Final Project Report
Mechanistically-Based In Silico Estimation of Dermal Absorption in the Workplace

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List of Terms and Abbreviations

Parameter	Units	Definition
b		Concentration of bound permeant in the corneocyte phase
c		Concentration of free permeant in the corneocyte phase
$\overline{D}$	-	Effective stratum corneum diffusivity
$D_{\mathrm{cor}}^{\mathrm{free}}$	cm^2s^{-1}	Diffusivity of unbound permeant within a corneocyte
D_{lip}	cm^2s^{-1}	Lateral diffusivity in SC lipids
$\overline{K}$		Stratum corneum partition coefficient
$\overline{k}_{\mathrm{f}}$	s^{-1}	Forward tissue-average binding rate constant
$K_{\mathrm{cor}}^{\mathrm{free}}$	-	Partition coefficient (with respect to water) of unbound permeant within a corneocyte
$k_{f,cor}$	s^{-1}	First order binding rate constant of free permeant in the corneocyte phase of the SC
K_{lip}	-	SC lipid/water partition coefficient
$K_{o/w}$	-	Octanol/water partition coefficient
$k_{r,cor}$	s^{-1}	First order binding rate constant in the corneocyte phase of the SC
$\overline{k}_{\mathrm{r}}$	s^{-1}	Reverse permeant tissue-average binding rate constant
PC_{pro}	-	Equilibrium ratio (mass of bound solute per unit mass of SC protein) / (mass of solute per unit mass of water in adjacent solution)

Project: Mechanistically-Based In Silico Estimation of Dermal Absorption in the Workplace
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Abstract

A mathematical model that closely mimics percutaneous absorption, tissue concentrations and clearance in human skin in vivo was developed. The model is implemented as an Excel™ workbook + add-in package and also as a Java™ program available on the NIOSH/CDC website. 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. A variety of components have been incorporated into the model workbook including: a multi-component vehicle model, a microscopic model of transport in human stratum corneum, a dermal vascular model including solute exchange through capillary loops and lymphatic clearance, and a disposition model for arbitrary doses of volatile organic compounds contacting the skin. Other developing components which have not yet been implemented in the workbook or web version include: slowly reversible binding and a polar pathway in the stratum corneum, transport through hair follicles, and a microscopic model for transport through viable epidermis. Progress has also been made toward quantification of potential effects of skin decontamination procedures on percutaneous absorption and the understanding of the effect of stratum corneum pH and buffer capacity on the transport of acids, bases and salts through skin.

Experimental refinement of the model parameters has been achieved through determination of keratin binding coefficients, measurement and interpretation of ionic transport of metal allergens through skin, and determination of the transport of solutes through full thickness dermis. Other significant experimental efforts include in vitro and in vivo skin decontamination experiments and in vitro skin transport experiments involving an acid or a base and its salt at various levels of ionization and dose.

Highlights/Significant Findings

During the past five years of support under the NIOSH award, a prototype three-layer skin permeation model developed during a previous round of funding was refined and expanded in significant ways. The technical components associated with each skin layer were improved, a second, web-based computational platform was developed, and use of the model has expanded into corporate toxicology and industrial hygiene settings. Far from being over, development work on the basic model framework in the PI and co-investigators' laboratories has expanded under additional support mechanisms including industry consortiums (Cosmetics Europe, Cefic), the US National Science Foundation and the US Food and Drug Administration. Furthermore, strong technical groups at two other academic institutions and at least two US companies have developed related skin absorption models built on other computational platforms, but using many of the components from the NIOSH-sponsored work. It is fair to say that the NIOSH award has sparked a flurry of activity in this area that will lead to more efficient dermal risk assessment methods for both government and industry.

Salient technical findings from the study include the following:

Aim 1: The evaporation of volatile organic chemicals (VOCs) from skin in a laboratory setting is more accurately characterized, yielding a more conservative estimate of skin absorption. This development spurred an outside group to build a parallel framework for dermal absorption of VOCs in occupational settings, using the skin components from our model. An experimental basis for better predicting the dermal absorption of weak acids and bases as a function of dose and ionization state has been laid.

