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Modeling of Human Dermal Absorption of Octamethylcyclotetrasiloxane (D_4) and Decamethylcyclopentasiloxane (D_5)

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In this study, data for human dermal absorption of octamethylcyclotetrasiloxane, D_4, and decamethylcyclopentasiloxane, D_5, through axilla skin *in vivo* are interpreted using pharmacokinetic models of dermal absorption by adding the dermal exposure route to inhalation physiologically based pharmacokinetics models developed previously. The compartmental model describing dermal absorption of these compounds included volatilization of the applied chemical from the skin surface, diffusion of absorbed chemical back to the skin surface and evaporation of this chemical from the skin surface after the applied dose had cleared from the application site, uptake from the skin compartment into blood, and a storage compartment within the skin. Data from exposures in volunteers (i.e., D_4 and D_5 concentrations in exhaled air and plasma) were used to estimate model parameters. In volunteers exposed to either D_4 or D_5, the maximum concentration of chemical in exhaled air reached a maximum at or prior to 1 h following administration of the test chemical. Based on model calculations, the percent of applied dose of D_4 that was absorbed into systemic circulation for men and women was 0.12 and 0.30%, respectively; for D_5 about 0.05% of the applied dose was absorbed for both men and women. For both D_4 and D_5, model calculations indicate that more than 83% of the chemical that reached systemic circulation was eliminated by exhalation within 24 h. These whole-body pharmacokinetic models for dermal absorption of two semi-volatile compounds provide a valuable tool for understanding factors controlling their dermal absorption through axilla skin and for applying results from these studies in consumer product risk assessments.

Key Words: **octamethylcyclotetrasiloxane (D_4); decamethylcyclopentasiloxane (D_5); dermal absorption; PBPK model.**

Octamethylcyclotetrasiloxane, D_4, and decamethylcyclopentasiloxane, D_5, are silicone fluids found in a broad range of consumer and industrial products. Studies on both D_4 (McKim *et al.*, 2001) and D_5 (Burns-Naas *et al.*, 1998) have indicated a low order of toxicity in the Fischer 344 rat. The general population and workers involved in industrial applications of D_4 and D_5 may be exposed to low levels of these lipophilic, semi-volatile compounds by the dermal and inhalation exposure routes.

Recently, the dermal absorption of D_4 and D_5 was studied through human abdominal skin *in vitro* and in rats *in vivo* (Jovanovic *et al.*, unpublished data). The rat *in vivo* study showed that >91% of applied neat D_4 and >89% of applied neat D_5 had volatilized from the skin application site by 24 h of application of the test chemical. Less than 1.0% of the applied dose for D_4 and less than 0.1% for D5 penetrated the skin (i.e., passed from the skin into systemic compartments). Similarly, *in vitro* dermal studies indicated that >88% and >91% of D_4 and D_5, respectively, volatilized from skin before penetrating. An average of 0.5% of applied D_4 and 0.04% of D_5 penetrated human skin *in vitro*.

Assessing dermal absorption of volatile and semi-volatile chemicals can be difficult because evaporation can lead to loss of chemical. However, recent dermal absorption studies have exploited the nature of volatile chemicals. *In vivo* dermal absorption of several volatile chemicals, e.g., xylene (Thrall and Woodstock, 2003), methyl chloroform (Poet *et al.*, 2000b), and trichloroethylene (Poet *et al.*, 2000a), has been studied by exposing rats or humans to a chemical and quantifying the concentration of chemical in the exhaled air using mass dpectrometry/mass spectrometry real-time analysis. In these studies, the resulting data have been analyzed with physiologically based pharmacokinetics (PBPK) models to infer the amount of chemical absorbed through skin from the amount of chemical in exhaled air. Here, we adopt a similar technique to analyze the human, *in vivo*, dermal absorption data.

In this pharmacokinetic study, the dermal absorption of D_4 and D_5 was examined following application to axilla skin of human volunteers and the concentrations of D_4 or D_5 in the blood and exhaled air were determined in six volunteers for up to 24 h following the exposure. These dermal absorption

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studies of neat D_4 and D_5 are used to develop a mathematical model describing the uptake of these compounds from skin to aid in data interpretation and to add the dermal exposure route to the inhalation PBPK models to develop a multiroute model for use in human risk assessment.

A variety of mathematical models describing dermal absorption during various types of exposures are available (Roberts *et al*., 2001), and choosing an appropriate model structure can be difficult. Because skin is a membrane, membrane models of the skin appear more realistic (Scheuplein, 1978) but can be mathematically cumbersome. Compartment models have been developed as an alternative and permit easy combination with available PBPK models for whole-body distribution of chemicals (McCarley and Bunge, 2001). Here, we present a compartment model describing the dermal absorption of D_4 and D_5 that includes the storage capacity of the skin and evaporation either from the neat chemical on the skin or from chemical absorbed in skin that has diffused back to the skin surface. *In vivo* dermal absorption studies of D_4 and D_5 in the rat show that a model structure including evaporation of D_4 or D_5 is essential for describing the kinetics (Jovanovic *et al*., unpublished data). The dermal absorption data in human volunteers were used to estimate model parameters. For each compound, the dermal absorption model was combined with a human inhalation PBPK model that was developed using pharmacokinetic studies of human volunteers exposed to D_4 or D_5 by inhalation (Reddy *et al*., 2004; Reddy *et al*., 2003). The whole-body PBPK models that include the dermal exposure route were then used to estimate the amount of chemical that reached the blood during the dermal exposures of human volunteers to D_4 or D_5.

MATERIALS AND METHODS

Human studies. Studies of dermal absorption of D_4 (Plotzke *et al*., 2000) and D_5 (Plotzke *et al*., 2002) in human volunteers were conducted at the University of Rochester after approval from the Institutional Human Subjects Review Board. In these studies, ^{13}C-labeled D_4 and D_5 were used so that siloxane absorbed during these experiments could be differentiated from that present in other sources (e.g., personal care products) and to increase the sensitivity of the analytical analysis. The D_4 and D_5 experiments both included three female and three male subjects. In the D_5 study, subjects were asked not to shave their underarms for several days prior to the study. For the D_4 study, it is not known if subjects were provided with that guideline. In two separate syringes, a total of 1.4 g ^{13}C-D_4 or ^{13}C-D_5 for men and 1.0 g for women was weighed. Subjects were positioned on their sides for the administration of the applied dose to their axillae. The contents of one syringe were administered to the indent of the axilla and allowed to absorb and evaporate for about 5 min. Then, the subject changed sides and the second half of the dose was administered to the other axilla. Because the test chemical was applied by different people during the two studies, the application area was different for D_4 and D_5. However, the area of the application site was measured and recorded during both studies (Table 1).

