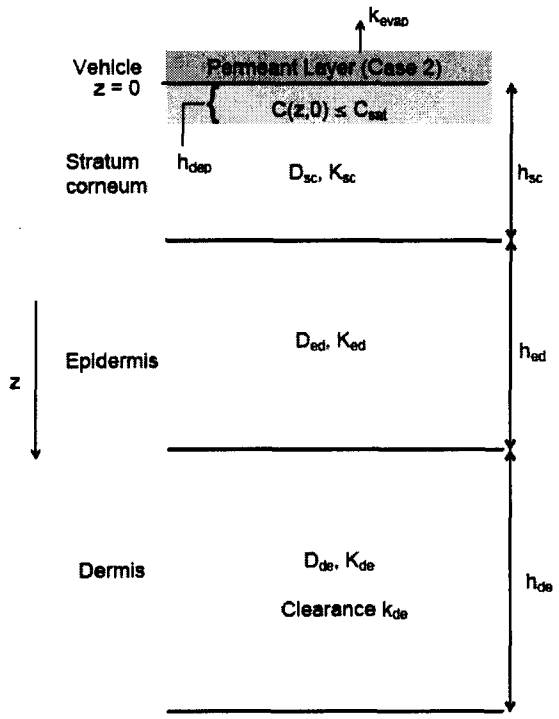

Figure 1. Schematic diagram of diffusion/ evaporation model for skin disposition of potentially volatile permeants.

A study of the schematic diagram shown in Figure 1 gives rise to three important questions: (1) Is it reasonable that a slab model with no internal microstructure can accurately represent skin transport? (2) How can appropriate transport parameters for the slab model be chosen prospectively? (3) How can the calculation be implemented? Each of these questions is addressed in the following sections. An example calculation for the fragrance ingredient, benzyl alcohol, is then presented showing the power of the technique, but also revealing some of its limitations. Complexity is incurred because many small, semi polar molecules like benzyl alcohol affect skin permeability, presumably by interacting with stratum corneum lipids. A general method of predicting these interactions is not yet known.

EFFECTIVE MEDIUM THEORY (AIM 1)

Although the "sc," "ed" and "de' slabs each have complex microstructures, they can be described macroscopically as effective homogeneous continua characterized by average diffusion and partition coefficients. Theory for this type of coarse-graining has a distinguished history in mathematical physics going back to the pioneering analyses of macroscopic conduction properties of composite media by Maxwell [31] and Rayleigh [32]. The scope of the approach was later extended by Brenner and others, as summarized by Brenner and Edwards [33]. An important finding from this research is that such an approach may be justified so long as the time scale of the phenomenon of interest is long compared to those of the relevant microscopic transport processes contributing to the observed effect. Long-standing belief that transport through the SC is describable as Fick's-law diffusion through an effective homogeneous membrane [34,35] has been confirmed recently in, e.g., an experimental study by Kalia et al. [36] and theoretical studies by Frasch and Barbero [37-39]. Using a two-dimensional

brick-and-mortar microstructural representation of stratum corneum, the latter investigators derived an effective diffusivity and partition coefficient for the system and showed how to more accurately predict the diffusive lag time from these parameters.

Our combined research groups have further developed the effective medium approach for modeling transport in the stratum corneum [23,24,40-42] and the dermis [29,30,43]. Substantial predictive power is evident in both cases. In the following section, formulas for the transport properties resulting from these investigations are presented. They are all derivable from the simple set of physical properties shown in Table 1.

Table 1. Required permeant physical properties for skin transport calculations. All properties are determined at skin temperature, normally taken to be 32°C. For a discussion, see [23].

Parameter	Units	Definition
MW	Da	Molecular weight
log K_{oct}	-	Octanol/water partition coefficient
S_w	g/cm^3	Water solubility of unionized form
P_{vp}	torr	Vapor pressure
pK_a	-	Ionization constant(s)[a]
f_u	-	Fraction unbound in a 2% albumin solution[b]
ρ	g/cm^3	Density

[a]The fraction nonionized (f_{non}) in the stratum corneum (pH 5) and viable skin tissues (pH 7.4) must be estimated. All pK_a values relevant to this calculation should be included.
[b]In the absence of experimental data, the method of Yamazaki and Kanaoka [44] may be employed to obtain this value [30].

EFFECTIVE TRANSPORT PARAMETERS FOR SKIN (AIMS 1-4)

STRATUM CORNEUM **(AIMS 1 & 4)**

Model-based calculation. The microstructural model from which the stratum corneum parameters are derived is shown schematically in Figure 2. The model is described in considerable detail in [40-42]. The features that distinguish this model from earlier entries in the field are: (1) a more realistic geometry with lipid pathways calibrated from microscopic examination of human stratum corneum [45]; (2) anisotropic lamellar lipids [46] with six bilayers separating opposing corneocytes; (3) permeable corneocytes that swell when the skin is hydrated [47,48] and also bind permeants [42]. To describe this system in the slab form shown in Figure 1, three parameters are needed: hsc, Dsc and Ksc. Here, Ksc is short for Ksc/pH, where Ksc/pH reflects the partition coefficient of the permeant between stratum corneum and buffer at a pH at which it is 100% unionized. Derivations of the formulas reported here may be found in [41] and [42].