Aim 2: An in vitro investigation of the so-called "wash-in effect" using DEET as a test permeant showed that all wash procedures examined reduced percutaneous absorption versus a no wash control. Urine samples from a parallel human in vivo study have not yet been analyzed due to personnel changes at CDC (where analytical services had been offered without cost to the project). After some delay, CDC has renewed its commitment to analyze the samples. Results from the human in vivo study are anticipated sometime in 2014. A prototype skin diffusion/convection model incorporating transient skin hydration and swelling effects was developed.

Aim 3: The theoretical framework for a model describing transport of ionic species including chromium and nickel salts through skin was developed and supported by an experimental study of the mobility of inorganic electrolytes in skin. A microscopic model for solute transport through viable epidermis was devised and supported with a fundamental analysis of the permeability of phospholipid bilayers, the primary component of epithelial cell membranes. The impact of slowly reversible binding of solutes to skin keratins was analyzed theoretically and confirmed experimentally to have a significant impact on transient solute transport in skin. The transport of permeants through dermis was more accurately simulated by improvements to the diffusivity, partitioning and capillary clearance models, a development that will also facilitate the consideration of thermoregulation and skin pathologies on dermal clearance. A

multicomponent diffusion model was developed to supplement the single component model used to date in this project. This enables the tracking of formulation excipients that can interact with the ingredient of interest and/or the skin.

Translation of Findings

The scientific findings from the study are widely published in the literature (28 peer-reviewed papers, 3 reviews and 3 book chapters) and many have been incorporated into a user-friendly Excel™ workbook + add-in package that can be used as a dermal risk assessment tool by toxicologists and industrial hygienists. The Excel program is freely distributed to users upon request. A web-based version of the program is available on the NIOSH/CDC website under the name Finite Dose Skin Permeation Calculator. The URL for this program is http://www.cdc.gov/niosh/topics/skin/finiteSkinPermCalc.html. The workbook program is periodically updated as new developments are made. Furthermore other scientific groups have begun to build on this code using different computational platforms and targeting a broader, international audience. The Excel™ and Java™ codes are copyrighted by the investigators and their collaborators; however, the scientific content is published in the open literature and other implementations of this material are encouraged.

Outcomes/Relevance/Impact

Our research is distinguished primarily by the attention given to physical chemistry, fundamental macrotransport theory, and skin microstructure and physiology in the developed mathematical models. This attention to detail has engendered a great deal of interest in the industrial toxicology community, which seeks non animal alternatives to risk assessment for both systemic and skin-related concerns. It has also stimulated interest in the industrial hygiene community, as evidenced by the recent introduction of two complementary computer codes for dermal risk assessment borrowing substantially from the present code. The UC investigators shared the technology in May, 2013 at a NASA sponsored webinar for industrial hygienists, and a colleague at the University of Illinois at Chicago is developing a “detuned” version of the software as a training module for undergraduate chemical engineers. A faculty member at the University of Texas School of Public Health is now using the Excel™ workbook version of the skin absorption software as part of a training program for undergraduate industrial hygiene. Development of the scientific underpinnings and the computational framework continues under renewed sponsorship from both industry (Cosmetics Europe, Cefic) and the US government (NSF, FDA). We anticipate that the computational tool developed in this project, and derivatives thereof, will play a significant role in dermal risk assessment over the next several decades.

The NIOSH support also contributed to graduate training in the STEMM disciplines. Since 2006 six Ph.D. students and one M.S. student were fully or partially supported under the grant. All but one of these students have graduated and all are living and working in the USA. Dr. Kasting received the 2012-13 Excellence in Doctoral Mentoring Award from the University of Cincinnati for his role in the training process.