TABLE 1
Parameters Used for Model Simulations of D_4 and D_5 Human Dermal Exposures[a]

	D_4		D_5	
	Women	Men	Women	Men
Age (years)[b]	30.3 ± 9.3	30.3 ± 11.8	36.7 ± 7.6	29.7 ± 3.5
Body weight (kg)[c]	60.0 [c]	70.0 [c]	59.6 ± 4.6	123 ± 26[d]
Alveolar ventilation (l/min)[e]	6.0	7.5	6.0	7.5
Cardiac output (l/min)[f]	6.63	6.63	6.07	6.70
Total area of both axillae (cm^2)[b]	30 ± 4	51 ± 21	61 ± 25	99 ± 30
Applied dose (g)[b]	0.96 ± 0.04	1.3 ± 0.05	0.94 ± 0.05	1.34 ± 0.05
Applied dose (mg/cm^2)	32	25	15.4	13.5
For $t < t_{clear}$: $\hat{k}_{evap}$ ($mg/cm^2/min$)[g]	0.15	0.15	0.071	0.071
For $t < t_{clear}$: $\hat{k}_1$ ($mg/cm^2/min$)[h]	6.1	5.1	3.0	2.6
For $t > t_{clear}$: k_{-1} (min^{-1})[i]	120	200	0.011	0.0055
k_{-2} (min^{-1})[i]	0.00064	0.00030	0.0000054	0.0000057
k_d (min^{-1})[i]	0.00085	0.0032	0.0084	0.00010
k_{-d} (min^{-1})[i]	0.010	0.050	0.0040	0.0066

[a]Complete parameterization for the D_4 and D_5 inhalation PBPK models may be found in Reddy *et al.* (2003) and Reddy *et al*., (2004), respectively.

[b]Reported values are the mean ± 1SD for three men or women.

[c]Body weights were not reported in the D_4 study, and so reference values were used.

[d]This weight is higher than the "Reference Man" weight of 70 kg. The three male subjects weighed 99.8, 120, and 151 kg (i.e., 220, 264, and 332 lb). The compartment volumes in the D_5 PBPK model were changed for the men to simulate obesity as described in the Materials and Methods section.

[e]Reference values were used.

[f]Calculated using the correlation (Brown *et al*., 1997): QC (l/min) = − 6.846 log (age, years) + 16.775.

[g]This parameter was set to the experimentally measured rate of evaporation.

[h]This parameter was set to the value required for the skin to clear of chemical in 5 min.

[i]These parameters were calculated by fitting the model to the data.

For the D_4 study, blood and exhaled air samples were obtained before the exposure and at 1, 2, 4, 6, and 24 h postexposure. For the exhaled air samples, subjects breathed 40 l of air, as determined using a dry test meter, into a specially adapted 40-l Tedlar bag using a Hans Rudolf nonrebreathing valve. For the D_5 study, blood samples were drawn before the exposure and at 30 min and 1, 2, 4, and 6 h, and exhaled air samples were obtained before the exposure and at 15, 30, 45, 60, 75, 90, 105, 120, 240, 360, and 1440 min. For the air samples before the exposure, a 40-l Tedlar bag was used, but for all remaining samples a 5-l Tedlar bag was used. The concentration of ^{13}C-D_4 or ^{13}C-D_5 in plasma was determined by extracting the sample with tetrahydrofuran and then analyzing the sample using gas chromatography with mass spectrometry (GC/MS) as described by Varaprath *et al*. (2000). The concentration of ^{13}C-D_4 or ^{13}C-D_5 in exhaled air was determined by trapping the D_4 or D_5 on Tenax tubes, desorbing the chemical into pure hexane, and using GC/MS analysis.

Determination of evaporation rates. Although evaporation characteristics of volatile silicones have been studied, the data could not be used for our purposes because the percent of applied dose that had evaporated was reported instead of the amount that had evaporated per area (Koini *et al*., 1999). A simple method was used to estimate the evaporation rate of neat D_4 and D_5. About 0.4 ml D_4 or D_5 was applied to an 8-cm diameter filter paper in a 9-cm diameter glass dish. This amount was chosen so that silicone fluid covered the entire filter paper at all times during the experiment. The dish was placed on a scale in a draft-free environment at 22°C. (The skin surface is typically about 32°C, but somewhat variable. We estimated the evaporation rate at room temperature, considering that a 10°C temperature difference would not be expected to alter the evaporation rate any more than twofold.) The weight of silicone fluid was recorded at time zero to determine the exact amount applied and 5 min later to determine the amount that had evaporated during that period. This timing is consistent with the human dermal absorption studies of D_4 and D_5 where the application site was only left undisturbed for about 5 min after the exposure because at that point the skin had dried. Although the rate of evaporation can decrease with time, over a period of 5 min for D_4 and D_5 the rate should remain constant (Koini *et al*., 1999). The mass balance equation describing the rate of change in the amount of chemical that has evaporated, Aevap, as a zero-order process is

$$\frac{\mathrm{dAevap}}{\mathrm{d}t} = \hat{k}_{\mathrm{evap}} \times \mathrm{SA}, \tag{1}$$

where $\hat{k}_{\mathrm{evap}}$ (mg/cm^2/min) is a rate constant for evaporation, SA is the surface area exposed, and t is the time. Thus, the evaporation rates for D_4 and D_5 were approximated as

$$\hat{k}_{\mathrm{evap}} = (\Delta M)/\mathrm{SA}/\Delta t, \tag{2}$$

where ΔM is the decrease in mass observed over the time period Δt, with $\Delta t = 5$ min.

Compartment model for dermal absorption. Here, we present a compartment model used to describe the dermal absorption of D_4 and D_5 (Fig. 1). During a dermal exposure to a neat, volatile chemical, the skin is exposed until the chemical has either evaporated or absorbed into skin (i.e., until the time required for the skin to clear of chemical, t_{clear}). Before the skin clears of chemical, evaporation and dermal absorption of the neat chemical are both described as zero-order processes (i.e., with rates $\hat{k}_{\mathrm{evap}}$ and $\hat{k}_1$ [mg/cm^2/min], respectively). Absorption into the skin is described as a zero-order process because the driving force for mass transfer (i.e., the concentration gradient) from a film of pure chemical on the skin is as high as it can be as long as the concentration of chemical in the skin remains well below saturation. After all the chemical has been cleared from the skin, chemical diffusion to and evaporation from the surface of the skin are controlled by a rate constant, k_{-1} (min^{-1}). Intercompartmental rate constants are also used to control the transfer to and from a deep skin compartment and from the skin to the blood (i.e., k_{-d}, k_d, and k_{-2} [min^{-1}], respectively). Here, we assume that the concentration of absorbing chemical in the blood remains low relative to the amount of chemical in the skin at the exposed site; thus, the rate constant for return of chemical from the bloodstream is unnecessary.

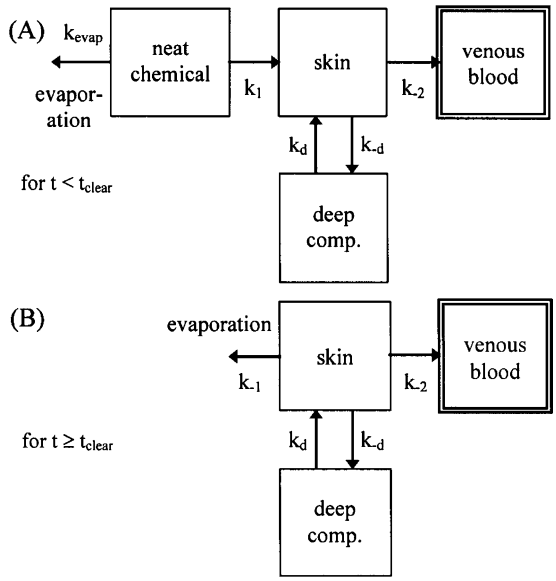

FIG. 1. Schematic diagram of the compartment (comp.) model for dermal absorption of D_4 and D_5 (A) before and (B) after all the chemical has evaporated or absorbed into the skin. The double line designates the compartment from the PBPK model to which the dermal absorption model is attached.