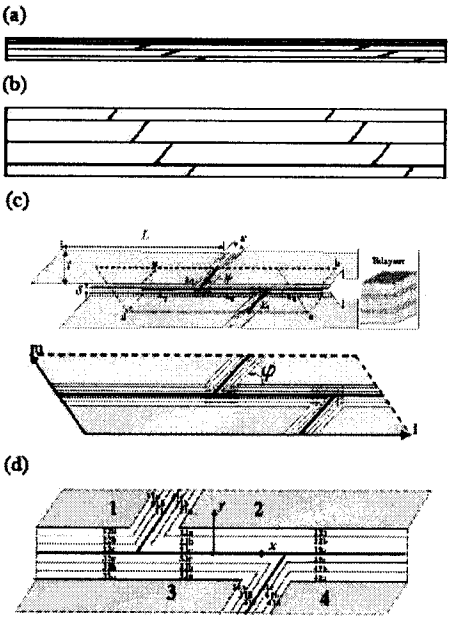

FIGURE 2. Definition sketch showing assumed model microstructure. (a) Structure for partially hydrated skin. (b) Structure for fully hydrated skin. (c) Schematic drawings indicating notation (not to scale). (d) Labeling scheme used to identify individual lipid bilayers and corneocytes within a unit cell.

We focus on the solution described as Model 2 for partially hydrated skin [41]. Model 2 refers to the postulated lipid bilayer arrangement between corneocytes and is the more likely of the two limiting arrangements described in [41]. "Partially hydrated" means stratum corneum containing an average water content of 30% w/w or 0.43 g H2O/g dry SC. Stratum corneum properties in the partially hydrated state are quite different from those in the fully hydrated state (73% w/w, 2.79 g H2O/g dry SC) which applies to most steady-state permeability measurements in vitro. The calculation of corneocyte phase transport properties Dcor and Kcor in [41] has furthermore been simplified to require only the molecular weight (MW) of the permeant. In [41] these properties are estimated from the molar volume of the permeant (VA) using hindered diffusion arguments. In the formulas below, Dcor and Kcor are calculated directly from MW by regressing the more accurately calculated VA-based values against MW for the 97 permeants analyzed in [41]. A maximum error of 41% in the Dcor values and 12% in the Kcor values is introduced by this procedure, leading to an rms error of 0.6% and a maximum error of 5% in the macroscopic properties Psc and Dsc. The higher accuracy for the latter parameters arises because most of the diffusive resistance of the stratum corneum lies in the lipid phase rather than the corneocytes.

The simplified formulas for partially hydrated stratum corneum transport properties are shown in Table 2. In these equations, MW is the gram molecular weight of the permeant and K_{oct} is its octanol/water partition coefficient. The "reduced" molecular weight MW_r = MW/100 is introduced as a matter of convenience for scaling the coefficients. Values of the partially hydrated stratum corneum permeability P_{sc} calculated from the relationships in Table 2 are lower than hydrated skin permeabilities by approximately a factor of three, deriving mainly from the lipid disruption

factor H_{trans} (eq. 4). However, geometrical swelling and corneocyte permeability factors also play a role. By combining the value of P_{sc} with the partition coefficient for partially hydrated stratum corneum, K_{sc}, [42] and its thickness h_{sc}, the effective diffusivity D_{sc} is obtained at the end of the process (eq. 15).

Table 2. Formulas for stratum corneum transport parameters for partially hydrated skin. The formulas are developed in Refs. [23] and [40-42].

Parameter	Units	Formula or value	Eq. #
Defining relationship		$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}\left(D_{sc} \frac{\partial C}{\partial x} \right)$ $0 \le C \le C_{sat}$	1
h_{sc}	cm	0.0013365	2
H_{lat}	-	3	3
H_{trans}	-	3	4
MW_r	-	MW/100	5
D_{lip}	$cm^2 s^{-1}$	$\left[1.24\times10^{-7} MW_r^{-2.43} + 2.34\times10^{-9}\right] / H_{lat}$	6
k_{trans}	$cm \cdot s^{-1}$	$0.1884 \cdot \left[\exp\left(-8.465 \cdot MW_r^{1/3}\right)\right] / H_{trans}$	7
K_{lip}	-	$0.43 \cdot (K_{oct})^{0.81}$	8
D_{cor}^{free}	$cm^2 s^{-1}$	$2.793\times10^{-6} MW_r^{-1.011}$	9
K_{cor}^{free}	-	$10\text{^}\left(-0.444 - 0.0655 \cdot MW_r - 0.00273 \cdot MW_r^2 + 0.000534 \cdot MW_r^3\right)$	10
σ		$D_{lip} K_{lip} / (D_{cor}^{free} K_{cor}^{free})$	11
R		$7.04642 \cdot k_{trans} / D_{lip}$	12
P_{sc}	$cm \cdot s^{-1}$	$\frac{D_{lip} K_{lip}}{h_{sc}\left(0.8979 \cdot \sigma + 5.536\times10^5 / R\right)}$ for $R \ge 100$.	13
K_{sc}	-	$0.040(K_{oct})^{0.81} + 0.359 + 4.057 \cdot (K_{oct})^{0.27}$	14
D_{sc}	$cm^2 s^{-1}$	$P_{sc} h_{sc} / K_{sc}$	15
h_{dep}	cm	$0.1 \cdot h_{sc}$	16
C_{sat}	g/cm^3	$K_{sc} S_w$	17
M_{sat}	$\mu g/cm^2$	$C_{sat} h_{dep} \times 10^6$	18

