

Biological Monitoring V: Dermal Absorption

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Chemicals believed to have the potential for significant dermal absorption are listed in the *Threshold Limit Values and Biological Exposure Indices for 1988-1989* booklet with a skin notation.⁽¹⁾ Since there are few means available to monitor dermal exposure using external measurements, biological monitoring is recommended "to determine the relative contribution of dermal exposure to the total dose" that the worker received during occupational exposure to chemicals with a skin notation.⁽¹⁾ Since systemic adverse effects are related to biological levels of the chemical or its metabolite, or to the total dose, biological monitoring is, under certain circumstances, a better safeguard than air monitoring data.

Quantitative data on dermal absorption of industrial chemicals are scattered and dermal notations are inconsistent.^(2,3) In the absence of inhalation exposure, significant concentrations of exposure indices were measured in blood, urine, and exhaled air of volunteers having dermal contact with liquid solvents which carry no skin notation.⁽⁴⁻⁶⁾ These studies indicate that a contribution of dermal exposure to the total dose is more common than is indicated by a skin notation.

Mechanism of Dermal Absorption

Skin is formed by layers of various cell types which, according to their composition and function, are identified as the three basic layers shown in Table I. Thickness of the layers, their weights, and perfusion are given for a resting reference human with a body weight of 70 kg, body height of 170 cm, and cardiac output of 6 L/min. The numbers are mean values which vary from one part of the body to another. If two numbers are given, the first value relates to males and the second to females.⁽⁷⁾

The surface area of the skin can be considered as equal to body surface area (SA),

which was estimated to average 1.8m² for a male and 1.6m² for a female (male: 70 kg, 170cm; female: 58kg, 160cm).⁽⁷⁾

Chemicals can penetrate through the stratum corneum and diffuse into the dermis where they enter into the capillary blood. The chemical is then carried by systemic circulation to other tissues where it is deposited, metabolized, and excreted.⁽⁸⁾ The rate limiting step in dermal absorption is either the penetration rate through the stratum corneum (uptake rate) or the removal rate of the chemical from the dermis (absorption rate). Both processes are influenced by physicochemical properties of the chemical, namely biosolubility, and by physiological status of the skin.

The absorption rates relate directly to blood perfusion of skin. Perfusion increases with the temperature of the environment and physical activity of the worker.⁽⁹⁾ Since cardiac output increases in a similar manner, it can be assumed that perfusion of dermis accounts for about 53 percent of cardiac output and perfusion of the hypodermis for about 2.5 percent.

Flux

The stratum corneum functions as a diffusion barrier. The penetration rate of a chemical through the stratum corneum is known as flux. Flux is defined as the amount of a chemical (mg or μ mol) that penetrates the stratum corneum upon direct contact with a defined unit of surface area of skin (cm²) during a defined unit of time (min,

hr).⁽¹⁰⁻¹³⁾ The penetration rate depends on the vehicle and state of aggregation in which the chemical is applied. Skin injury increases the penetration rate.

Percutaneous penetration is a passive diffusion process mediated by two pathways: intercellular (polar) pathway and transcellular (lipophilic) pathway. Penetration rates for both pathways are directly related to solubility of the chemical in water and lipids and indirectly to molecular weight. Numerous models have been proposed for determining flux from physical properties of the drug. These models have been recently critically reviewed by Osborne.⁽¹⁴⁾ A model can be applied to the prediction of dermal absorption potential of industrial chemicals (organic nonelectrolytes). The model providing reasonable prediction of flux⁽¹⁵⁾ can be described by the following equation:

$$FI = \frac{C_{sat}}{15} (0.038 + 0.153 P) e^{-0.016 MW}$$

where:

FI = flux in mg/cm²/hr

C_{sat} = the concentration of saturated chemical in aqueous solution of the chemical in mg/ml

P = octanol-water partition coefficient

MW = molecular weight

e = base of the natural logarithm.