Scientific Report

The overall objective of this project was to develop a sophisticated, yet accessible computational tool for estimating dermal absorption and skin concentrations of hazardous chemicals in the workplace under a variety of exposure conditions. The three specific aims were (briefly): (1) to calibrate the current microscopic model with additional laboratory data; (2) to develop a skin swelling and decontamination model; and (3) to develop advanced components for the microscopic model. The status of each of these areas is described below.

Aim 1. Microscopic model calibration

1. This sub-Aim was designed to calibrate the partitioning of solutes into partially hydrated stratum corneum (SC). A new set of experiments employing benzoic acid (a weak acid) and propranolol (a weak base) and salts thereof was conducted by Matthew Miller. Both dose and effective pH on skin were varied, the latter by varying the proportion of salt in the mixture. The results can be qualitatively interpreted in terms of a composite skin model involving both lipid and polar pathways in the SC. Large doses of acid or base buffer the SC pH at that of the vehicle, whereas the SC buffers the pH of small doses. This experiment shows the partitioning of these compounds into two SC compartments and is closely related to sub-Aim 3.1. The work is summarized in a draft manuscript which we expect to publish when we have a better quantitative explanation.

2. Absorption and evaporation studies involving finite doses of volatile solvents applied to skin have been completed. The work is summarized in two Ph.D. theses [1-2] and three published papers [3-5]. One additional manuscript is under development (R. Gajjar, GBK). This work, along with associated analysis of pesticide disposition studies conducted in our laboratories [6-9] has lead to a re-parameterization of the evaporative mass transfer coefficient associated with volatilization of compounds from skin. These changes are implemented in the working model by lowering the default wind velocity for indoor and outdoor exposures. They result in higher absorption estimates for highly volatile solvents and for skin sensitizers such as formaldehyde and glutaraldehyde. From the industrial hygiene perspective, the risk assessment for such compounds is now more conservative (i.e., higher estimated absorption for a given exposure). From a mechanistic perspective, the estimated skin concentrations associated with threshold skin sensitization doses are higher.

   A recent development that complements our in vitro evaporation work is worth mentioning. Dr. Charles Weschler at UMDNJ/Rutgers and colleagues at Tsinghua University in Beijing have developed an in vivo model for dermal uptake of volatile organic chemicals that is paired with the skin diffusion model developed in this project. The manuscript describing this work is in a late stage of review [10]. Thus the NIOSH support for our project has indirectly led to another useful tool for estimating dermal uptake of chemicals in occupational settings.

3. The methodology study for determination of transport and partition coefficients in human

dermis in vitro described in the Year 2 progress report is complete and is the subject of a published paper [11]. The results explain why some of the dermis/water partition coefficients reported in the literature are low relative to in vivo conditions. This finding is of considerable importance to calibration of the spreadsheet diffusion model from in vitro diffusion data. We have now studied one more lipophilic compound, parathion, using the side-by-side diffusion cell methodology, and published a paper on these results [12] The work was conducted by graduate student R. Ibrahim.

We expanded this investigation to include a theoretical study of the clearance of both lipophilic compounds and proteins from human skin in vivo. This work builds upon our earlier published studies in this area [13-16]. The main thrust of the effort was to add the concept of diffusing proteins and lymphatic clearance to the previously developed dermis clearance model. The lymphatic component was calibrated through an analysis of the clearance of ^{125}I-albumin from human and animal tissues. Using the newly expanded model, we reanalyzed the ex vivo skin concentration data reported by Kretsos et al. [16], as well as additional data from Schaefer that have recently come to our attention. This work is captured in a Ph.D. thesis [17] and also a recent published paper [18]. Results are incorporated into the working version of our spreadsheet diffusion model. This work represents an extension of the original plan for sub-Aim 1.3. It is expected to lead to better predictions of skin concentrations in vivo following exposure to lipophilic chemicals. This is important in order to understand the mechanism of skin toxicity for hazardous chemicals, including contact allergens, as well as the mechanism of action for topical drugs.