Before all the D_4 or D_5 has cleared from the skin, the mass balance equation describing the amount of chemical on the application site, Aapp, is

$$\frac{\mathrm{dAapp}}{\mathrm{d}t} = -\hat{k}_{\mathrm{evap}} \times \mathrm{SA} - \hat{k}_1 \times \mathrm{SA} \quad \text{for } 0 < t < t_{\mathrm{clear}}. \tag{3}$$

By assuming that the chemical forms a uniform layer on the skin and that the skin is flat, the parameter t_{clear} can be calculated as the time when Aapp decreases to zero. During this initial period, the amount of chemical in the skin, Askin, can be calculated using the equation

$$\begin{aligned}\frac{\mathrm{dAskin}}{\mathrm{d}t} &= \hat{k}_1 \times \mathrm{SA} - k_{-2} \times \mathrm{Askin} + k_d \times \mathrm{Adeep} \\ &\quad - k_{-d} \times \mathrm{Askin} \quad \text{for } 0 < t < t_{\mathrm{clear}},\end{aligned} \tag{4}$$

where Adeep is the amount of chemical in the deep skin compartment. Equation 4 is written assuming that D_4 and D_5 are not metabolized in the skin. After the application site is cleared of chemical, the driving force for mass transfer has reversed because the skin contains chemical but the air over the skin acts like an infinite sink. D_4 and D_5 can be eliminated from the skin by diffusion to and evaporation from the surface and by blood clearance. The mass balance equation describing Askin becomes

$$\begin{aligned}\frac{\mathrm{dAskin}}{\mathrm{d}t} &= -k_{-1} \times \mathrm{Askin} - k_{-2} \times \mathrm{Askin} + k_d \times \mathrm{Adeep} \\ &\quad - k_{-d} \times \mathrm{Askin} \quad \text{for } t \geq t_{\mathrm{clear}}.\end{aligned} \tag{5}$$

Using the following equation, Adeep can be calculated:

$$\frac{\mathrm{dAdeep}}{\mathrm{d}t} = k_{-d} \times \mathrm{Askin} - k_d \times \mathrm{Adeep} \quad \text{for } t > 0. \tag{6}$$

The rate at which chemical is absorbed systemically from the skin is calculated using the equation:

$$\frac{\mathrm{dAabs}}{\mathrm{d}t} = k_{-2} \times \mathrm{Askin} \quad \text{for } t > 0, \tag{7}$$

where Aabs is the amount absorbed systemically, i.e., the amount of applied compound that reaches the blood. At the beginning of the exposure, the amount of chemical on the skin is equal to the applied dose, the skin and deep skin compartments are free of chemical, and no penetration into cutaneous blood has occurred (i.e., at $t = 0$, Aapp = the amount of D_4 or D_5 applied to the axillae, Askin = 0, Adeep = 0, and Aabs = 0).

This model was used to analyze the data from the dermal absorption studies of D_4 and D_5 in humans (i.e., concentrations of absorbing chemical in the plasma and exhaled air following application of D_4 or D_5 to each axilla in turn). To accomplish this analysis, this dermal absorption model was combined with PBPK models describing D_4 and D_5 disposition in humans as shown in Figure 2. Because half of the dermal dose was applied to one axilla at time zero and the remaining half of the dose was applied to the other axilla 5 min later, two identical skin compartment models (i.e., one for each axilla) were included in the PBPK model. Additionally, it was assumed that while chemical was being applied to the second axilla, evaporation did not occur from the first axilla because the first arm was pressed under the body, which prevented the axilla from being open to the air. The skin compartment models act as input functions to the PBPK model, but the skin itself is included in the slowly perfused compartment. Chemical that penetrated the skin was assumed to enter the venous blood from the exposed site. The model equations were solved using Berkeley Madonna (Macey & Oster, Berkeley, CA).

The PBPK models for D_4 (Reddy *et al.*, 2003) and D_5 (Reddy *et al.*, 2004) are described in detail elsewhere but are discussed briefly here. The D_4 PBPK model was developed using data from ^{14}C-D_4 inhalation exposures with human volunteers. In the PBPK model development, a deep compartment in the fat, a mass transfer resistance in the slowly perfused compartment, and a pool of unavailable D_4 in the blood were required to adequately describe all the pharmacokinetic data. The D_5 PBPK model, based on the D_4 model but developed using data from a study of human volunteers exposed to D_5 by inhalation, included deep compartments in the lungs and liver and a pool of unavailable D_5 in the blood. For both D_4 and D_5, the unavailable form in the blood, presumably bound to lipoproteins, was produced in the liver, secreted to blood, and cleared into the fat.

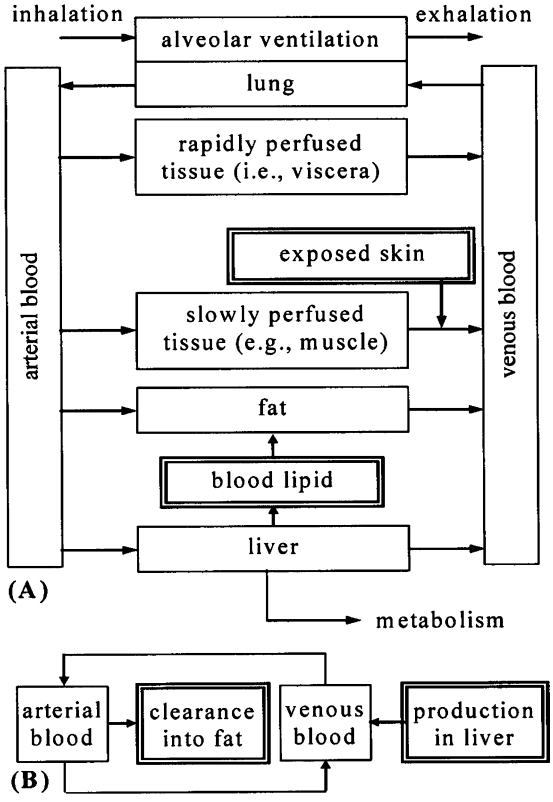

FIG. 2. Schematic diagram of (A) the generalized PBPK model structure and (B) the submodel for the transport of unavailable chemical in blood lipids used for both D_4 (Reddy *et al.*, 2003) and D_5 (Reddy *et al.*, 2004) pharmacokinetics in humans. The double lines designate variables from other components of the model.

Compartment model parameterization. The compartment model for dermal absorption requires the estimation of six parameters (Table 1). The value of $\hat{k}_{evap}$ was determined experimentally and calculated using Equation 2. Because the skin looked dry 5 min after the application of D_4 and D_5, the rate constant $\hat{k}_1$ was set so that the skin cleared of chemical in 5 min. Although the exact value of t_{clear} is not precisely known for an accurate estimation of $\hat{k}_1$, a rough estimate of this parameter is accurate enough for the model simulations because a large range of values for this parameter result in similar pharmacokinetic profiles (data not shown). This method of estimating $\hat{k}_1$ results in the model simulating rapid absorption of chemical into the skin where it is available for systemic absorption; the rationale for choosing this model behavior will be addressed in detail in the Discussion section. The remaining four parameters were estimated by comparing experimentally determined and model-calculated concentrations of D_4 and D_5 in the exhaled air and plasma following the dermal exposure.

