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Mathematical Description of the Uptake of Hydrocarbons in Jet Fuel into the Stratum Corneum of Human Volunteers

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Abstract

The objective of this research was to develop a mathematical description of uptake of aromatic and aliphatic hydrocarbons into the stratum corneum of human skin *in vivo*. A simple description based on Fick's Laws of diffusion was used to predict the spatiotemporal variation of naphthalene, 1- and 2-methylnaphthalene, undecane, and dodecane in the stratum corneum of human volunteers. The estimated values of the diffusion coefficients for each chemical were comparable to values predicted using *in vitro* skin systems and biomonitoring studies. These results demonstrate the value of measuring dermal exposure using the tape-strip technique and the importance of quantifying of dermal uptake.

Keywords

dermal; hydrocarbons; jet fuel; membrane model; tape-stripping; transport

Introduction

The protective function of the skin is provided by the epidermis, which is comprised of the stratum corneum (SC) and the viable epidermis (VE). It is the SC, however, that provides the main resistance to the uptake of hydrophobic chemicals (Elias 1989; McCarley and Bunge 2001). The SC is an approximately 20 μm thick membrane comprised of ordered corneocytes each less than 1 μm in thickness (Marks *et al.* 1981). The corneocytes originate from the keratinocytes of the basal layer of the VE through a process of programmed cell differentiation called keratinization (Elias 1989; Kalinin *et al.* 2001). The dominant mechanism of chemical transport across the SC is thought to be diffusion; therefore, mathematical models for predicting the transport of drugs and chemicals across human skin are based on Fick's laws of diffusion (George *et al.* 2004; Kubota and Ishizaki 1986; Reddy *et al.* 1998; Tojo 1987). Diffusion-based models have been used in drug discovery research, but have not been widely used to study the dermal uptake of occupational and environmental toxicants.

Previous studies have shown that dermal exposure to jet propulsion fuel type 8 (JP-8) can cause direct damage to the SC (Singh *et al.* 2003) as well as an increased release of IL-8, IL-1 α , TNF- α , and MCP-1 α from epidermal keratinocytes (Chou *et al.* 2003). Although adverse effects

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have been observed after dermal exposure to jet fuel, only one study in which whole-body dermal exposures to jet fuel were measured has been published to date (Chao *et al.* 2005; Chao *et al.* 2006). The researchers in this study measured the exposures of U.S. Air Force personnel using tape-strips and found that dermal exposures varied widely, ranging from 100 ng·m⁻² to 4.9 mg·m⁻² (Chao *et al.* 2005). Although these results provided the first set of human dermal exposure data for jet fuel, the interpretation of exposure measurements may be imprecise due to the limited understanding of JP-8 transport mechanisms across human skin *in vivo*.

Kim *et al.* (Kim *et al.* 2006b) used pharmacokinetic (PK) models to quantify the bioavailability of jet fuel from dermal exposures. These PK models were developed using data collected from dermal-only exposed human volunteers in a controlled laboratory setting where 1.0 ml of jet fuel was applied to the forearm of human volunteers, and trace levels of aromatic (i.e., naphthalene, 1-methyl naphthalene, 2-methyl naphthalene) and aliphatic (i.e., n-decane, undecane, n-dodecane) hydrocarbons were measured in whole blood (Kim *et al.* 2006a). A four-compartment dermatopharmacokinetic (DPK) model was used to accurately predict the time-course of the six jet fuel components in blood. In more recent work, the DPK model was extended to incorporate the inhalation route of exposure so that the relative importance of dermal and inhalation routes of exposure could be assessed (Kim *et al.* 2007). Until now, the skin has been treated as a homogeneous well-mixed layer in PK models. This assumption seemed to suffice, but a more realistic model would be one that describes mathematically the diffusion of chemicals driven by a concentration gradient within the skin. This approach requires direct sampling of contaminant levels in the skin.