Aim 2. Application of models to occupational risk assessment

2.1. Aim 2.1 calls for implementation of the Kasting-Miller-Bhatt (KMB) Excel®-based dermal absorption model in a user-friendly web format. This was achieved in late 2011 through a collaboration between the UC group, an independent contractor (Adam Fedorowicz), and NIOSH Morgantown personnel (Fred Frasch and NIOSH web programmers). The product is a web-based application called the Finite Dose Skin Permeation Calculator, available on the NIOSH/CDC website at http://www.cdc.gov/niosh/topics/skin/finiteSkinPermCalc.html. Dr. Frasch was a consultant on the project from its inception and was highly instrumental in implementing the web version.

2.2. Aim 2.2 involved production of a non-steady state skin washing model that incorporates prediction of permeation of both water, to mimic hydration and swelling, and a non-ionic organic compound. A specific goal was to simulate skin washing to permit computational investigation of the so-called “washing-in effect”. This activity complements experimental activities described under Aim 2.3. The code has been developed in MATLAB by co-investigator John Kissel (Univ. of Washington) and relies heavily on prior work by Kasting and Barai [19] and Kasting et al. [20] for description of concentration dependent diffusivity of water and water sorption within corneocytes. Transport in the skin is treated as a one-dimensional process. Use of the model to simulate uptake of organic compounds prior to

hydration will permit testing of the impact of washing on transport of material already in the stratum corneum into the bloodstream. A platform presentation of this work was presented at the (NIOSH-sponsored) 5th Occupational and Environmental Exposures of Skin to Chemicals (OEESC) meeting in Toronto in June, 2011 [21]. Updated results were incorporated in a platform presentation at the 2012 ISES meeting in Seattle [22]. Development work is continuing in the Kissel laboratory.

2.3. Aim 2.3 included i*n vivo* experimental investigations that were scheduled to occur in both Years 3 and 4. Due to delay in coordinating required human subject approval processes at both UW and at UC, the human trials did not get underway until Year 4. Nevertheless, a full complement of subjects was enrolled in Year 4 and the in vivo part of the study has been complete for some time. The study design is shown in Table 1. Each of 18 volunteers (9 male, 9 female) participated in 4 trials, giving 72 total trials. Variables were initial skin load of DEET (5 or 30 μg/cm^2), delay until washing (10 or 40 minutes) and washing technique (water only, soap and water, dilute ethanol). Skin loads were chosen to fall on either side of the estimated upper stratum corneum saturation load (M_{sat}) for DEET as estimated in the KMB model. The order of the individual trials was randomized.

Samples collected included 24-hour urines for the day prior to and four days after exposure, skin-wash solutions and cotton swabs. Skin-wash solutions were analyzed for DEET at UC by graduate student Jennifer Karr. Urine samples were to be analyzed by CDC at no cost to the project. A change in personnel at CDC has caused further delay. However, CDC has now renewed its promise to analyze the urine samples (which are in freezer storage). Once analytical results are available (anticipated to be sometime in 2014), results will be evaluated by analysis of variance.

Activities conducted under Aim 2.3 also included review of published experiments in which washing was either the focus of the investigation or, more commonly, was conducted incidentally, but could be evaluated post hoc. That review produced an M.S. thesis at UW [23] and a poster presentation at the 2011 ISES meeting [24]. A critical review of a subset of that literature, consisting of cases directly germane to examination of the wash-in hypothesis, is near completion and will be submitted to a journal in November, 2013.

Table 1. Human in vivo washing trials conducted in Year 4.

subjects	skin load [μg/cm^2]	delay to washing [min]	wash method*
M1, M2, M3, F1, F2, F3	30	10	WO
M1, M2, M3, F1, F2, F3	30	40	WO
M4, M5, M6, F4, F5, F6	5	10	WO
M4, M5, M6, F4, F5, F6	5	40	WO

M7, M8, M9, F7, F8, F9	30	10	S
M7, M8, M9, F7, F8, F9	30	40	S
M1, M2, M3, F1, F2, F3	5	10	S
M1, M2, M3, F1, F2, F3	5	40	S
M4, M5, M6, F4, F5, F6	30	10	E
M4, M5, M6, F4, F5, F6	30	40	E
M7, M8, M9, F7, F8, F9	5	10	E
M7, M8, M9, F7, F8, F9	5	40	E

* WO = water only; S = soap and water; E = ethanol.