The dermal/inhalation model was fit to the average values of plasma concentrations and concentrations in exhaled air of men and women separately, resulting in separate sets of model parameters for men and women. Although both whole blood and plasma concentrations of D_4 and D_5 were determined, parameter estimation was done using plasma concentrations to be consistent with the earlier inhalation models that were also developed using plasma data. In the D_5 dermal absorption study, the males had higher body weights than typical (Table 1), with a mean body weight of 123 kg. Therefore, for the analysis of the D_5 male data, the volumes of tissue compartments were changed to simulate obese men (i.e., it was assumed that the liver, lung, and the rapidly perfused tissue compartment were the same size as for a 70-kg person, that the blood compartment remained at 0.059% of body weight, that the slowly perfused compartment [which includes muscle] was 20% bigger than that of a 70-kg person, and that the fat compartment was about 48% of body weight). Metabolic capability was assumed to be similar to that of a 70-kg person, instead of scaling the metabolic rate constant by body weight. For D_5, the ratio of the concentration of D_5 in the venous return to the concentration of D_5 in exhaled air was used to estimate model parameters describing the pool of D_5 sequestered in the blood.

Optimum parameters were estimated using the multiple curve-fitting routine in Berkeley Madonna as described by Reddy *et al.* (2003). Sensitivity analysis was used to verify that the model parameters could be determined based on the available data and that the model parameters were necessary to describe the pharmacokinetics from the dermal exposures. The model code is available from the corresponding author upon request.

RESULTS

D_4 and D_5 Dermal Absorption in Human Volunteers

For both D_4 and D_5, chemical was detected in the bloodstream within an hour of the dermal exposure (Tables 2 and 3). For D_4, the highest measured plasma and exhaled air concentrations for all subjects occurred at the earliest time that data were collected (i.e., 1 h following the exposure). Maximal blood concentrations must have occurred earlier than the 1-h

TABLE 2
Concentrations of D_4 in Exhaled Air and Plasma in Humans Following a Dermal Exposure[a]

		Female subjects				Male subjects			
	Time (h)	1	2	3	Average[b]	1	2	3	Average[b]
Concentration in exhaled air, ng/l	0	4.0[c]	0.2[c]	0.1[c]	1.4 ± 2.2[c]	0.1[c]	0.2[c]	ND	0.165[c]
	1	27	240	67	110 ± 110	15	73	3.1	30 ± 37
	2	12	60	13	29 ± 28	5.6	12	1.5	6.2 ± 5.0
	4	8.7	14	5.9	9.6 ± 4.3	1.9	4.6	0.90	2.5 ± 1.9
	6	5.2	7.2	3.2	5.2 ± 2.0	1.1	3.3	0.80	1.7 ± 1.4
	24	1.1	1.3	0.50	0.97 ± 0.42	0.33	0.90	0.20	0.48 ± 0.37
Concentration in plasma, μg/l	0	ND	ND	ND	ND	ND	ND	ND	ND
	1	6.5	7.02	3.94	5.8 ± 1.6	0.85	2.6	1.9	1.8 ± 0.9
	2	4.77	4.84	2.19	3.9 ± 1.5	0.58	1.8	1.4	1.2 ± 0.6
	4	2.72	2.34	1.24	2.1 ± 0.8	0.45	0.53	1.1	0.67 ± 0.34
	6	2.13	1.26	0.49	1.3 ± 0.8	0.30	0.66	0.88	0.61 ± 0.29
	24	NQ	0.31	0.12	—[d]	ND	0.24	0.30	—[d]

[a]These data were reported by Plotzke *et al*. (2000). ND means that no D_4 was detected and NQ indicates that the amount of D_4 was not quantifiable.
[b]Reported values are the mean ± 1SD for three men or women.
[c]The air samples had a small, variable ^{13}C-background level due to the reuse of a Rudolf valve, despite efforts to decontaminate the valve between uses.
[d]For one subject, the amount of D_4 was below the detection limit or the limit of quantification, and so the average value was not reported and this data point was not used for parameter estimation.

sampling time. The concentrations of D_4 in exhaled air and plasma were higher in women than in men. By 24 h, the amount of D_4 in exhaled air had returned to background levels. For the D_4 study, interindividual variability was significant, especially for the concentration of D_4 in exhaled air. For example, the lowest and highest peak concentrations of D_4 in exhaled air were 3.1 and 240 ng/l, respectively, while the lowest and highest peak concentrations of D_4 in plasma were

TABLE 3
Concentrations of D_5 in Exhaled Air and Plasma in Humans Following a Dermal Exposure[a]

		Female subjects				Male subjects			
	Time (h)	1	2	3	Average[b]	1	2	3	Average[b]
Concentration in exhaled air, ng/l	0	2.2[c]	3.0[c]	2.3[c]	2.5 ± 0.5[c]	NQ	NQ	1.9[c]	0.98 ± 0.82[c]
	0.25	320	710	350	460 ± 220	700	150	1000	620 ± 430
	0.5	260	700	91	350 ± 310	1700	140	1000	930 ± 770
	0.75	420	370	260	350 ± 80	1600	680	210	830 ± 700
	1	120	360	150	210 ± 130	2300	220	230	920 ± 1200
	1.25	150	320	91	190 ± 120	520	280	180	330 ± 170
	1.5	220	180	47	150 ± 90	740	360	270	460 ± 250
	1.75	170	120	29	110 ± 70	670	300	98	350 ± 290
	2	350	110	36	160 ± 160	620	250	58	310 ± 280
	4	96	49	16	53 ± 40	120	24	22	55 ± 55
	6	64	15	7.5	29 ± 31	26	17	7.4	17 ± 9
	24	18	5.6	5.0	9.6 ± 4.5	3.9	13	6.3	7.6 ± 4.4
Concentration in plasma, μg/l	0	ND	ND	ND	ND	ND	ND	ND	ND
	0.5	0.53	1.4	0.65	0.87 ± 0.49	1.2	0.25	1.1	0.86 ± 0.53
	1	0.95	2.0	0.77	1.2 ± 0.7	1.7	0.70	1.2	1.2 ± 0.5
	2	0.92	1.8	0.50	1.1 ± 0.7	1.6	0.97	0.90	1.2 ± 0.4
	4	0.90	1.5	0.34	0.91 ± 0.58	1.2	0.61	0.62	0.79 ± 0.31
	6	0.75	0.82	0.21	0.52 ± 0.33	0.88	0.51	0.47	0.49 ± 0.23

[a]These data were reported by Plotzke *et al*. (2002). ND means that no D_5 was detected and NQ indicates that the amount of D_5 was not quantifiable.
[b]Reported values are the mean ± 1SD for three men or women.
[c]The air samples had a small, variable background level that may have been from contamination of the equipment.

0.85 and 7.02 μg/l, respectively (Table 2). However, true peak concentrations are unknown with D_4 for most subjects since concentrations were already falling at the earliest sampling period. There might be less variability if true peak concentrations were available.