Numerical constants are derived from parameters pertinent to the diffusion process through the stratum corneum. The

TABLE I. Diagram of Skin Layers

		Thickness, μ m	Weight, g	Perfusion, L/min
Epidermis	stratum corneum	10	100.90	0
	dead cells living cells	40		
Dermis	proteins, blood cells	1250	2500:1700	0.2
Hypodermis	connective tissue	1375:6600	7500:13000	0.15
	fat (adipose tissue)			

nential expression in equation 1 indicates that the flux of chemicals with large molecules is negligible. A molecular weight of 500 has been given as a practical limit, although this may not be the case for diseased skin.¹²⁾

In vitro flux can be determined experimentally by measuring the diffusion rate across an excised section of stratum corneum.^(16,17) Flux can also be determined *in vivo* either by measuring the losses of a chemical which has been hermetically

applied to a defined area of the skin⁽⁵⁾ or by measuring the elimination of the chemical and its metabolites.^(4,6,18,19) The results of measurements depend on the method employed. Values obtained by measurements of elimination should be cautiously applied since the pharmacokinetic pattern for dermal absorption is rarely fully appreciated. Because of regional variations in skin permeability, the measurements depend on the region where chemical contact with the skin took place.⁽¹¹⁾

Regional variability in absorption can be attributed to cell size and penetration rate. Significant species differences in dermal penetration have been reported.⁽²⁰⁾ If the chemical is applied in a vehicle (solution, air, ointment), the penetration rate depends on the concentration and solubility of the chemical in the vehicle.⁽¹¹⁾ The wide spread of experimentally-determined penetration rates is apparent from examples compiled in Table II (column Fl_{meas}).

TABLE II. Dermal Absorption Potential of Chemicals with BEIs

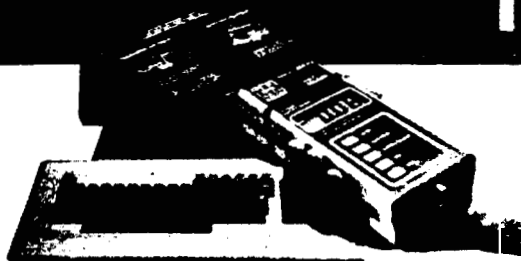
Predict. TLV		TLV mg/m ³	MW	Log P	H ₂ O sol. mg/ml	λ_{w-gas}	Fl_{meas} (Ref.)	fl	Fl^*	Fl^*
	Nonvolatile (SVP < 5 torr)									
e x	Aniline	10	93.1	0.90	34.0		0.5 (23) 3.0 (24)	0.64	0.0075	
e x	DMAC	35	87.1	-0.77	943.0			1.00	0.026	
• x	DMF	30	73.1	-1.01	944.0		2-8 (25)	1.03	0.023	
• x	Furfural	8	96.1	0.99	83.0		0.2 (19)	1.82	0.006	
e x	Nitrobenzene	5	123.1	1.85	1.9		9×10^{-4} (12) 0.2-3 (26)	0.19	0.004	
• x	Parathion	0.1	291.3	3.81	0.024		0.6 (27)	0.015	7×10^{-5}	
• x	PCP	0.5	266.4	5.01	0.0008			0.012	0.0004	
e x	Phenol	19	94.1	1.48	67.0		0.004 (12) 0.2-0.7 (23) 0.03 (32)	4.62	0.014	
o x	Styrene	215	104.0	2.95	0.30		0.06 (18) 12.0 (33)	0.52	0.161	
	Volatile (SVP > 5 torr)									
•	Benzene	30	78.1	2.13	1.78	2.8	0.19 (32)	0.70	0.022	9.5
e x	Carbon disulfide	30	76.1	2.00	2.94	0.8	0.05 (28)	0.89	0.022	55.1
	Chlorobenzene	350	112.6	2.46	0.50	41		0.24	0.26	1.8
							0.06 (32)			1.8
3	Ethyl benzene	435	106.2	3.15	0.20	1.7	0.16 (29) 28 (29)	0.53	0.33	
o	n-Hexane	180	86.2	3.94	0.014	1.1	6×10^{-5} (32)	0.31	0.14	0.19
• x	Methyl alcohol	260	32.0	-0.77	791.0	1900	8.3 (12) 11.5 (30,31)	2.02	0.195	6.2
o	Methyl chloroform	1900	133.4	2.40	4.4	0.93	0.37 (32)	1.64	1.42	71.0
o	MEK	590	72.1	0.28	353.0	254		2.45	0.44	20.8
	Perchloroethylene	335	165.8	2.60	0.40	0.43	0.005 (32) 0.24 (32)	0.11	0.25	14.0
o	Toluene	375	92.1	2.69	0.60	2.2	0.047 (32) 18 (5)	0.69	0.28	4.1
o	Trichloroethylene	270	131.5	2.29	1.10	1.5		0.27	0.20	11.0
o	Xylene	435	106.2	3.14	0.18	1.7	0.006 (32) 0.13 (33) 7.0 (5)	0.50	0.33	1.6