For finite dose calculations, the concept of a deposition depth, h_{dep}, a saturation concentration, C_{sat}, and a saturation dose, $M_{sat} = h_{dep} \times C_{sat}$, are extremely useful [23,24,49,50]. The concept derives from a picture of the upper stratum corneum as a relatively permeable, desquamating layer into which topically applied permeants are rapidly deposited [23]. The C_{sat} parameter imposes a solubility limit of the permeant in the stratum corneum, and the ratio of applied dose to M_{sat} – the "reduced dose", M_r – distinguishes a large dose from a small one. According to the convention in [23], a small dose is described by $M_r \le 1$ and is designated as Case 1. A large dose, described by $M_r > 1$, is designated as Case 2. Large doses show qualitatively different behavior than small doses, as may be seen from Figure 3. Solubility limitations (C_{sat}) and skin capacity limitations (M_{sat}) are among the reasons that finite dose skin absorption problems are inherently more difficult than steady state permeability calculations. Another is that the math is harder.

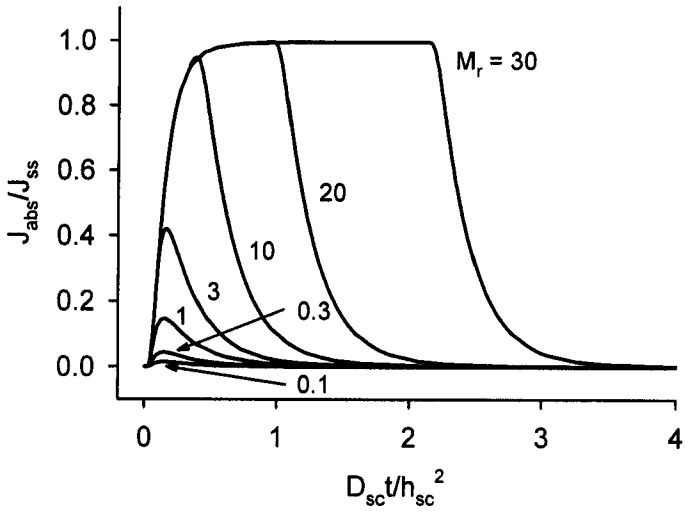

Figure 3. Transient absorption flux for a moderately volatile permeant [23]. The "reduced dose" M_r = Applied Dose / M_{sat} determines the boundary between small and large doses. For small doses ($M_r \leq 1$) the absorption curves have the same shape and are dose-proportional.

Experimentally based calculation. If an experimental value of the steady-state permeability coefficient from aqueous solution is available, an alternative means of calculating stratum corneum transport properties should be used. This method comprises the following steps [24]:

1. Start with the measured skin permeability coefficient, k_p. Calculate the hydrated stratum corneum permeability, P_{sc} (hydrated), as

$$\frac{1}{P_{sc}(\text{hydrated})} = \frac{1}{k_p} - \frac{h_{ed}}{D_{ed}K_{ed}} - \frac{1}{K_{de}(D_{de}k_{de})^{1/2}} \tag{19}$$

   where the epidermis and dermis parameters are taken from Tables 3 and 4. Unless the compound is highly lipophilic, this correction may be omitted and P_{sc} (hydrated) $\cong k_p$. *Note*: The series resistance model leading to eq. 19 follows from the steady-state analysis in [29] and is also discussed in [30].

2. Calculate the partially hydrated skin permeability, P_{sc}, as

$$P_{sc} = P_{sc}(\text{hydrated}) \cdot \frac{P_{sc}^{\text{model}}(\text{partially hydrated})}{P_{sc}^{\text{model}}(\text{hydrated})} \tag{20}$$

   where the ratio on the right corrects the experimental value to the partially hydrated state using the model calculation [41]. As the model is presently parameterized (Table 2), this ratio is essentially 1/3 [24].

3. Calculate the remaining stratum corneum parameters according to eqs. 14-18 (Table 2).

Independent of whether the model-based calculation or the experimentally based calculation of stratum corneum properties is employed, one further correction is advised. The permeant

solubility in stratum corneum, C_{sat}, and the related saturation dose, M_{sat}, are key parameters in the transient diffusion calculation. C_{sat} is estimated from water solubility, S_w, and stratum corneum/water partition coefficient, K_{sc}, according to eq. 17. This approach of equating a partition coefficient, K_{sc} (which is defined for infinitely dilute solutions), to a solubility ratio, C_{sat}/S_w, works well for poorly soluble permeants, but can lead to substantial errors for more soluble permeants whose presence affects the structure of either stratum corneum or water. It is our experience that C_{sat} may be significantly overestimated by eq. 17 for very soluble permeants [50]. In the absence of a better approximation than eq. 17, we recommend imposing a limit on C_{sat} based on experimental evidence. The current limit for our calculations for all permeants except water is C_{sat} = 0.300 g/cm^3, which is the measured value for ethanol in stratum corneum containing 30% water content [51]. For water, C_{sat} may be as high as 0.79 [47]. Imposition of these limits avoids the mistake of calculating skin absorption based on unrealistically high stratum corneum concentrations. Therefore, for all permeants except water, eq. 17 is modified to

$$C_{sat} = \min(K_{sc}S_w, 0.300\,\mathrm{g/cm^3}) \tag{21}$$

If the 0.300 g/cm^3 limit for C_{sat} is selected, a revised K_{sc} is then calculated as

$$K_{sc} = C_{sat}/S_w \tag{22}$$

effectively replacing eq. 14.