With D_5, the lowest and highest peak concentrations of D_5 in exhaled air were 350 and 2300 ng/l, respectively (Table 3). The peak concentrations in exhaled air occurred at 1 h for one subject, at 45 min for two subjects, and at 15 min (i.e., the earliest time that air samples were obtained) for three subjects. The peak plasma concentrations occurred later (i.e., at 1 h for five subjects and at 2 h for the remaining subjects). The concentration of D_5 in exhaled air was higher in men than in women for the first 2 h, but blood concentrations for men and women were similar at all times. By 24 h, the amount of D_5 in exhaled air had not yet decreased to background levels.

Modeling Results for D_4 and D_5 Dermal Absorption in Human Volunteers

The experimentally determined rates of evaporation of D_4 and D_5 were estimated to be 0.15 ± 0.04 and 0.071 ± 0.027 mg/cm^2/min, respectively (mean ± 1SD for $n = 4$). In their studies of the evaporation characteristics of volatile silicones, Koini *et al.* (1999) also found that D_4 evaporated faster than D_5. In their study, during the first 5 min more than seven times more D_4 evaporated than D_5. This discrepancy could be because the surface area covered by D_4 on the filter paper was larger than that covered by D_5 in the earlier study. From model calculations that incorporated the experimentally determined evaporation rates, only about 3 and 2.5% of the applied doses of D_4 and D_5, respectively, evaporated from the skin before it had cleared of chemical (i.e., in the first 5 min, after which it is assumed that all the chemical applied to the skin had evaporated or absorbed into the skin). Although the evaporation rate of D_4 was about two times faster than the evaporation rate of D_5 and similar doses were applied to the skin, the calculated percent of applied dose that evaporated within 5 min was similar for both chemicals because D_5 was applied to a larger area than D_4 (Table 1).

Data and model simulations for the concentration of D_4 in plasma and exhaled air following the dermal exposure were compared for men and women (Fig. 3). Although this analysis suggests that most of the applied dose of D_4 may have absorbed into the skin compartment, more than 99% of the D_4 that entered the skin diffused back to the surface and evaporated before systemic absorption could occur. Model calculations indicated that for women 0.30% and for men 0.12% of the applied dose were systemically absorbed. The major route of D_4 elimination following human inhalation exposures was exhalation (Reddy *et al.*, 2003), and the same was true for dermal exposures. For example, model calculations showed that of the 2.9 mg that had systemically absorbed in women, 83% had been exhaled and 10% had been metabolized by 24 h (Table 4).

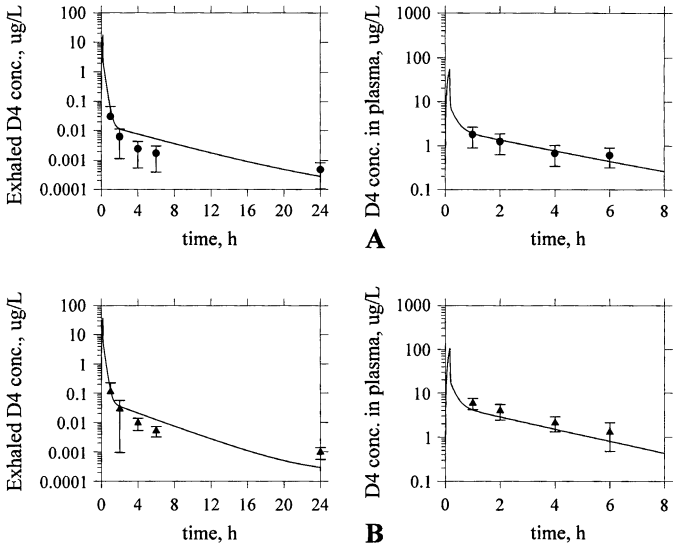

FIG. 3. Semi-log plots of measured and simulated concentrations of D_4 in exhaled air and plasma following a human dermal exposure for (A) men (●) and (B) women (▲). The error bars represent 1SD for $n = 3$. These data were reported by Plotzke *et al.* (2000).

Data and model simulations for the D_5 concentrations in plasma and exhaled air following the dermal exposure were also compared for men and women (Fig. 4). As with D_4, this analysis suggests that most of the applied dose may have entered the stratum corneum during the 5-min drying time but more than 99% of the D_5 that entered the skin evaporated back out before systemic absorption could occur. Model calculations indicated that 0.051 and 0.050% of the applied dose were absorbed systemically for women and men, respectively. Consistent with D_5 inhalation exposures (Reddy *et al.*, 2004), exhalation was the most important route of elimination for D_5 (Table 4). In women, e.g., model calculations showed that of the 0.48 mg that was absorbed into systemic circulation, 92% had been exhaled and 1.6% had been metabolized by 24 h.

Model calculations indicate that more D_4 than D_5 was systemically absorbed during the dermal exposures (Table 4). However, plasma concentrations of D_4 and D_5 were similar and concentrations in exhaled air were higher for D_5 than for D_4 (Tables 2 and 3). Based solely on the experimental data, it could appear that more D_5 was absorbed than D_4. However, D_5 penetrated the skin more slowly than D_4. This difference is illustrated by the estimated rate constants for absorption into systemic circulation; e.g., k_{-2} was 3.0×10^{-4} min^{-1} for men exposed to D_4 and 5.7×10^{-6} min^{-1} for men exposed to D_5 (Table 1). For D_5, peak concentrations could be readily identified from the time course data. For D_4, however, dermal absorption was more rapid than it was for D_5, and the peak concentrations in blood and exhaled air occurred prior to the first sampling period (e.g., in women exposed to D_4, the model-calculated peak plasma concentration was 105 μg/l at 10 min after the exposure, but the experimentally determined maximum

TABLE 4
Summary of PBPK Model Calculations for Human D_4 and D_5 Dermal Exposures[a]

	D_4		D_5	
Model calculation	Women	Men	Women	Men
Maximum concentration in plasma (μg/l)	105	54	1.0	1.2
Time that maximum concentration occurred (min)	10	10	59	21
Percent of applied dose that was absorbed systemically	0.30	0.12	0.051	0.050
Amount systemically absorbed (mg)	2.9	1.6	0.48	0.67
Amount eliminated by exhalation in 24 h (mg)	2.4	1.4	0.44	0.62
Percent of systemically absorbed dose eliminated by exhalation in 24 h	83	88	92	93
Amount metabolized in 24 h (mg)	0.30	0.15	0.0076	0.0097
Percent of systemically absorbed dose metabolized in 24 h	10	9.4	1.6	1.4

[a]These results are all calculated using the PBPK model including the dermal exposure route. The maximum concentration in plasma and time to reach the maximum plasma concentration do not correspond to the data shown in Tables 2 and 3, but instead refer to the model-simulated values.