The objective of the present study was to develop a mathematical description of transport of jet fuel components across human skin *in vivo*. To accomplish this, we built upon previously published models of the skin (Pirot *et al.* 1997; Reddy *et al.* 1998; Reddy *et al.* 2002). Similar to other membrane models, we described the transport of jet fuel components across the skin using Fick's laws of diffusion. We optimized our model using tape-strip data collected from dermal-only exposed human volunteers (Kim *et al.* 2006a). The tape-strip method provides both depth-profile and time-course information for contaminants in the SC. These results aid development of strategies and models for quantification of dermal uptake of chemicals into the stratum corneum of human skin *in vivo*.

Materials and Methods

Experimental design

The overall study design has been previously published (Kim *et al.* 2006a), and is briefly summarized below. Ten ethnically-diverse volunteers (five female and five male) were recruited for the dermal exposure study. Exposures were conducted inside a chamber with dimensions of 20.3 cm width × 20.3 cm length × 18.8 cm height and a total volume of 7706 cm³. The volunteer's forearm was placed palm up inside the exposure chamber, and two aluminum application wells (dimensions 2.5 cm × 4.0 cm = 10 cm² per well) were pressed against the skin to prevent JP-8 from spreading during the experiment (Figure 1). A total of 1 ml of neat JP-8 was applied to the skin. The exposure chamber was sealed for the duration of the experiment. Immediately at the end of the 30 min exposure period, the exposure site was wiped with gauze pads to stop penetration and remove residual jet fuel. The site of application was tape-stripped 10 consecutive times. Removal of all tape-strips took approximately 15 min, i.e., 45 seconds per tape-strip. Individual tape-strips were placed in 10 ml of acetone containing 1 µg/ml of internal standards (naphthalene-d₈ and dodecane-d₂₆). All tape-strip samples were stored in 20 ml vials (I-CHEM, Rockwood, TN) and refrigerated at 4°C until analyzed by quantitative analytical chemistry. Approval for this study was obtained from the Institutional Review Board on Research Involving Human Subjects (School of Public Health, The University of North Carolina at Chapel Hill, Chapel Hill, NC).

Sample analysis

Tape-strip samples were analyzed by gas chromatography-mass spectrometry (GC-MS). A Thermoquest Trace GC (Thermo Electron Corporation, Austin, TX) coupled with a Combi Pal autosampler (CTC Analytics, Zwingen, Switzerland) and a Finnigan Polaris Q quadrupole ion trap MS (Thermo Electron Corporation) in electron ionization mode, was used for the chemical analysis. Separation of the sample was done with a fused-silica capillary column, 30 m × 0.25 mm internal diameter, coated with a mixture of 5% diphenyl:95% dimethyl polysiloxane (0.25 μm film thickness, RTX-5MS, Restek Corporation, Bellefonte, PA). The oven temperature for analysis was 40°C (3 min) and then 10°C/min to 290°C (10 min). One μl of sample was directly injected into the inlet. The ions used for quantitation were m/z 128 (naphthalene), 142 (1-methyl and 2-methyl naphthalene), 136 (naphthalene-d₈), 71 (n-decane, n-undecane, n-dodecane), and 98 (dodecane-d₂₆).

Membrane model description

The membrane model accounts for diffusive transport through the SC and incorporates tape-stripping effects as well (Reddy *et al.* 2002). A schematic of the surface, the interface between surface and skin, and the SC during tape-stripping is shown in Figure 2. We consider mass transfer in two compartments: (1) a surface-SC interface, and (2) the SC itself. Not all of a chemical that is in the surface layer is available for absorption into the SC (McDougal and Boeniger 2002). It is the amount of contaminant in the surface layer that is adjacent to the SC (i.e., monolayer) that is available for dermal uptake; we define this as the interface. The first tape-strip can be treated as a measure of chemical in this layer (Shah 2001).