2.4. Aim 2.4 activities include testing of the KMB model, and its underlying concepts, against data reported in the prior literature and more general investigation of exposure (especially loading) conditions on chemical absorption.

A paper [25] providing a general summary of commonly encountered deficiencies in evaluation of dermal exposures and proposing the use of dimensional analysis to inform interpretation of dermal absorption experiments was published in 2011. That paper fostered additional effort at a NIOSH sponsored workshop held in conjunction with the OEESC meeting in Toronto. The product of that workshop was another paper [26] dealing more generally with interpretation of finite dose dermal absorption experiments that was co-authored by Drs. Frasch, Kasting and Kissel (and others). Vanillylnonamamide data generated in the Kasting laboratory were used to illustrate a key point, the influence of loading regime on fractional absorption. Dr. Kissel utilized this same information in a presentation at the 2013 joint meeting of ISES, ISEE and ISIAQ in Basel [27]. Dr. Kissel and a colleague also responded (via two letters [28-29]) to a pair of publications that purported to find substantial discrepancies between dermal permeabilities estimated via in vitro and in vivo methods, pointing out that the discrepancies were artifacts of overt calculation errors. Use of in vitro methods is essential to the larger project that is the basis for this report.

In addition, pilot funds were obtained from UW DEOHS to supplement NIOSH funding and permit additional experimental activity in the Kissel laboratory. The experiments involved use of a nebulizer to deposit radio-labeled chlorpyrifos and pentachlorophenol onto skin coupons. Failure to recover by washing served as a surrogate for absorption (an assumption subsequently confirmed by solubilization of the skin coupons and assessment of mass balance). Washing recovery at loads between roughly 1 and 500 ng/cm^2 was investigated. Fractional absorption well in excess of previously reported values obtained at much higher skin loads was observed for both compounds. A manuscript describing this work [30] received generally positive reviews and is under further revision. A poster based on the work was presented at the 2010 ISES/ISEE meeting and was updated at the OEESC meeting in Toronto in 2011 [31-32].

An important area of inquiry with respect to predictive ability of the KMB model is

permeation and penetration of relatively high molecular weight and high log $K_{o/w}$ compounds. An additional tool under development in the Kissel lab is an indoor fate and transport model oriented toward SVOCs. A unique feature of this model is incorporation of a multi-compartment human (with skin modeled as a membrane) into the indoor environment. The human component permits testing of modeling features of the KMB model, especially as regards permeation and partitioning in the epidermis and dermis, against additional case studies involving SVOCs. Ongoing aspects of this work were presented at the 2010 ISES/ISEE meeting, the 2011 and 2013 OEESC meetings and the 2012 ISES meeting in Seattle [25,33-38].

Aim 3. Advanced model components

3.1. Aim 3.1 involved incorporation of a second pathway through the stratum corneum that allows for the permeation of hydrophilic compounds through the skin. Such a development can lead to plausible skin concentration estimates for compounds such as kanamycin, nickel chloride and potassium dichromate. We approached this problem from both a theoretical and experimental direction. We adapted a more complete theory for transport of charged solutes through charged pores available in the colloid science literature (e.g. [39-40]) to the porous pathway problem and also implemented a calculation for polyvalent ions in a charged, homogeneous matrix [41]. This work was conducted by a Ph.D. student with a strong engineering background (T. LaCount). Ms. LaCount has carefully reproduced the complex calculations in the above references and applied them to the skin polar pathway problem. In addition she conducted an experimental study of metal ion transport through skin using conductivity and electromotive force techniques which is described in a recent publication from our group [42]. The theoretical work is summarized in a draft manuscript that will be submitted to the *Journal of Membrane Science* [43], and all of the studies will be included in Ms. LaCount's PhD thesis (anticipated March, 2014). Work in this area continues in the PI's laboratory under separate sponsorship from the NSF and the industrial chemicals consortium Cefic.