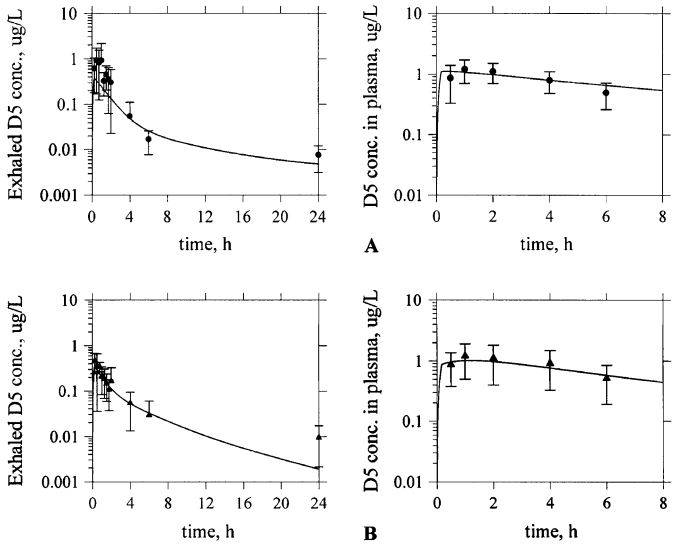

FIG. 4. Semi-log plots of measured and simulated concentrations of D_5 in exhaled air and plasma following a human dermal exposure for (A) men (•) and (B) women (▲). The error bars represent 1SD for $n = 3$. These data were reported by Plotzke *et al.* (2002).

plasma concentration was 5.8 μg/l at the first sampling time of 1 h). For this reason, the *in vivo* experimental results are consistent with more D_4 penetrating the skin than D_5. Additionally, the percent of applied dose absorbed systemically was about 2.5 times higher in women than in men for D_4, but for D_5, the percent of applied dose absorbed systemically was similar in women and men. For the D_5 study, subjects were asked not to shave their underarms for several days prior to the study, which may explain this difference between the two studies.

For both D_4 and D_5, the dermal absorption model more closely described blood concentrations than concentrations of chemical in exhaled air. The large variability of the measurements of D_4 and D_5 in exhaled air (Figs. 3 and 4) made it difficult to capture this behavior in the simulations. However, matching the time course concentrations of D_4 and D_5 in plasma is often the key requirement of a model needed for risk assessment purposes (i.e., the maximum concentration of a compound in the plasma or the area under the curve for plasma concentration time course data is often considered to be most related to pharmacodynamic effects), and the plasma concentrations of D_4 and D_5 are well described.

During parameter estimation for the D_5 data set, it was determined that values for the parameters describing the generation and clearance of unavailable D_5 in the blood (i.e., the rate constant for hepatic production of D_5 in blood mobile lipid pool, Kmlp, and the clearance of unavailable D_5 from mobile lipid pool to the fat, CLmlp) estimated using the data from the human inhalation exposure did not result in good fits for the dermal absorption data. During the human inhalation exposure, the values of these parameters were estimated as $\text{Kmlp} = 0.076 \pm 0.036\ \text{min}^{-1}$ and $\text{CLmlp} = 0.046 \pm 0.027$ l/min (mean ± 1SD for $n = 5$). The calculated value of the ratio of the concentration of chemical in the venous return to the concentration of chemical in exhaled air (i.e., Cv/Cex) is controlled by these parameters (Reddy *et al.*, 2004), but this ratio could not be simulated for the dermal data without adjusting the values of Kmlp and CLmlp. By examining the ratio Cv/Cex, it was determined that $\text{Kmlp} = 0.50\ \text{min}^{-1}$ and $\text{CLmlp} = 0.033$ l/min were better parameter estimates for model application with the dermal absorption data set. This discrepancy may be due in part to data limitations in the inhalation model development; the D_5 concentration in exhaled air was only available for up to 20 min after the exposure ended, and the ratio Cv/Cex could not be examined. Another possible explanation for the discrepancy could be physiological variability (e.g., the three male subjects exposed to D_5 were obese with a mean body weight of 123 kg [Table 1], while the subjects in the D_5 inhalation study used to develop the D_5 inhalation PBPK model had a mean body weight of 88 kg).

DISCUSSION

Skin Compartment Model Structure

In rats and humans, the physiological structure of skin is a multilayered membrane (Komarek *et al.*, 2000; Scheuplein,

1977). For many chemicals, the outermost skin layer, the stratum corneum, is the rate-limiting barrier for mass transfer into and through skin. For highly lipophilic chemicals, the underlying viable epidermis can also act as a significant barrier (Cleek and Bunge, 1993; Reddy *et al*., 2000). The dermis, located beneath the epidermis, is a highly vascularized tissue that usually has sufficient blood flow to efficiently clear away all chemical passing through the epidermis. After a dermal exposure to a chemical ends and the skin is cleaned, the stratum corneum can act as a storage depot that slowly releases chemical into the viable epidermis and bloodstream. Physiologically relevant compartment models have been developed to match specific characteristics of membrane models (e.g., the flux and amount of chemical in the skin at steady state) (McCarley and Bunge, 2000) and are easy to incorporate into pharmacokinetic models. Because the data available for parameter estimation are for dermal absorption through the axilla, some of the assumptions made in the development of typical dermal absorption models (e.g., that mass transfer through sweat glands and hair follicles is unimportant) might not be applicable. For this reason, we represented the skin using a more empirical compartment model.

The *in vivo* dermal absorption data for D_4 in the rat have been modeled previously by Sarangapani *et al*. (2003), who extended an inhalation PBPK model in the rat to the intravenous, oral, and dermal delivery routes. Sarangapani *et al*. (2003) modeled dermal absorption as a bolus dose to a topical compartment on top of the exposed skin. The model included the volatilization of D_4 from the topical compartment. In the dermal absorption model presented here, a more detailed representation of skin was developed because the data set provided information regarding the characteristics of the skin depot.

The present model was developed for volatile chemicals that can evaporate from the skin surface. D_4 and D_5 evaporate relatively slowly; only about 3 and 2.5% of the applied doses of D_4 and D_5, respectively, evaporated from human skin *in vivo* before it had cleared of chemical (based on the rate of evaporation of D_4 and D_5 measured experimentally). The skin appeared dry 5 min after application of D_4 or D_5, suggesting that perhaps these lipophilic chemicals dissolve rapidly into at least the outermost layers of the skin compartment. However, during D_4 and D_5 *in vitro* studies with human skin and *in vivo* studies with rat skin, the majority of applied chemical was recovered from the charcoal baskets covering the exposed sites. These chemicals must diffuse back to the skin surface and evaporate from the surface after absorption into the stratum corneum. This behavior is consistent with the observation that the amount of D_4 absorbed into and through the viable skin layers in the rat *in vivo* decreased with time (Jovanovic *et al*., unpublished data). Diffusion back to the surface with evaporation of chemical from the skin is an essential addition to a dermal absorption model for these compounds.

The dermal absorption model developed here assumed that the observation that skin appeared dry 5 min after the application of D_4 or D_5 was primarily due to absorption into the stratum corneum (after which the driving force for mass transfer reverses, resulting in chemical evaporating out of skin). However, the assumption of rapid absorption conflicts with the theory that skin behaves like a membrane. If skin were behaving as a membrane, the lag time through the stratum corneum, t_{lag}, could be roughly estimated using a correlation proposed by Reddy *et al*. (2000) (i.e., $t_{lag}(h) = 0.7 \times 10^{0.006 \times MW}$). The value of t_{lag} would be estimated to be about 10 h for D4 (MW = 297) and 29 h for D5 (MW = 371). For times less than t_{lag}, it would be expected that chemical would not have had sufficient time to penetrate the membrane and enter systemic circulation. Based on the rapid appearance of D_4 and D_5 in the exhaled air following administration of the test compound, this assumption of rapid absorption into the skin compartment seems more reasonable than the alternative, i.e., that chemical remains on the skin surface. It remains to be determined whether this absorption behavior is due to charactetrisitcs of the application site (i.e., axilla skin) or the chemical properties of D_4 and D_5 (e.g., high hydrophobicity and low surface tension).