For a given chemical species, the corresponding mathematical model is (Crank 1975; Roberts *et al.* 2001)

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x} \left(D_{sc} \frac{\partial C_{sc}}{\partial x} \right) \quad (1)$$

where C_{sc} is the species concentration in the SC, D_{sc} is the effective diffusivity of the species in the SC, $t \in [0, T_{exp}]$ is time, and $x \in [0, L_{sc}]$ represents depth into the SC. The model initial and boundary conditions are

$$C_{sc}(x,0)=0, x \in [0, L_{sc}] \quad (2)$$

$$C_{sc}(0,t)=C_d, t \leq T_{exp} \quad (3)$$

$$C_{sc}(X_{TS}^i, t)=0, t_{TS}^i < t \leq t_{TS}^{i+1} \quad (4)$$

$$C_{sc}(L_{sc}, t)=0, t \in [0, T_{exp}] \quad (5)$$

Here, C_d is the dose concentration in the SC, and T_{exp} is the experimental exposure time. X_{TS}^i represents the location of the i th tape-strip that is taken at time t_{TS}^i

$$X_{TS}^i = i\delta_{TS}, \quad i=0, \dots, N_{TS} \quad (6)$$

where δ_{TS} is the thickness of the stratum corneum removed with each tape-strip and N_{TS} is the total number of tape-strips.

Equation 2 – Equation 6 above reflect several assumptions about the experimental system. Equation 2 assumes that background levels of the modeled species are zero. Equation 3 reflects our assumption that the first tape measurement is a reasonable estimate for the contaminant dose partitioned from the source vehicle. Boundary conditions at the surface are incorporated

through Equation 4, which states that zero concentration exists at the surface after each tape-strip removal and that this interface moves with time according to a constant thickness of the stratum corneum removed with each tape-strip (δ_{TS}). In this respect, our approach differs from that published by Reddy et al. (2002), where no diffusive flux was assumed at the interface. Last, zero concentration boundary conditions at the SC-blood interface are used in Equation 5, since the uptake rate by the blood was assumed to be large with respect to the diffusive transport time scales. Although a more general mathematical model for the experimental system would involve explicit representations of both a liquid-phase, contaminant vehicle as well as a systemic blood compartment (Reddy *et al.* 1998), Equation 1 – Equation 6 are deemed appropriate given the focus here on diffusive transport through the SC.

Analytical solutions to Equation 1 – Equation 6 are not readily available when the movement of the SC surface is incorporated. For this reason, a numerical solution was used. Before discretizing, Equation 1 – Equation 6 were nondimensionalized using $\tilde{x} = x / L_{sc}$, $\tilde{t} = t / T_{exp}$, and $\tilde{C}_{sc} = C_{sc} / C_d$. That is, the model coordinate $\tilde{x} = 1$ corresponds to the full extent of the SC, $\tilde{t} = 1$ is the experimental time of exposure, and the dimensionless effective diffusion coefficient is $\tilde{D} = D_{sc} T_{exp} / L_{sc}^2$ (Crank 1975). To solve Equation 1 – Equation 6, a method of lines approach was taken (Schiesser 1991). Specifically, a cell-centered finite volume discretization was used in space (Reddy *et al.* 1998) and, a well-known variable-order, variable step-size differential algebraic equation integrator DASPK (Brenan *et al.* 1996), was used for the resulting temporal approximation.

In addition to providing a prediction of species concentrations in the SC as a function of space and time, estimates of tape-strip concentrations were required. The i th tape-strip concentration was calculated using the numerical solution to Equation 1 – Equation 6.

$$\bar{C}_{TS}^i = \frac{1}{\delta_{TS}} \int_{x_{TS}^{i-1}}^{x_{TS}^i} C(x, t_{TS}^i) dx \quad (7)$$

The trapezoidal rule was used to approximate the spatial integral in Equation 7.

Parameter optimization

To obtain effective diffusion parameter estimates, we used a numerical solution for the above model formulation along with a Levenberg-Marquardt (Vogel 2002) algorithm to minimize weighted L^2 errors between measured tape-strip concentrations ($\bar{C}_{TS}^i$) and the model predictions given by Equation 7. A relative weighting for each measured value was assigned as