DERMIS **(AIM 2)**

The dermis is a fibrous matrix that is largely acellular. Collagen and elastin fibers hinder the diffusion of macromolecules, and the glycosaminoglycans (GAGs) which fill much of the interfiber spaces hinder transport of both large and small molecules due to their fine herringbone structure [30]. There is a vascular plexus approximately 1 mm deep in the skin, which gives rise to a system of capillary loops that extend nearly to the dermal-epidermal junction. This system has been described in detail by Braverman [52].

A microscopic model for transport in the dermis may be derived by considering a system of capillary loops (Figure 4). Mathematical analysis of solute diffusion and absorption by the capillaries [43,53] shows that the system may be modeled as a homogeneous matrix with a uniform clearance in the upper dermis. This analogy has been described in some detail [29] and the effective partitioning, diffusivity and clearance values for mammalian dermis have been estimated [30]. The latter analysis suggests that both partitioning and diffusivity of small lipophilic permeants in dermis are functions of non covalent binding to extravascular serum proteins. They may be related to the ionization state of the permeant f_{non} (fraction nonionized at pH 7.4) and to $1/f_u$, where f_u is the fraction unbound in a 2% albumin solution as shown in eqs. 25-28 (Table 3). Steric and charge exclusion are also factors, leading to partition coefficients less than unity for small hydrophilic permeants (e.g., glucose [54]) and considerably smaller values for macromolecules such as albumin [30]. For low molecular weight, moderately lipophilic compounds the relationships in Table 3 serve as a working model for transport in dermis. The defining transport relationship for the distributed clearance model is given in this table as eq. 23. The unique part of this relationship are the parameters k_{free} and k_{de} representing capillary clearance. For small lipophilic compounds, the intrinsic clearance k_{free}

applying to freely diffusing solute is approximately constant as it is limited by blood flow. However, the effective clearance k_{de} applying to total solute concentration is modified by the same binding factor modifying diffusivity and partition coefficient.

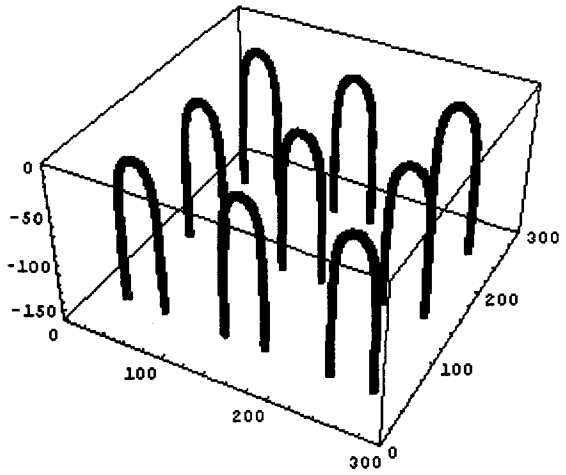

Figure 4. Three dimensional array of capillary loops forming the basis of the dermal micro-transport model described in [43].

Table 3. Formulas for dermis transport parameters [30].

Parameter	Units	Formula or value	Eq. #
Defining relationship		$\frac{\partial C}{\partial t} = -D_{de}\frac{\partial^2 C}{\partial x^2} - k_{de}C$	23
h_{de}	cm	0.20	24
K_{free}		0.6	25
K_{de}[a]	-	$K_{free}(0.68 + 0.32/f_u + 0.001 f_{non} K_{oct})$	26
D_{free}		$10\text{^}(-4.15 - 0.655 \log MW)$	27
D_{de}	$cm^2 s^{-1}$	$D_{free}/(0.68 + 0.32/f_u + 0.001 f_{non} K_{oct})$	28
k_{free}	s^{-1}	0.0022[b]	29a
k_{de}	s^{-1}	$k_{free}/(0.68 + 0.32/f_u + 0.001 f_{non} K_{oct})$	29b

[a]Equation 26 expresses K_{de} with respect to a pH 7.4 aqueous solution, i.e., $K_{de/pH\ 7.4}$. To express K_{de} relative to a solution in which it is completely nonionized, the corresponding formula is [30]

$$K_{de/non} = K_{free}[(0.68 + 0.32/f_u)/f_{non} + 0.001 K_{oct}] \quad (26A)$$

[b]Value assumes blood-flow limited clearance and is derived from data for rat [30].