Notes:

MW = molecular weight log P = logarithm of octanol-water partition coefficient H₂O sol. = saturated aqueous solution λ_{w-gas} = water-gas partition coefficient Fl_{meas} = experimentally determined flux (references are in parenthesis) fl = flux predicted using equation 1 Fl^* = critical flux as determined by equation 5 Fl^* = critical flux for dermal absorption of vapors (equation 7) symbol 'o' on the left side of the table indicates the dermal absorption potential while '•' indicates dermal toxicity potential (see text); 'x' indicates skin notation in TLV-BEI booklet⁽¹⁾ Bold number indicates dermal absorption potential for vapor

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Dermal Absorption in Industrial Settings

The amount of dermally-absorbed chemical is directly related to exposure duration and surface area of the exposed skin, and it is affected by the form of the chemical contacting the skin. Since dermal and pulmonary absorptions are pharmacokinetic processes, the absorption rate changes with time. Moreover, dermal absorption is affected by the physical activity of the worker, namely by the skin temperature and increased perfusion of the dermis in the exposed area of the skin.^(8,21) Factors influencing the absorbed amount are summarized in Table III.

Form of Chemical

Dermal absorption in an industrial setting can occur upon exposure to vapors or upon direct dermal contact with liquid chemicals or with their solutions. Condensation of vapors of chemicals with low vapor pressure on the body surface can significantly increase dermal absorption of vapors.⁽¹⁹⁾ Dermal absorption of solids (dust, aerosols, etc.) can be facilitated by their dissolution in perspiration. The dermal penetration rate of dissolved chemicals appears to be directly related to their concentration and indirectly to their solubility in a solvent. A prolonged contact with liquids usually results in biochemical changes in skin and skin permeability.⁽¹³⁾

Exposed Area of Skin

While the surface area of skin exposed to vapors, gases, and aerosols usually corresponds to the body surface area, the surface area of skin exposed to liquids is difficult to estimate. In an industrial setting, the area of body surface exposed to liquids usually accounts for only a small fraction of body surface. SA Hands are usually subjected to exposure to liquids. It was estimated that the surface area of one hand (up to the wrist) accounts for 2.5 percent of SA, and the area of an outstretched palm and fingers accounts for 1 percent of SA.⁽⁷⁾ The area exposed to dust or aerosols can account for a large fraction of body surface. Spills or contaminated clothing can also result in exposure of a large body surface.

Duration of Exposure

The duration of dermal exposure to vapors, aerosols, and dust can be considered equal to the length of a shift. On the other hand, the duration of dermal contact with liquids or solutions depends on the working process involved and the personal skills and hygiene of the worker.