$$W_i = \frac{1}{\bar{C}_{TS}^i + 10^{-6}}, \quad i=2, \dots, N_{TS} \quad (8)$$

To avoid added uncertainty due to the impact of the source on the initial tape-strip values, we neglected tape-strips one and two in the parameter fit. A tolerance of 10^{-6} was used for the Levenberg-Marquardt algorithm. The forward numerical model for transport through the SC used 200 cells along with relative and absolute temporal integration tolerances of 10^{-4} , so that error in the numerical solution was negligible. Again, C_d was taken from the first tape-strip measurement but assumed to be constant over the entire exposure interval. The normalized thickness of the stratum corneum removed with each tape-strip was $\delta_{TS} / L_{sc} = 2.5 \times 10^{-2}$. In addition, the Levenberg-Marquardt algorithm was combined with a global search for initial estimates in attempt to avoid local minima in the least squares objective function.

Results

Experimental

The average age of the volunteers was 27, which ranged from 21 to 37 years old. Seven of the study volunteers were Caucasians, one Asian, one African American, and one was mixed Asian-Caucasian. The mean body mass index was 21 kg/m² and ranged from 19–25 kg/m².

JP-8 was absorbed into the skin during the 30 min exposure period as all compounds were quantifiable in the tape-strip samples (Table 1). As expected, the mass per cm² for each chemical decreased rapidly with successive tape-strips. The highest mass per cm² was found in the first tape-strip. The aromatic compounds were quantifiable in all tape-strip samples. Similarly, undecane and dodecane were quantified in all tape-strip samples while decane was not quantifiable after the 4th tape-strip (Table 1). Since the first tape-strip was not included in the parameter optimization step (see Parameter optimization above), decane was not analyzed further.

Model simulations

Comparisons of model predictions and data are shown in Figure 3 and Figure 4. The membrane model was used to predict the amount, expressed as mass of compound divided by the applied dose, in each layer of the SC. Simulations were conducted for naphthalene, 1-methyl naphthalene, 2-methyl naphthalene, undecane, and dodecane. The model was used to predict the rapid decline of the amount in the successive tape-strips for these five components of JP-8. In these figures, the sharp “dog-leg” reflects the fact that a significant amount of mass is removed when the first tape strip is taken, and this represents an abrupt change in the boundary conditions for the model. Figure 4 also shows the spatial profile of naphthalene in the SC as a function of location along the diffusion path. The density of the curves in the upper layers of the SC versus the deeper layers suggests that naphthalene penetrates the SC very rapidly. Similar spatial profiles were observed for 1-methylnaphthalene, 2-methylnaphthalene, undecane, and dodecane.

Table 2 summarizes the identified effective diffusion parameters for the SC. The diffusion coefficient was estimated for each individual by dividing the dimensionless value of D_{sc} by the path length of diffusion. We assumed a thickness of 20×10^{-4} cm for the thickness of the SC (McCarley and Bunge 2001). The coefficient of variation (CV) varied across compounds, ranging from 13% for dodecane to 58% for 1-methylnaphthalene.

Discussion

The quest for both effective dermal drug delivery and accurate dermal penetration of environmental toxicants for risk assessment require an understanding of transport of chemicals across human skin. The importance of dermal exposure to occupational and environmental hazards has been known for a long time (Walton and Witherspoon 1925). However, it is only recent that dermal exposures have become more evident as inhalation exposures decrease by preventive measures and increased use of personal protection (Semple 2004). Yet, dermal exposure standards do not exist in the U.S. The limitations of setting dermal exposure standards are due to the lack of standardized techniques for quantifying dermal exposures and the poor biological relevance of most of these techniques used to date. There are currently three types of techniques to measure dermal exposure: surrogate skin, removal, and a fluorescent tracer, all of which have their own limitations (Fenske 1993). In our study, we chose to measure dermal exposure using a removal method, tape-stripping. The advantage of tape-stripping is that it provides a measure of a chemical concentration in the SC and, thus, represents a biologically relevant measure of exposure. The tape-strip technique has been used in bioequivalence studies

of topically applied therapeutic agents (Pershing *et al.* 2003; Shah 2001). Furthermore, the tape-strip technique can be used to understand the spatiotemporal variation of hazardous contaminants in the skin.