VIABLE EPIDERMIS **(sub AIM 1.9)**

The viable epidermis is the thin, cellular epithelial layer sandwiched between the dermis and the stratum corneum. Its thickness in humans varies from about 50 to 100 μm due to the articulated nature of the dermis. Less is known about the transport properties of this layer than either stratum corneum or dermis because it is difficult to isolate. Due to its cellular structure, it presents a set of obstacles to solute transport different from those of dermis. In particular, hydrophilic solutes that do not easily cross cell membranes are confined to the tortuous

extracellular space and experience longer diffusion pathways than do lipophilic solutes. This problem may be modeled using an extracellular fluid diffusivity modified by a tortuosity factor and void fraction [55] or, alternatively, with an effective medium approach. The latter is more easily generalized to cover both hydrophilic and lipophilic solutes, as tortuosity and void fraction are functions of membrane permeability.

There is not yet a microscopic model for epidermal transport on which to base an effective medium model. There are, however, experimental diffusivity and permeability values for hydrophilic solutes in other cellular tissues [55,56] and an experimental value for glucose diffusivity in epidermis from our laboratory [54]. Schultz and Armstrong [55] found the permeabilities of extracellular solutes in rat diaphragm to be about one-thirtieth to one-fiftieth of their values in water. Although they modeled this in terms of a tortuous diffusion model, the effective medium approach would assign most of this reduction to an effective diffusivity D_{ed}. We determined upper and lower limits for glucose diffusivity in epidermis to be one-eighth and 1/200th of aqueous diffusivity using a combination of desorption and permeability measurements [54]. Considering both of the above results, it is evident that eqs. 27-28, which yield diffusivity values one-fifth to one-twentieth of aqueous diffusivity [30], is a reasonable starting point for epidermal diffusivity estimation. This is a working approximation until better estimates are developed. With a comparable level of uncertainty, we choose to represent K_{ed} with eqs. 25-26, developed for dermis. As a comparison, the calculated value for K_{ed} for glucose according to eqs. 25-26 is 0.6 versus a measured value of 0.81 ± 0.06 [54]. The working values for transport parameters in the viable epidermis are summarized in Table 4.

Table 4. Formulas for viable epidermis transport parameters [30].

Parameter	Units	Formula or value	Eq. #
Defining relationship		$\frac{\partial C}{\partial t} = -D_{ed}\frac{\partial^2 C}{\partial x^2} - k_{ed}C$	30
h_{ed}	cm	0.0100	31
K_{ed}	-	Eqs. 25-26 (Table 3)[a]	-
D_{ed}	cm^2s^{-1}	Eqs. 27-28 (Table 3)[a]	-
k_{ed}	s^{-1}	0 (in absence of skin metabolism)	32

[a]These relationships are placeholders until a more complete analysis is available.

EVAPORATIVE LOSS MODEL (AIM 3)

Volatile permeants are lost from the skin surface at a rate governed by their vapor pressure, density, thermodynamic activity and mass transfer coefficient at the skin-air interface. The working model for this calculation is summarized in Table 5. Thermodynamic activity is taken to be unity for a pure liquid or solid residing on the skin surface (Case 2) and $C(0,t)/C_{sat}$ for permeant dissolved in the upper stratum corneum (Case 1). Here, $C(0,t)$ is the concentration just below the skin-air interface and C_{sat} is the solubility of the permeant in the stratum corneum (cf. Table 2). For Case 2, M_{surf} is the mass of permeant residing on the skin surface. The gas phase mass transfer coefficient k_g (eq. 35) is taken from the chemical spills literature [57] per a suggestion from N-Dri-Stempfer and Bunge [58] as discussed in [23]. The overall mass transfer coefficient, $k_{evap}\cdot\rho$, is then calculated by assuming liquid-vapor equilibrium and ideal gas behavior at the skin-air interface (eq. 36). This has been termed the Raoult-Dalton model for evaporative loss [59].

Table 5. Formulas for evaporative loss calculation [23,24,50].

Parameter	Units	Formula or value		Eq. #
Defining relationships		$D_{sc}\left.\frac{\partial C}{\partial x}\right\|_{x=0} = k_{evap} \cdot \frac{\rho}{C_{sat}} \cdot C(0,t)$	Case 1	33
		$-\frac{dM_{surf}}{dt} = k_{evap} \cdot \rho + D_{sc}\left.\frac{\partial C}{\partial x}\right\|_{x=h_{dep}}$	Case 2	34
k_g	cm/s	$1.756\, u^{0.78} / MW^{1/3}$		35
k_{evap}	cm/s	$k_g \frac{P_{vp} MW}{(0.76\times 10^6)\rho RT}$		36[a]

[a]Units for Eq. 36 are P_{vp} (torr), MW (g/mol), ρ (g/cm^3), T (K) and R = 0.0821 Latm/Kmol.

IMPLEMENTATION OF TRANSPORT MODEL (AIM 5)

The relationships shown in Tables 2-5, combined with appropriate boundary conditions [23,29] and the physical properties inputs from Table 1, constitute a well-posed system of partial differential equations describing transient transport of volatile substances applied to skin. In order to produce numbers from these relationships, the simultaneous equations (eqs. 1, 23, 30) must be solved. A wide variety of tools including commercial software programs is available for this task. We have developed our own computer code using the finite difference approach discussed in [23]. Essentially, the Visual Basic code for stratum corneum + vehicle from [23] was modified by adding the viable epidermis and dermis layers. The calculation is implemented as an add-in operating under Microsoft Excel®, with an associated spreadsheet to calculate the various properties and output results as tables and graphs.