Several published skin compartment models do not allow for the reservoir capability of the stratum corneum (Reddy *et al*., 1998). For such models, as soon as the exposure ends the skin empties of chemical. Two aspects of the model presented here capture the ability of the skin to store chemical. First, instead of chemical partitioning from the skin into the blood, a rate constant controls the release of chemical into the blood, which allows the skin to act as the rate-limiting barrier to dermal penetration. Second, consistent with the model structure required to describe the dermal absorption of D4 in the rat (Sarangapani *et al*., 2003), a deep skin compartment, required to describe dermal absorption of D_4 and D_5 in humans, allows the simulation of the slow release of chemical stored in the skin into the cutaneous blood after the exposure ends.

The model presented here outlines factors that appear to be most important for dermal absorption of volatile chemicals. However, other factors not considered here might also be important, and possible alternative mechanisms could also be consistent with the data presented here. But the model proposed here can be used to design better experiments to elucidate the mechanisms underlying dermal absorption of volatile chemicals in future work. For example, these modeling results suggest that tape stripping data during the first 15 min following exposure to determine the distribution of chemical in the stratum corneum would provide useful information for understanding dermal absorption.

Model Limitations

The dermal absorption model presented here was developed using data for axilla skin exposed to neat D_4 or D_5. Because

the skin in various regions of the body has different physiological properties (Scheuplein, 1977), the rate and extent of dermal absorption may be different for different regions of skin. During human, *in vivo*, dermal exposures to ^{14}C-cortisol (Feldmann and Maibach, 1967), ^{14}C-malathion, and ^{14}C-parathion (Maibach *et al*., 1971), axilla skin absorbed between 3.6 and 7.4 times more chemical in 24 h than forearm skin. Thus, a model developed using axilla dermal absorption data may not predict dermal absorption accurately for exposures of other locations of skin. However, when using the skin model developed from axilla data for risk assessment purposes, the estimate of dermal absorption should be higher than expected for exposures of less permeable anatomic regions (e.g., the skin of the forearm and abdomen), resulting in a conservative estimate of risk.

Peak D_4 plasma concentrations occurred before the first blood, and exhaled air samples were obtained at 1 h. Model estimates of the peak D_4 blood concentration may be inaccurate because there were no data available in the critical time region. Nonetheless, our model was able to simulate the concentrations of D_4 in the plasma and exhaled air in volunteers following a dermal exposure to D_4.

Comparison of D_4 and D_5 Pharmacokinetics

In an *in vitro* study with abdominal skin, about 8.5 times more D_4 than D_5 had penetrated into the receptor fluid in 24 h. Similarly, in an *in vivo* rat study, 4.9 times more D_4 than D_5 was systemically absorbed (Jovanovic *et al*., unpublished data). During the human study with application to the axilla, in women systemic absorption was 6.0 times higher for D_4 than for D_5, and in men systemic absorption was 2.4 times higher for D_4 than for D_5, even though the same dose of D_5 was applied to a larger exposure area. For both D_4 and D_5, exhalation is the primary route of elimination (Table 4), but more D_5 is expected to be eliminated by exhalation than D_4 because D_5 has a lower blood:air partition coefficient than D_4 (i.e., 0.4 compared to 1). In contrast, according to model calculations more D_4 was metabolized than D_5 (e.g., in women exposed to D_4 and D_5, 10 and 1.6% of the systemically absorbed dose was metabolized in 24 h, respectively, Table 4). Hepatic clearance of D_4 in humans is sufficiently high that total metabolic clearance is limited by liver blood flow (Reddy *et al*., 2003), and D_5 also appears to have high hepatic clearance (Reddy *et al*., 2004). However, metabolism was not a major pathway of elimination for either of these compounds following the dermal exposures because exhalation, both first-pass and continued exhalation, was so efficient that not very much of the dermally absorbed dose of D_4 or D_5 reached the liver for metabolism. Because PBPK models include physiologically meaningful blood flows, simulating the absorption of compound through the skin, into the venous blood, and through the lungs, before circulation through the rest of the body, the first-pass effect of the lungs for these dermal exposures could be accurately represented.

PBPK Model Structure

After an inhalation exposure has ended, the ratio of the concentration of chemical in the venous return to the concentration of chemical in exhaled air (i.e., Cv/Cex) is expected to remain constant over time for cases with simple partitioning between blood and air in the lungs (Reddy *et al*., 2003), and the same is expected to be true for dermal exposures. After humans were exposed to 10 ppm ^{14}C-D_4 by the inhalation exposure route, the ratio Cv/Cex increased from 4.8 soon after the exposure ended to 430 one day after the exposure ended. During the human dermal exposure to D_4, the ratio Cv/Cex increased from 170 one hour after the exposure began (mean for six subjects, Table 2) to 560 one day after the exposure began (mean for four subjects with detectable plasma concentrations, Table 2). Similar behaviors have been noted in inhalation and dermal studies with rats (Andersen *et al*., 2001, Sarangapani *et al*., 2003). To describe this behavior, the conventional PBPK model structure (e.g., that developed by Ramsey and Andersen, 1984) was modified to include the production of a sequestered form of D_4 that was produced in the liver, transported in the blood, and cleared into the fat, which resulted in model predictions that were consistent with the observation that the ratio Cv/Cex increased with time (Reddy *et al*., 2003).

The same increase in plasma concentrations relative to concentrations in exhaled air occurred in human volunteers with dermal exposures to D_5 (Fig. 5). For D_5, the ratio Cv/Cex increased from 2.5 thirty minutes after the exposure began to 37 six hours after the exposure began (mean of six subjects, Table 3). The spike in the model-simulated values of Cv/Cex at very short times occurs when the deep lung compartment in the D_5 PBPK model fills up, causing less D_5 to be exhaled. At later

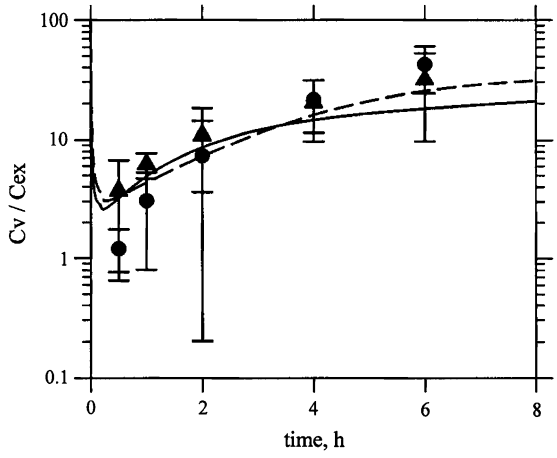

FIG. 5. Measured and simulated values of Cv/Cex as a function of time for men (●, dashed lines) and women (▲, solid lines) following a dermal exposure to D_5. The error bars represent 1SD for $n = 3$.

times, the rise in Cv/Cex over time can only be simulated in the model by including the time-varying production of the sequestered form of D_5 in blood. Although the ratio Cv/Cex was lower for D_5 than it was for D_4 (e.g., 6 h after the dermal exposure began, Cv/Cex was about 380 for D_4 compared to 37 for D_5), it still increased with time. Thus, for D_4 and D_5 a PBPK model structure incorporating a pool of unavailable chemical in the blood, likely associated with blood lipoproteins, is required for describing pharmacokinetics during human inhalation and dermal exposures, although the quantitative contribution of the various processes varies between the two compounds.