To accurately predict the spatiotemporal nature of uptake across the SC, a mathematical model is needed that incorporates both of these dimensions. Membrane models do just this, but a paucity of dermal exposure studies have used membrane models to describe the uptake of contaminants across the skin because of the mathematical complexity associated with implementing such models. In our study, the interpretation of tape-strip measurements of dermal exposure required an understanding of the spatial and temporal nature of diffusion across the SC.

Here, we report on the successful application of a mathematical model to quantify the uptake of chemicals deposited on the skin surface into deeper layers. We implemented a one-compartment representation of the SC. The skin is a multilayered membrane of which the primary barrier function is controlled by the SC and the VE, but the SC is the rate-limiting barrier to the penetration of lipophilic compounds. Therefore, our equations were derived assuming that the SC controls the rate of dermal absorption.

There are limited opportunities to compare our results to published data from other studies; a paucity of studies have investigated uptake of neat chemicals into the skin of human volunteers. Most studies have focused on measuring uptake using *in vitro* systems under steady-state conditions (McDougal *et al.* 2000). Although not directly comparable, we have converted McDougal *et al.*'s permeability coefficients into D_{sc} using a skin thickness of 560 μm : these are $4.7 \times 10^{-7} \text{ cm}^2/\text{min}$, $1.5 \times 10^{-7} \text{ cm}^2/\text{min}$, $2.3 \times 10^{-8} \text{ cm}^2/\text{min}$, and $1.3 \times 10^{-8} \text{ cm}^2/\text{min}$ for naphthalene, 1-methyl and 2-methyl naphthalene, undecane, and dodecane. The values we report in the current study are a factor of 3.7 (range: 0.3 to 11) less than those reported by McDougal *et al.* (2000). One possible reason for this difference is differences in fat composition (and its impact on diffusion pathways) between rat and human skin; further investigation of these *in vitro* and *in vivo* experimental differences appears necessary.

In dermal risk assessment, it is not uncommon to estimate of diffusivity using quantitative structure-activity relationship (QSAR) models like the Potts and Guy regression (Potts and Guy 1992):

$$\log \frac{D_{sc}}{L_{sc}} = -2.8 - 0.006 MW \quad (9)$$

where MW is the species molecular weight. Using equation 9, we calculated D_{sc} values of $9.0 \times 10^{-9} \text{ cm}^2/\text{min}$, $7.4 \times 10^{-9} \text{ cm}^2/\text{min}$, $6.1 \times 10^{-9} \text{ cm}^2/\text{min}$, and $5.0 \times 10^{-9} \text{ cm}^2/\text{min}$ for naphthalene, 1-methyl and 2-methyl naphthalene, undecane, and dodecane, respectively. These estimates are a factor of 20 (range: 2 to 53) less than the values reported by McDougal *et al.* (2000). Comparisons to D_{sc} values reported in our study show that that the Potts and Guy regression predictions are a factor of 7 less (range: 5 to 10). The above comparisons illustrate the inaccuracy of using D_{sc} calculated using an algorithm that was developed for describing dermal absorption of hydrocarbon from an aqueous vehicle. Thus, incorrect application of D_{sc} calculated from the Potts and Guy regression can result in underestimating the internal dose. Conversely, for predicting dermal exposures that are consistent with internal dose metrics (i.e., for conducting reverse dosimetry and/or animal-to-human extrapolations), a higher exposure level would be estimated if the Potts and Guy regression is used; this would not be considered a conservative approach to dermal risk assessment.

The membrane model presented in our study represents an improved description of dermal uptake from previously published models. One of the limitations of previous models is that

they do not account for the impact of tape-stripping on transport through the SC. In this respect, no diffusive flux is typically assumed at the interface. The removal of contaminants with successive tape-stripping will impact the concentration gradient. Our description of diffusive transport states that zero concentration exists at the surface after each tape-strip removal, and that this interface moves with time according to the point at which each tape-strip sample is collected. Therefore, our model is a more accurate description of diffusive transport given the impact of the sequential tape-stripping procedure, and can therefore be used to better understand dermal uptake of contaminants. Furthermore, these results demonstrate the value of measuring dermal exposure using the tape-strip technique and the importance of quantification of dermal exposure.