EXAMPLE CALCULATIONS FOR A FRAGRANCE INGREDIENT (AIM 5 and sub AIM 3.3)

The nature of the solution to the problem depicted in Figure 1 and described by eqs. 1-36 can be illustrated by considering the skin disposition of a fragrance ingredient applied to skin either neat or from a highly volatile solvent. We choose as an example benzyl alcohol, applied as a dilute solution in ethanol. This compound has been studied in our laboratory, both in vitro [18,24] and in vivo [20]. Its physical properties, experimental skin permeability and derived skin transport properties are listed in Table 6. For the following calculations, we choose the experimentally based skin transport parameters listed in Table 6. Thus, the saturation dose (M_{sat}) is taken to be 40.1 μg/cm^2. Doses less than 40.1 μg/cm^2 dissipate in a dose-proportional manner, whereas larger doses do not (cf. Figure 3).

Figure 5 shows the overall disposition of a small applied dose (0.9 μg/cm^2, M_r = 0.022) and a large applied dose (127 μg/cm^2, M_r = 3.17) as a function of wind velocity above the skin surface. The evaporated fraction increases with wind velocity, as intuitively expected. For a given value of the wind velocity, the fractional absorption of the small dose (Figure 5a) is higher than that of the larger dose (Figure 5b). How may this be explained?

Table 6. Physical properties and derived skin transport parameters for benzyl alcohol. The temperature for all calculations has been taken to be 32°C.

Parameter	Units	Value	
Input properties			
MW	Da	108	
log K_{oct}	-	1.10	
S_w	g/cm^3	0.0429	
P_{vp}	torr	0.18	
ρ	g·cm^{-3}	1.04	
f_u		0.37[a]	
f_{non}		1	
Experimental skin transport properties			
k_p (hydrated)	cm·s^{-1}	4.69×10^{-6}	
Derived properties		*Model based*	*Experimental based*
P_{sc} (hydrated)	cm·s^{-1}	[1.01×10^{-6}][b]	4.69×10^{-6}
P_{sc}	cm·s^{-1}	0.32×10^{-6}	1.74×10^{-6}
D_{sc}	cm^{2}s^{-1}	0.49×10^{-10}	3.32×10^{-10}
K_{sc}		8.71	6.99
h_{sc}^2/D_{sc}	hours	10.1	1.77
C_{sat}	g·cm^{-3}	0.374	0.300
M_{sat}	μg·cm^{-2}	49.9	40.1
D_{ed}	cm^{2}s^{-1}	2.15×10^{-6}	
K_{ed}	-	0.93	
D_{de}	cm^{2}s^{-1}	2.15×10^{-6}	
K_{de}	-	0.93	

[a]Calculated from model of Yamazaki and Kanaoka [44].
[b]Calculated as in [41]. For comparison, the value calculated from the Potts-Guy equation [60] is 0.66×10^{-6} cm·s^{-1}.

The answer lies in the deposition depth, h_{dep} (cf. Figure 1). According to this concept, small doses of skin permeants are rapidly deposited into the upper stratum corneum. The evaporation rate from the deposition layer is slower than that from the surface because the compound must diffuse back to the surface before it can be released. The deposition layer concept is supported by detailed analyses of the skin disposition of DEET [49] and benzyl alcohol [24] and by ongoing work in our laboratories on volatile solvents. Based on in vitro absorption studies with ethanol and benzene [50], the deposition layer appears to be particularly important to understanding solvent absorption, which is higher than might be expected from finite dose models lacking this feature (cf. [38] and eqs. 29-35 of [23]).

Figure 6 shows representative transient absorption profiles for benzyl alcohol applied to skin. The model curves are compared to in vitro human skin absorption data from [24]. The small doses (Figure 5a) are better described by the model than the large doses (Figure 5 b), for which the absorption rate is underpredicted. This discrepancy can be corrected by employing a concentration-dependent diffusivity for benzyl alcohol in stratum corneum, as described in [24]. By allowing the diffusivity to increase three-fold between low concentrations and the solubility limit C_{sat}, the agreement is substantially improved (inset to Figure 5b). This skin penetration enhancement effect is also evident in the dose-dependence for benzyl alcohol [24] and DEET [49] absorption, which goes opposite to that shown in Figure 6. A model for predicting such skin permeability enhancement effects is clearly needed to obtain quantitative agreement with absorption data for compounds like benzyl alcohol. We would anticipate similar findings for many other skin permeation enhancers.