TABLE III. Factors Affecting Dermal Absorption

	Effect Grading
I Physicochemical properties of the chemicals	
solubility in: water	↑↑
nonpolar solvents	↑↑
diffusion coefficient	↑↑
molecular weight	↓
volatility ^a	↓
II Physiological and anatomical parameters of the exposed skin	
thickness of the stratum corneum	1
hydration of epidermis	↑↑
perfusion of dermis	↑
lipid content in external layers of skin	↑↑
disease state of skin	↑↑
III Form of exposure:	
exposed area of skin	↑↑
duration of dermal exposure ^c	↑↑
state of aggregation	
vehicle: concentration in vehicle	↑↑
solubility in vehicle	↓
environmental temperature	↑
humidity	↑
physical activity of the worker	↑
exposure by other routes (intensity and duration)	↑

^aFactors enhancing dermal absorption (positive correlation) are indicated by "↑"; factors reducing dermal absorption (negative correlation) are indicated by "↓". The most significant effects are indicated by a double ↑ or ↓.

^bIndirect effect; exhalation reduces the dose entering the systemic circulation.

^cIncludes the effect of lag-period (see "Pharmacokinetic Considerations" in text).

Pharmacokinetic Considerations

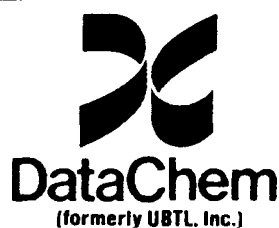
Penetration rate (flux) through the stratum corneum is influenced by the physiological status of the skin at the exposed area. Certain changes in the penetration rate usually appear at the beginning of the exposure during a so-called lag-period.⁽¹³⁾ During the lag-period, the concentration buildup in the epidermis and dermis takes place. At the same time, the most significant biochemical changes in the stratum corneum are induced by contact with the chemical. Otherwise, the penetration rate, under stable dermal exposure conditions, remains constant. On the other hand, the absorption, i.e., the transfer of the chemical from the dermis into capillary blood, is a diffusion process dependent on the dermis-blood concentration gradient and the diffusion coefficient itself. Since concentrations of the chemical in the exposed dermis and blood rise at different rates, the dermal absorption rate is a function of time.^(8,21) The absorption rate is affected not only by the dermal rate but also by the supply of the chemical from other routes, of which inhalation is the most common in industrial settings. When the uptake and elimination processes approach steady state, dermal and pulmonary absorption rates are more or less constant and time independent.

Interaction Between Dermal and Pulmonary Absorption of Volatile Chemicals

There are three similarities in the kinetic pattern of inhalation and dermal exposures.

1. The absorption rates are dictated by diffusion of chemicals through the cellular structure of parenchymal tissues and are related to biosolubility.
2. In an industrial setting, both exposures are enduring.
3. The absorbed amount is equally dispersed in the entire cardiac output prior to entering the systemic circulation.

The interaction between dermal and pulmonary absorption is apparent if the studied chemical is a gas or a volatile chemical, moderately soluble in blood (examples are hydrophobic organic solvents). These chemicals, when absorbed dermally, are partly removed in the lung by exhalation.^(4-6, 21) Consequently, the dermal absorption reduces or suppresses the pulmonary uptake prior to making its contribution to the body burden. Thus, the dermal uptake of volatile chemical has less effect on biological levels than dermal uptake of nonvolatile chemicals. However,



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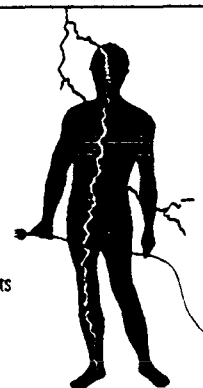


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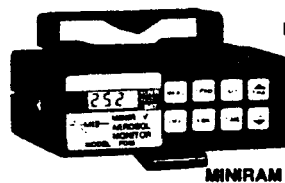
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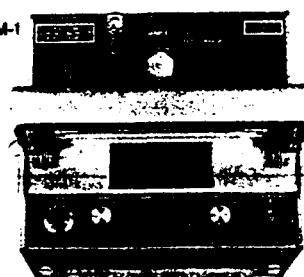
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Criteria for significant dermal absorption potential can be selected arbitrarily, depending on which effect of dermal absorption is under consideration. Thus, we can decide that biological monitoring of inhalation exposure is appropriate only if the absorbed amount of chemicals does not exceed 30 percent of the pulmonary uptake during an occupational inhalation exposure to the threshold limit value-time weighted-average (TLV-TWA), or if dermal absorption of volatile chemicals does not increase the arterial blood concentration 30 percent above the concentration reached during occupational inhalation exposure to the TLV-TWA.⁽²²⁾ The hypothetical flux, which meets this criterion, is further referred to as critical flux, Fl^* .