Our description of dermal uptake consisted of passive diffusion across the SC. This is not the only mechanism of uptake across the skin. For example, chemicals can be taken up through hair follicles. However, the total area contributed by hair follicles represents less than 10% of SC, thus it is not a major contributor to dermal uptake (Shah 2001). Other pathways described in the literature include lateral diffusion along lipid bilayers and diffusion through pores (Mitragotri 2003). We did not examine these alternate pathways. However, the impact of these minor pathways may be significant for low dermal exposure levels and, thus, these pathways should be incorporated in future modeling efforts.

Conclusion

Membrane models have not been used extensively in the past because of the mathematical rigor needed to calibrate and validate such models. Consequently, the chemical space of our understanding of dermal uptake has been limited. We used a combination of the tape-strip technique and mathematical modeling to quantify the levels of naphthalene, 1-methylnaphthalene, 2-methylnaphthalene, undecane, and dodecane in the different layers of the SC at different time points. The model and experimental data were used to estimate the diffusion coefficient for each component of JP-8. Overall, the approach taken in this study has furthered our understanding of dermal uptake of aromatic and aliphatic hydrocarbons *in vivo*. A natural extension of the model would be to include a liquid phase, multi-component source vehicle and a systemic blood compartment. Future work should incorporate such biologically relevant descriptions into a generalizable model that improves understanding of dermal exposures to hazards.

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References

- Brenan, KE.; Campbell, SL.; Petzold, LR. The numerical solution of initial value problems in differential-algebraic equations. Philadelphia: Society for Industrial and Applied Mathematics; 1996.
- Chao YC, Gibson RL, Nylander-French LA. Dermal exposure to jet fuel (JP-8) in US Air Force personnel. *Ann Occup Hyg* 2005;49:639–645. [PubMed: 16006502]
- Chao YC, Kupper LL, Serdar B, Egeghy PP, Rappaport SM, Nylander-French LA. Dermal exposure to jet fuel JP-8 significantly contributes to the production of urinary naphthols in fuel-cell maintenance workers. *Environ Health Perspect* 2006;114:182–185. [PubMed: 16451852]
- Chou CC, Riviere JE, Monteiro-Riviere NA. The cytotoxicity of jet fuel aromatic hydrocarbons and dose-related interleukin-8 release from human epidermal keratinocytes. *Arch Toxicol* 2003;77:384–391. [PubMed: 12851741]
- Crank, J. The mathematics of diffusion. Oxford, [Eng]: Clarendon Press; 1975.