3.2. Microscopic diffusion model of viable epidermis.

Work on Aim 3.2 was completed in 2012 and resulted in a rich array of output related to transport in viable cellular tissues and also the underlying transport properties of the phospholipid bilayers comprising the main component of cell membranes. The central manuscript describing the viable epidermis microscopic model appeared in the *Biophysical Journal* in 2013 [44]. The associated work on phospholipid bilayer permeability may be found in [45] with two related articles on 1,9-decadiene [46-47], the partition model (lipophilicity scale) for phospholipid bilayers.

Work to add binding to soluble proteins in the viable epidermis to the microscopic model continues under separate sponsorship from the NSF. Once this piece is completed we plan to design a way to connect the output of the microscopic viable epidermis model

with the full, three-layer skin diffusion model [48]. This exercise is non trivial because it requires the explicit introduction of a bound solute concentration, and the nature of the microscopic model involves a more elaborate effective medium scheme.

3.3. Solute binding to stratum corneum (SC) constituents, and implications for kinetics of dermal absorption from chemical exposure.

We are pleased to report closure on Aim 3.3 in a way that exceeded the original expectations of the project. A single theoretical publication was anticipated originally, but project effort ultimately led to two published papers appearing in 2011 [49-50].

We made the considered decision not only to work out the microscopic theory underlying the tissue binding phenomenon [49], but also to validate it with reference to definitive set of experiments [50]. The goal here was to make available to the occupational safety and dermal absorption community a concrete case study demonstrating the analysis of binding to fully understand and accurately predict the time course of chemical transport through the SC, as well as the actual disposition of chemical within the tissue. This work was a collaborative effort with Dr. H. Frederick Frasch (Health Effects Laboratory, National Institute for Occupational Safety and Health, Morgantown, West Virginia 26505).

Summary of key outcomes

The first paper [49] presents a comprehensive theoretical analysis of the microscopic physics underlying a critical weakness of most diffusion models of dermal absorption to date. Traditional diffusion models represent SC tissue as an effective continuum characterized for a given solute in terms of two parameters: (i) its partition coefficient $\overline{K}$ (indicating affinity for the SC relative to a reference solvent, usually taken to be aqueous solution); and (ii) its diffusion coefficient $\overline{D}$ in the SC. In an important paper, Anissimov and Roberts [51] demonstrated that fitting the observable kinetics of water diffusion through SC leads to different ($\overline{K}$, $\overline{D}$) pairs depending on the transient analyzed (permeation versus desorption). They showed further that the inconsistency was removed by acknowledging solute binding to the tissue, and explicitly incorporating this phenomenon into the model.

What was still missing was the link between the tissue-average (effective) binding and unbinding rates, determined as empirical parameters by data fitting, and the underlying microscopic basis for them, namely on and off rate constants for binding to keratin and other constituents of the corneocyte phase. This link is developed rigorously in [49] within the framework of a two-phase model of SC microstructure. A novel asymptotic analysis ultimately casts this link in terms of readily usable algebraic formulas demonstrated to accurately approximate detailed numerical solutions of the microscopic diffusion problem (Eqs. (54), (55), (62) and (63) in [49]).

To validate the theory, we sought a definitive data set that would unambiguously define the kinetics of binding for a significant permeant. After assessing the literature we came to the conclusion that existing data were insufficient for this purpose, in part because: (i) reported results on transient permeation are often based on the traditional two-parameter ($\overline{K}$, $\overline{D}$) framework and/or an associated graphical construction for data analysis; and (ii) experiments need be taken to longer times for full characterization of the transient behavior. Thus, Dr. Frasch undertook an independent experimental study measuring equilibrium binding and permeation kinetics for theophylline. Project effort was crucial to modeling and ultimately unraveling the meaning of the data.