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REFERENCES

Andersen, M. E., Sarangapani, R., Reitz, R. H., Gallavan, R. H., Dobrev, I. D., and Plotzke, K. P. (2001). Physiological modeling reveals novel pharmacokinetic behavior for inhaled octamethylcyclotetrasiloxane in rats. *Toxicol. Sci.* **60,** 214–231.

Brown, R. P., Delp, M. D., Lindstedt, S. L., Rhomberg, L. R., and Beliles, R. P. (1997). Physiological parameter values for physiologically based pharmacokinetic models. *Toxicol. Ind. Health* **13,** 407–484.

Burns-Naas, L. A., Mast, R. W., Meeks, R. G., Mann, P. C., and Thevenaz, P. (1998). Inhalation toxicology of decamethylcyclopentasiloxane (D_5) following a 3-month nose-only exposure in Fischer 344 rats. *Toxicol. Sci.* **43,** 230–240.

Cleek, R. L., and Bunge, A. L. (1993). A new method for estimating dermal absorption from chemical exposure. 1. General approach. *Pharm. Res.* **10,** 497–506.

Feldmann, R. J., and Maibach, H. I. (1967). Regional variation in percutaneous penetration of ^{14}C cortisol in man. *J. Investig. Dermatol.* **48,** 181–183.

Jovanovic, M. L., McMohon, J. M., McNett, D. A., Tobin, J. M., and Plotzke, K. P. In vitro and in vivo percutaneous absorption of ^{14}C-octamethylcyclotetrasiloxane (^{14}C-D_4) and ^{14}C-decamethylcyclopentasiloxane(^{14}C-D_5). 670. *Regul. Toxicol. Pharm.* (Submitted).

Koini, T., Berthiaume, M. D., and Huber, A. (1999). Volatile silicones—their evaporation characteristics. *SOFW J.* **125,** 22–25.

Komarek, V., Gembardt, C., Krinke, A., Mahrous, T., and Schaetti, P. (2000). Synopsis of the organ anatomy. In *The Laboratory Rat* (G. J. Krinke, Ed.). Academic Press, San Diego, CA.

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

McCarley, K. D., and Bunge, A. L. (2000). Physiologically relevant two-compartment pharmacokinetic models for skin. *J. Pharm. Sci.* **89,** 1212–1235.

McCarley, K. D., and Bunge, A. L. (2001). Pharmacokinetic models of dermal absorption. *J. Pharm. Sci.* **90,** 1699–1719.

McKim, J. M., Kolesar, G. B., Jean, P. A., Meeker, L. S., Wilga, P. C., Schoonhoven, R., Swenberg, J. A., Goodman, J. I., Gallavan, R. H., and Meeks, R. G. (2001). Repeated inhalation exposure to octamethylcyclotetrasiloxane produces hepatomegaly, transient hepatic hyperplasia and sustained hypertrophy in female Fischer 344 rats in a manner similar to phenobarbital. *Toxicol. Appl. Pharmacol*, 172, pp. 83–92.

Plotzke, K. P., Utell, M. J., and Looney, J. R. (2000). *Absorption, Distribution and Elimination of 13C-D4 in Humans After Dermal Administration.* EPA document. 86010000007.

Plotzke, K. P., Utell, M. J., and Looney, J. R. (2002). *Absorption, Distribution and Elimination of 13C-D5 in Humans After Dermal Administration.* EPA document. 84030000008.

Poet, T. S., Corley, R. A., Thrall, K. D., Edwards, J. A., Tanojo, H., Weitz, K. K., Hui, X., Maibach, H. I., and Wester, R. C. (2000a). Assessment of the percutaneous absorption of trichloroethylene in rats and humans using MS/MS real-time breath analysis and physiologically based pharmacokinetic modeling. *Toxicol. Sci.* **56,** 61–72.

Poet, T. S., Thrall, K. D., Corley, R. A., Hui, X. Y., Edwards, J. A., Weitz, K. K., Maibach, H. I., and Wester, R. C. (2000b). Utility of real time breath analysis and physiologically based pharmacokinetic modeling to determine the percutaneous absorption of methyl chloroform in rats and humans. *Toxicol. Sci.* **54,** 42–51.

Ramsey, J. C., and Andersen, M. E. (1984). A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. *Toxicol. Appl. Pharmacol.* **73,** 159–175.

Reddy, M. B., Andersen, M. E., Morrow, P. E., Dobrev, I. D., Varaprath, S., Plotzke, K. P., and Utell, M. J. (2003). Physiological modeling of inhalation kinetics of octamethylcyclotetrasiloxane (D_4) in humans during rest and exercise. *Toxicol. Sci.* **72,** 3–18.

Reddy, M. B., Guy, R. H., and Bunge, A. L. (2000). Does epidermal turnover reduce percutaneous penetration? *Pharm. Res.* **17,** 1414–1419.

Reddy, M. B., McCarley, K. D., and Bunge, A. L. (1998). Physiologically relevant one-compartment pharmacokinetic models for skin. 2. Comparison of models when combined with a systemic pharmacokinetic model. *J. Pharm. Sci.* **87,** 482–490.

Reddy, M. B., Tobin, J. M., McNett, D. A., Jovanovic, M. L., Utell, M. J., Morrow, P. E., Plotzke, K. P., and Andersen, M. E. (2004). Physiological modeling of decamethylcyclopentasiloxane (D5) inhalation kinetics in rats and humans. *Toxicologist* **78**(S-1), 420.

Roberts, M. S., Anissimov, Y. G., and Gonsalvez, R. A. (2001). Mathematical models in percutaneous absorption. (Reprinted from Percutaneous Adsorption, 1999, 3–55). *J. Toxicol. Cutaneous Ocul. Toxicol.* **20,** 221–270.

Sarangapani, R., Teeguarden, J., Andersen, M. E., Reitz, R. H., and Plotzke, K. P. (2003). Route-specific differences in distribution characteristics of octamethylcyclotetrasiloxane in rats: analysis using PBPK models. *Toxicol. Sci.* **71,** 41–52.

Scheuplein, R. (1977). Permeability of the skin. *Handbook of Physiology. Section 9: Reactions to Environmental Agents,* (D.H.K. Lee), pp. 299–322. Waverly Press, Inc, Maryland, MD.

Scheuplein, R. (1978). Permeability of the skin: a review of major concepts. *Curr. Probl. Dermatol.* **7,** 172–186.

Thrall, K. D., and Woodstock, A. D. (2003). Evaluation of the dermal bioavailability of aqueous xylene in F344 rats and human volunteers. *J. Toxicol. Environ. Health A* **66,** 1267–1281.

Varaprath, S., Seaton, M., McNett, D. A., Cao, L., and Plotzke, K. P. (2000). Quantitative determination of octamethycyclotetrasiloxane (D_4) in extracts of biological matrices by gas chromatography-mass spectrometry. *Int. J. Environ. Anal. Chem.* **77,** 203–219.