- Elias PM. The stratum corneum as an organ of protection: old and new concepts. *Curr Probl Dermatol* 1989;18:10–21. [PubMed: 2663357]
- Fenske RA. Dermal exposure assessment techniques. *Ann Occup Hyg* 1993;37:687–706. [PubMed: 8304685]
- George K, Kubota K, Twizell EH. A two-dimensional mathematical model of percutaneous drug absorption. *Biomed Eng Online* 2004;3:18. [PubMed: 15202943]
- Kalinin A, Marekov LN, Steinert PM. Assembly of the epidermal cornified cell envelope. *J Cell Sci* 2001;114:3069–3070. [PubMed: 11590230]
- Kim D, Andersen ME, Chao YC, Egeghy PP, Rappaport SM, Nylander-French L. PBTK modeling demonstrates contribution of dermal and inhalation exposure components to end-exhaled breath concentrations of naphthalene. *Environ Health Perspect* 2007;115:894–901. [PubMed: 17589597]
- Kim D, Andersen ME, Nylander-French LA. Dermal absorption and penetration of jet fuel components in humans. *Toxicol Lett* 2006a;165:11–21. [PubMed: 16497449]
- Kim D, Andersen ME, Nylander-French LA. A dermatotoxicokinetic model of human exposures to jet fuel. *Toxicol Sci* 2006b;93:22–33. [PubMed: 16801332]
- Kubota K, Ishizaki T. A diffusion-diffusion model for percutaneous drug absorption. *J Pharmacokinet Biopharm* 1986;14:409–439. [PubMed: 3772740]
- Marks R, Nicholls S, King CS. Studies on isolated corneocytes. *Int J Cosmet Sci* 1981;3:251–259.
- McCarley KD, Bunge AL. Pharmacokinetic models of dermal absorption. *J Pharm Sci* 2001;90:1699–1719. [PubMed: 11745728]
- McDougal JN, Boeniger MF. Methods for assessing risks of dermal exposures in the workplace. *Crit Rev Toxicol* 2002;32:291–327. [PubMed: 12184506]
- McDougal JN, Pollard DL, Weisman W, Garrett CM, Miller TE. Assessment of skin absorption and penetration of JP-8 jet fuel and its components. *Toxicol Sci* 2000;55:247–255. [PubMed: 10828255]
- Mitragotri S. Modeling skin permeability to hydrophilic and hydrophobic solutes based on four permeation pathways. *J Control Release* 2003;86:69–92. [PubMed: 12490374]
- Pershing LK, Nelson JL, Corlett JL, Shrivastava SP, Hare DB, Shah VP. Assessment of dermatopharmacokinetic approach in the bioequivalence determination of topical tretinoin gel products. *J Am Acad Dermatol* 2003;48:740–751. [PubMed: 12734504]
- Pirot F, Kalia YN, Stinchcomb AL, Keating G, Bunge A, Guy RH. Characterization of the permeability barrier of human skin in vivo. *Proc Natl Acad Sci U S A* 1997;94:1562–1567. [PubMed: 9037093]
- Potts RO, Guy RH. Predicting skin permeability. *Pharm Res* 1992;9:663–669. [PubMed: 1608900]
- Reddy MB, McCarley KD, Bunge AL. Physiologically relevant one-compartment pharmacokinetic models for skin. 2. Comparison of models when combined with a systemic pharmacokinetic model. *J Pharm Sci* 1998;87:482–490. [PubMed: 9548902]
- Reddy MB, Stinchcomb AL, Guy RH, Bunge AL. Determining dermal absorption parameters in vivo from tape strip data. *Pharm Res* 2002;19:292–298. [PubMed: 11934236]
- Roberts, MS.; Anissimov, YG.; Gonsalvez, RA. Mathematical models in percutaneous absorption. In: Bronaugh, RL.; Maibach, HI., editors. *Percutaneous Absorption*. Boca Raton: Taylor and Francis Group, LLC; 2001.
- Schiesser, WE. The numerical method of lines : integration of partial differential equations. San Diego: Academic Press; 1991.
- Seiple S. Dermal exposure to chemicals in the workplace: just how important is skin absorption? *Occup Environ Med* 2004;61:376–382. [PubMed: 15031402]
- Shah VP. Progress in methodologies for evaluating bioequivalence of topical formulations. *Am J Clin Dermatol* 2001;2:275–280. [PubMed: 11721645]
- Singh S, Zhao K, Singh J. In vivo percutaneous absorption, skin barrier perturbation, and irritation from JP-8 jet fuel components. *Drug Chem Toxicol* 2003;26:135–146. [PubMed: 12816398]
- Tojo K. Random brick model for drug transport across stratum corneum. *J Pharm Sci* 1987;76:889–891. [PubMed: 3440932]
- Vogel, CR. Computational methods for inverse problems. Philadelphia PA: Society for Industrial and Applied Mathematics; 2002.

Walton DC, Witherspoon MG. Skin absorption of certain gases. J Pharmacol Exp Ther 1925;26:315–324.