The outcome is intriguing, and has important implications. Theophylline binding to the corneocyte phase (keratin and other constituents) is quantified by the rate law

binding rate = $k_{f,cor}\, c - k_{r,cor}\, b$, $k_{f,cor} = 1.84 \times 10^{-4}\ s^{-1}$, $k_{r,cor} = 1.29 \times 10^{-4}\ s^{-1}$,

where c and b denote the free and bound concentrations in the corneocyte phase. This phase is easy to pass through relative to perpendicular diffusion through the intercellular lipid phase, which is rate limiting with a diffusion coefficient of

$D_{lip} = 3.31 \times 10^{-12}\ cm^2/s$.

These figures demonstrate conclusions of great significance for the accurate estimation of transient chemical penetration from dermal exposures namely: "(i) depending on the duration and nature of a... chemical exposure, a significant fraction if not (more likely) most of the total dermal absorption typically occurs in the transient regime before diffusion has settled down to steady state; and (ii) binding strongly influences the macroscopically observable kinetics of the process. Thus, accurate modeling of dermal absorption requires an approach that explicitly incorporates transient diffusion and binding…. [Our] paper defines the extension of [the 'brick-and-mortar' modeling] approach to incorporate slow binding of solute to the microstructure, and yields two specific conclusions about it. Specifically, the extended 'brick-and-mortar' model must generally introduce forward ("on") and reverse (''off'') binding rate constants for [the corneocyte] phase (….$k_{f,cor}$ and $k_{r,cor}$) in addition to the partition and diffusion coefficients… K_{lip}, D_{lip}, K_{cor} and D_{cor}…. The first conclusion is that binding does not alter the determination of [the tissue-average partition and diffusion coefficients] $\overline{K}$ and $\overline{D}$. Thus, the results for [the tissue-average binding rate constants] $\overline{k}_f$ and $\overline{k}_r$ can literally be appended to the coarse-grained parameter set resulting from any existing (non-binding) 'brick-and-mortar' model. Second, these effective binding rate constants are determined by explicit formulas involving only the volume fractions of the two phases and other properties thereof already considered (Eqs. (54), (55), (62) and (63)). No solution of any additional diffusion problem is required" ([49], pp. 2034–2035).

It is also worthwhile to gauge the consistency of the new transient binding analysis with the brick-and-mortar theory for partition and steady state permeability coefficients developed in the previous funding cycle of this project [52-54]. The data in [50] yield a

numerical determination for the amount of bound theophylline as

PC_{pro} = 4.14.

This quantity represents the equilibrium ratio (mass of bound solute per unit mass of SC protein) / (mass of solute per unit mass of water in adjacent solution), and it implies a ratio of bound to free theophylline equal to ~1.4. Our earlier two-phase model of SC partition coefficients [55] yields the *a priori* estimate

PC_{pro} = 5.33.

for this compound, which agrees remarkably well with the actual experimentally determined value. Thus, the picture of substantial bound additional to free solute holdup associated with the corneocyte phase — previously gleaned from a careful steady state analysis — is vindicated by the complete transient data.

The preceding results bring a unified closure to the framework for quantitative modeling of dermal absorption from chemical exposure. Much if not most absorption occurs in the transient phase, and an accurate calculation thereof must be based on explicit calculation of the co-evolution of free and bound chemical concentrations in SC.

As with the viable epidermis, we plan to incorporate solute binding to the SC into the full, three-layer skin diffusion model [48].

3.4 Aim 3.4 involved incorporation of a realistic representation of hair follicles into the skin absorption model, with the objective of better representing the skin transport and tissue concentrations of compounds that accumulate in the follicle. Considerable literature data exist to document the importance of this pathway, e.g. [56-59]. We have completed a detailed microscopic model of anagen hair follicles that is currently summarized in the form of a Ph.D. thesis from the SUNY group [60]. The follicular concentrations of fluorescent dyes measured by Grams [57-58] were used for model calibration and testing. A manuscript drawn from this work was submitted to the *Journal of Theoretical Biology* [61] and is still undergoing revision following an extensive review.