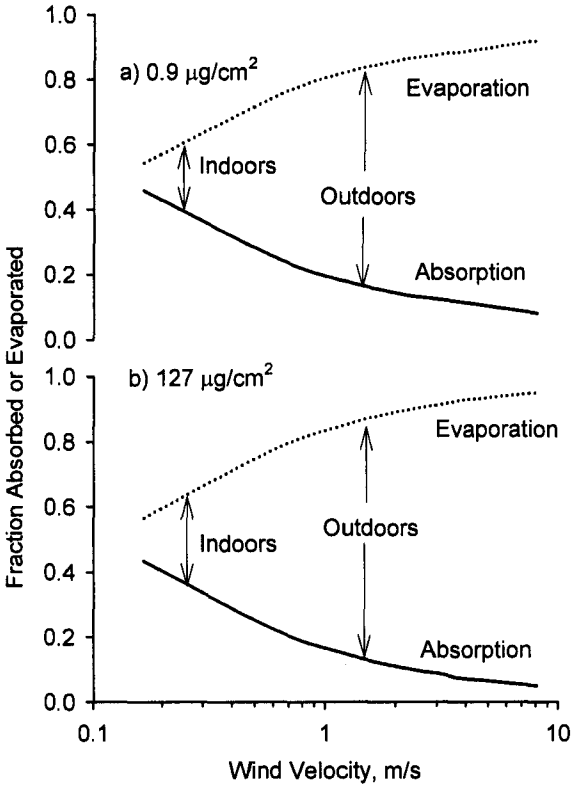

Figure 5. Calculated effect of wind velocity (u) on skin disposition of benzyl alcohol. (a) Small dose (M_r = 0.022; Case 1); (b) Large dose (M_r = 3.17; Case 2). Arrows mark recommended choices for indoor and outdoor exposure scenarios. The fractional absorption is higher for the small dose because more of the dose is initially deposited into the upper skin layers. For highly volatile solvents, the difference is larger [50].

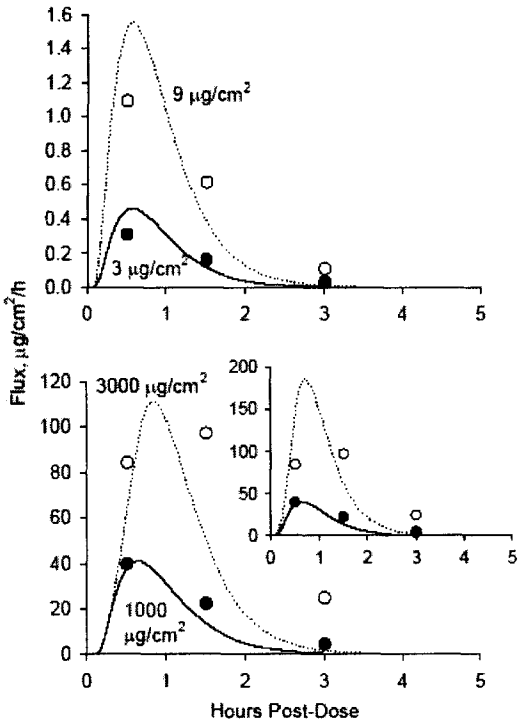

Figure 6. Absorptive flux of benzyl alcohol applied to human skin in vitro. (a) Small doses; (b) Large doses. The experimental data are taken from [24] and the theoretical curves from the model described in this chapter using a wind velocity of 1.5 m/s. Absorption rates for the larger doses are underpredicted due to skin permeability enhancement by benzyl alcohol as described in [24]. This can be corrected (inset) by allowing a concentration-dependent diffusivity for the permeant in the stratum corneum as described in the text.

Figure 7 shows an additional way in which the transient absorption/evaporation model may be employed. Concentration profiles within each skin layer throughout the course of absorption are automatically generated during the calculation. For some problems, these skin concentrations are more important than systemic absorption estimates. For example, the efficacy of topical drug or the allergenicity of a fragrance ingredient or a preservative is likely to be related to skin concentrations. The computer model allows one to estimate peak concentration (C_{max}) and

time-to-peak concentration (t_{max}) at an arbitrary depth in the tissue. The utility of such calculations in interpreting contact allergy dose-response data has recently been discussed [61].

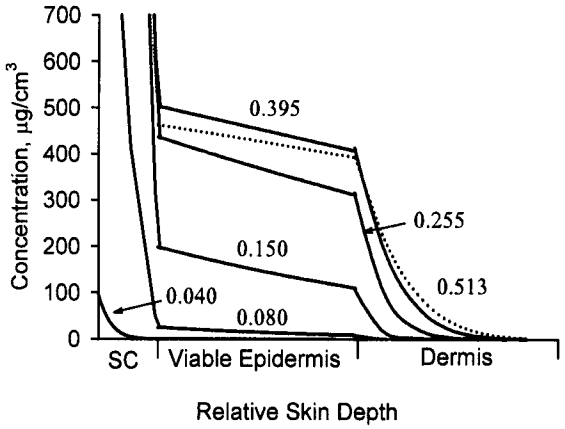

Figure 7. Calculated concentration profiles in lower skin layers for benzyl alcohol following topical application of 127 µg/cm^2 in ethanolic solution at a skin temperature of 37°C and a wind velocity of 0.25 m/s. The numbers on the graph reflect hours post-dose. Layer thicknesses are scaled for better visibility. According to the calculation, a maximum mid-epidermal concentration (C_{max}) of 450 µg/cm^3 was achieved at a time (t_{max}) of 0.395 h.