Abbreviations

C_{sc} , Concentration of chemical in the stratum corneum
 C_d , Dose concentration of chemical in the stratum corneum
 $\tilde{C}_{sc}$, Dimensionless concentration of chemical in the stratum corneum
 CV, Coefficient of variation
 $\hat{C}_{ts}^i$, Measured tape-strip concentration of chemical
 $\tilde{C}_{ts}^i$, Predicted tape-strip concentration of chemical
 D , Dimensionless effective diffusivity of the chemical in the stratum corneum
 DPK, Dermatopharmacokinetic
 D_{sc} , Effective diffusivity of the chemical in the stratum corneum
 δ_{TS} , Thickness of the stratum corneum removed with each tape-strip
 JP-8, Jet-Propulsion Fuel 8
 L_{sc} , Thickness of the stratum corneum
 MW, Molecular weight
 N_{TS} , Total number of tape-strips
 PK, Pharmacokinetic
 QSAR, Quantitative structure-activity relationship
 SC, Stratum corneum
 SD, Standard deviation
 t , Time
 τ , Dimensionless time
 T_{exp} , Duration of the exposure
 t_{ts}^i , Time at which the i^{th} tape-strip is taken
 VE, Viable epidermis
 W_i , Relative weighting for measured tape-strip values in parameter estimation
 x , Position in the stratum corneum
 $\tilde{x}$, Dimensionless position in the stratum corneum
 X_{ts}^i , Location of the i^{th} tape-strip

Exposure System

Tape-stripping Procedure

Figure 1.
Schematic of the exposure system and tape-strip procedure.

Figure 2. Schematic of the stratum corneum and mathematical model used to describe the diffusion of jet fuel components during the tape-stripping procedure.

Figure 3.

Spatial profile of naphthalene in the SC as a function of location along the diffusion path (A). Also shown is a comparison of model prediction and tape-strip data (B). The dots represent data points, and the line represents model predictions. In Figure 4B, the concentration in the tape-strip was normalized by the concentration at the interface between the surface and the SC. The time at which each tape-strip measurement was made is normalized by the experimental exposure time.

Figure 4.

Comparison of model predictions and tape-strip measurements for (A) 1-methylnaphthalene, (B) 2-methylnaphthalene, (C) undecane, and (D) dodecane. The dots represent data points, and the line represents model predictions. The concentration in the tape-strips is normalized by the concentration at the interface between the surface and the stratum corneum. The time at which each tape-strip measurement was made is normalized by the experimental exposure time.

Table 1
Percent of amount in the surface layer (average of all study volunteers) for aromatic and aliphatic hydrocarbons by tape-strip number.
The first tape-strip was used to quantify the amount of chemical in the surface layer (i.e., monolayer) that is adjacent to the stratum corneum (McDougal and Boeniger 2002; Shah 2001).

Tape Strip	Naphthalene	1-Methylnaphthalene	2-Methylnaphthalene	Undecane	Dodecane
2	7.9	8.6	9.0	7.2	9.3
3	3.5	2.9	3.1	2.9	3.4
4	2.5	1.3	1.4	1.8	1.5
5	1.2	0.7	0.7	1.2	0.9
6	1.4	0.6	0.6	1.0	0.7
7	1.2	0.4	0.4	0.7	0.6
8	0.6	0.3	0.3	0.6	0.5
9	0.9	0.2	0.2	0.4	0.4
10	0.8	0.2	0.2	0.4	0.3

Table 2
Summary of the estimated diffusion coefficients ($\text{cm}^2/\text{min} \times 10^{-8}$) for each study volunteer. Diffusion coefficients were estimated assuming a thickness of 20×10^{-4} cm for the stratum corneum.

Volunteer	Naphthalene	1-Methylnaphthalene	2-Methylnaphthalene	Undecane	Dodecane
1	1.6	3.6	3.7	2.2	3.8
2	3.6	5.8	5.7	4.1	5.7
3	2.7	4.7	4.8	4.3	4.7
4	4.1	5.0	5.2	3.1	4.4
5	5.4	6.4	5.7	5.3	4.9
6	5.6	7.6	7.5	6.0	6.2
7	5.2	6.7	6.5	5.0	5.3
8	6.2	0.0	0.0	3.4	4.8
9	3.6	0.0	0.0	3.4	4.9
10	4.6	6.3	6.1	4.9	5.6
D_{sc} Mean $\pm$ SD	4.2 ± 1.4	4.6 ± 2.7	4.5 ± 2.6	4.2 ± 1.2	5.0 ± 0.7
D_{sc} CV (%)	33	58	57	28	13