3.5. Aim 3.5 involved development of a multicomponent heat and mass transfer model for simulating topical exposures from complex vehicles. The complexity of the model has been scaled back from the ambitious plan in the research proposal; nevertheless we have progressed the mass transfer part. A new version of a spreadsheet-based program, 4C3L 3.0, solves the problem of disposition from a multi-component formulation applied to the skin so that the disposition of each ingredient is tracked instead of just one particular compound of interest. Unlike the “immobile” vehicle model of the previous version [48], the thickness of the vehicle phase can change with time as its components disperse. And unlike the “volatile” solvent option of the previous version, the components are not assumed to have dispersed (e.g., evaporated) immediately after application, but have intermediate disposition times. The presence of each component on the surface of the skin generally affects the activity of the other components at the surface. The volume of

each ingredient is now taken into account when the thickness of the vehicle layer is computed. (Previously, the volume of the permeant of interest was neglected.) Another improvement is that the activity of each component is now proportional to the mole fraction of its saturation in the "active" phase, rather than being computed on a mass per unit volume fraction basis as the previous model had been.

The predictions of this new multicomponent vehicle model have been compared to a variety of experimental data. In particular, absorption through human cadaver skin of small to moderate doses of vanillylnonamide from a propylene glycol vehicle [62] is predicted significantly better with the multicomponent vehicle model than either the immobile vehicle or volatile vehicle models. The vanillylnonamide data demonstrate that the multicomponent vehicle model provides an improved prediction of absorption of a compound applied in a moderately dissipating vehicle. The ability of the simulation to track the disposition of all applied ingredients is the main reason for this improvement. This work is summarized in a draft manuscript with expected submission for publication in early 2014.

Publications and Presentations

Since the submission of the project proposal the following articles have been published:

1 Two accepted, peer-reviewed manuscripts have appeared in print [14,63].
2 Two submitted, peer-reviewed articles were accepted and appeared in print [16,52].
3 Twenty-six new peer-reviewed articles [3-5,7-9,11-12,25,28-29,42,44-47,64-70], three reviews [26,48,71] and two book chapters summarizing the computational model [72-73] have appeared in print.
4 One additional book chapter [74] is in press.
5 Five Ph.D. dissertations and one M.S. thesis related to the project have been approved [1-2,6,17,23,60] and the respective degrees awarded.
6 Numerous presentations have been made to academic, industrial and government audiences [21-22,24,27,31-38,53,75-109]

Peer-reviewed manuscripts published or accepted: 30
Book chapters: 3
Reviews: 3
Submitted manuscripts: 1
PhD Dissertations: 5
MS Theses: 1
Outside presentations: 51+

Dr. Kasting also received the 2012-13 Excellence in Doctoral Mentoring Award from the University of Cincinnati. One such award is presented annually. The award "recognizes full-

time graduate school faculty for outstanding and sustained guidance and support of students as they move through the process of becoming experts in their chosen fields." A record of this event may be found on the UC Graduate School website at http://grad.uc.edu/student-life/awards/mentoring.html.

Dissemination of Computer Software

Although not part of the original research proposal, we took the opportunity to work with Dr. Fred Frasch at NIOSH Morgantown to put the developed computer software up on the NIOSH/CDC website for use by industrial hygienists. In order to do this we commissioned a contractor, Dr. Adam Fedorowicz, to develop a Java version of the software. The Java program, named Finite Dose Skin Permeation Calculator, has been available on the website at http://www.cdc.gov/niosh/topics/skin/finiteSkinPermCalc.html since late 2011. We budgeted additional funds for this effort in Project Year 9 in order to make continuous improvements to the prototype version. An updated program has been prepared, but it is not yet implemented on the website as of the writing of this report (October, 2013).

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