SUMMARY

Volatile compounds in cosmetic formulations rarely if ever achieve steady-state absorption profiles following application to the skin. Their disposition is governed by physical properties (molecular weight, lipophilicity, solubility, vapor pressure, density) and environmental factors (temperature, wind velocity) as well as the dose and the formulation in which they are applied. A working model to calculate this disposition from simple formulations has been presented. Some of the model components are not yet completely characterized and require additional research. In particular, the extent to which small molecules affect their own permeation rates through the stratum corneum is generally unknown. Key features that make the present computational model potentially more useful than other transient skin absorption models are (1) microscopically-based components for stratum corneum and dermis; (2) the incorporation of hydration effects and solubility limits in the stratum corneum; and (3) the concept of a deposition depth and an associated saturation dose that defines the transition from small to large doses of permeant on the skin.

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PUBLICATIONS

Twenty-eight publications and approximately thirty presentations have resulted from the work. These include seventeen journal articles, six MS and PhD theses and four book chapters.

Summary of completed studies:
- 17 peer-reviewed published papers
- 4 PhD dissertations
- 2 MS theses
- 4 book chapters
- ~30 talks and posters presented at national meetings and university forums

Peer-reviewed research articles

Aim 1: Stratum corneum model

Wang T-F, Kasting GB, Nitsche JM [2006]. A multiphase microscopic model for stratum corneum permeability. I. Formulation, solution and illustrative results for representative compounds. J Pharm Sci 95:620-649.

Nitsche JM, Wang T-F, Kasting GB [2006]. A two-phase analysis of solute partitioning into the stratum corneum. J Pharm Sci 95:649-666.

Wang T-F, Kasting GB, Nitsche JM [2007]. A multiphase microscopic model for stratum corneum permeability. II. Estimation of physicochemical parameters and application to a large permeability database. J Pharm Sci 96:3024-3051.

Aim 2: Dermis model

Kretsos K, Kasting GB, Nitsche JM [2004]. Distributed diffusion-clearance model for transient drug distribution within the skin. J Pharm Sci 93:2820-2835.

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Aim 3: Finite dose absorption and evaporation

Saiyasombati P, Kasting GB [2003]. Disposition of benzyl alcohol following topical application to human skin in vitro. J Pharm Sci 92:2128-2139.

Saiyasombati P, Kasting GB [2003]. Two-stage kinetic analysis of fragrance evaporation and absorption from skin. Int J Cosmet Sci 25:235-243.

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Kasting GB, Miller MA [2006]. Kinetics of finite dose absorption through skin 2. Volatile compounds. J Pharm Sci 95:268-280.

Miller MA, Bhatt V, Kasting GB [2006]. Absorption and evaporation of benzyl alcohol from skin. J Pharm Sci 95:281-291.

Aim 4: Skin hydration effects

Kasting GB, Barai ND [2003]. Equilibrium water sorption in human stratum corneum. J Pharm Sci 92:1624-1631.

Kasting GB, Barai ND, Wang T-F, Nitsche JM [2003]. Mobility of water in human stratum corneum. J Pharm Sci 92:2326-2340.

Aim 5: User-friendly interface

See the first two book chapters listed below. Two additional peer-reviewed articles describing the interface (not included in this report) were published in 2008.

Dissertations and theses

Bhatt, V [2007]. Absorption and evaporation of pesticides from human skin. PhD Dissertation, College of Pharmacy. University of Cincinnati.

Santhanam A [2004]. Mathematical model to predict the skin disposition of DEET and other volatile compounds, MS Thesis, College of Pharmacy, University of Cincinnati, Cincinnati, OH.

Saiyasombati P [2003]. Mathematical model for predicting the percutaneous absorption of perfume raw materials. PhD Dissertation, College of Pharmacy. University of Cincinnati.

Wang T-F [2003]. Microscopic models for the structure and permeability of the stratum corneum barrier layer of skin. PhD Dissertation, Department of Chemical Engineering. State University of New York: Buffalo.

Kretsos K [2003]. Transport phenomena in the human skin. PhD Dissertation, Department of Chemical Engineering. State University of New York: Buffalo.

Barai ND [2002]. Effect of hydration on skin permeability, MS Thesis, College of Pharmacy, University of Cincinnati, Cincinnati, OH.

Book chapters

Kasting GB, Miller MA and Nitsche JM [2008]. Absorption and evaporation of volatile compounds applied to skin. In Dermatologic, Cosmeceutic and Cosmetic Development (K.A. Walters and M.S. Roberts, eds.), pp.385-400. Informa Healthcare USA, New York.

Nitsche JM and Kasting GB [2008]. Biophysical models for skin transport and absorption. In Dermal Absorption and Toxicity Assessment (M.S. Roberts and K.A. Walters, eds.), pp.249-267. Informa Healthcare USA, New York.

Kasting GB [2005]. Estimating the absorption of volatile compounds applied to skin. In *Dermal Absorption Models in Toxicology and Pharmacology* (JE Riviere, ed.), Taylor and Francis, New York.

Kasting GB, Miller MA, Talreja PS [2005]. Evaluation of stratum corneum heterogeneity. In *Percutaneous Absorption, 4th ed.* (RL Bronaugh and HI Maibach, eds.), Marcel Dekker, New York, pp. 193-212.