Critical flux can be determined by comparing the dose resulting from inhalation exposure to the TLV-TWA with the dose resulting from the same inhalation exposure but with additional dermal exposure of a defined area of skin. We arbitrarily chose to calculate critical flux for exposure of 2 percent of the body surface to a liquid and for whole-body exposure to a TLV concentration of vapors. Thus, during inhalation exposure only, the dose, D , is equal to pulmonary uptake:

$$D = \dot{V}_{alv} (TLV - c_{alv}) T \quad (2)$$

and during simultaneous inhalation and dermal exposures at which the dose and biological levels increased by 30 percent

$$1.3D = \dot{V}_{alv} (TLV - 1.3 c_{alv}) T + Fl^* \times EA \times T \quad (3)$$

where:

$\dot{V}_{alv}$ = alveolar ventilation in L/hr
 c_{alv} = alveolar concentration in mg/L
 T = exposure duration in hours
 EA = exposed body surface in cm².

After substituting from Equation 2 into Equation 3, the equation can be rearranged to calculate the critical flux:

$$Fl^* = \frac{0.3 \times TLV \times \dot{V}_{alv}}{EA} \quad (4)$$

After substituting $\dot{V}_{alv} = 900$ L/hr and $EA = 360$ cm², the critical flux (expressed in mg/cm²/hr) can be related to the TLV (expressed in mg/L) by a simple expression:

$$Fl^* = \frac{3}{4} TLV \quad (5)$$

Similarly, critical flux for whole body exposure to vapors can be derived, assuming

that the concentration of the chemical in the epidermal water is equilibrated with the concentration in the ambient air:

$$Fl_{vap}^* = \frac{EA}{SA} FL^* \frac{1000 c_{sat}}{TLV A} \quad (6)$$

where:

SA = body surface (= 18000 cm²)
 c_{sat} = saturated aqueous solution of the chemical in mg/ml
 A = the appropriate water-gas partition coefficient

The expression obtained after substitution indicates that the critical flux for vapors depends only on the solubility and volatility of the chemical.

$$Fl_{vap}^* = 15 \frac{c_{sat}}{\lambda} \quad (7)$$

To evaluate toxicity potential of dermal absorption, we used the algorithm described above, but we arbitrarily assumed that toxicity is associated with tripling the dose and biological levels. Such critical fluxes, Fl^{**} and Fl_{vap}^{**} respectively, are described by the following equations:

$$Fl^{**} = 5 TLV \text{ and} \quad (8)$$

$$Fl_{vap}^{**} = 100 \frac{c_{sat}}{\lambda}$$

The potential for dermal toxicity can be overestimated if the TLV is based on irritation or discomfort.

Dermal Absorption Potential of Chemicals with BEIs

Organic chemicals for which BEIs are recommended are listed in Table II. The table lists the parameters used for calculation of flux and critical flux. Dermal absorption can significantly influence the biological levels if the predicted flux is larger than the critical flux, Fl^* . Such dermal absorption potential is indicated by "O" on the left side of the table. Chemicals with the dermal absorption exceeding Fl^{**} are indicated by "x". Chemicals with such extensive dermal absorption usually carry a skin notation in the TLV table (in Table II indicated by "x").

The notation of dermal absorption potential is not necessarily an indicator of increased health risk. It indicates, however, that the correlation between air measurements and biological measurements can be weakened or nonexistent. Under such circumstances, biological monitoring provides information on total exposure of workers and not on inhalation exposure in the workplace.

Constants for prediction of flux using Equation 1 can be found in references 34-39. Water-gas partition coefficients can be found in reference 40.

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