American Journal of Industrial Medicine 17:617–635 (1990)

Dermal Absorption Potential of Industrial Chemicals: Criteria for Skin Notation

V. Fiserova-Bergerova, PhD, J. Thomas Pierce, PhD, and P.O. Droz, PhD

A dermal penetration rate (flux). predicted from physical properties of I32 chemicals. is suggested as an index of the dermal absorption potential of industrial chemicals. The prediction is designed for organic nonelectrolytes. Two reference values are recommended as criteria for skin notation: 1) dermal absorption potential. which relates to dermal absorption raising the dose of nonvolatile chemicals or biological levels of volatile chemicals 30% above those observed during inhalation exposure to TLV–TWA only — dermal absorption of chemicals belonging to this category should be considered when data obtained by biological monitoring are interpreted: and 2) dermal toxicity potential. which relates to dermal absorption that triples biological levels as compared with levels observed during inhalation exposure to TLV–TWA only. Chemical3 belonging in this category should carry a skin notation. The toxicity criteria may not be valid for chemicals whose TLVs are based on preventing irritation and discomfort.

Key words: body burden (effect of dermal absorption on). flux, inhalation exposure (interaction with dermal exposure), model for dermal penetration, prediction of dermal absorption of industrial chemicals. solubility (effect on absorption of industrial chemicals)

INTRODUCTION

Factors affecting dermal absorption of industrial chemicals were recently reviewed and the inconsistencies in the "skin denotation" by different authorities engaged in setting safety criteria were pointed out [Grandjean et al., 1988; Scansetti et al., 1988; Hansen, 1982]. These inconsistencies are attributed to the following factors: 1) the lack of systematic studies of dermal absorption of industrial chemicals; 2) disparate information on the dermal absorption rate obtained by different methods; 3) dependence of dermal absorption rate on exposure and environmental conditions; and 4) a lack of criteria defining the significance of dermal absorption in an industrial setting. The skin notation situation cannot be improved without understanding the mechanism of dermal absorption. without the availability of a simple method for quantitative evaluation of dermal absorption potential, and without the establishment of criteria for biological significance of dermal absorption in an industrial setting.

Department of Anesthesiology. University of Miami School of Medicine. Miami (V.F.-B.).
Medical College of Virginia. Richmond (J.T.P.).
Institute for Occupational Health Sciences. University of Lausanne. Lausanne. Switzerland (P.O.D.).
Address reprint requests to Dr Vera Fiserova-Bergerova (Thomas). Dept. of Anesthesiology. University of Miami School of Medicine. P.O. Box Y016370. Miami. FL 33101.
Accepted for publication October 26. 1989.

Theoretical models developed for the evaluation of dermal absorption of drugs [Albery and Hadgraft, 1979; Berner and Cooper. 1987; Dugard, 1983; Guy et al., 1985; Hansen. 1982; Kuabota and Ishizaki, 1986; Michaels et al., 1975] can be used to elucidate the mechanism of dermal absorption of industrial chemicals and to predict their penetration rate through the stratum corneum from physicochemical properties of the chemicals. These models describe percutaneous penetration as a diffusion process mediated by two pathways: an intercellular (polar) pathway and a transcellular (lipophilic) pathway. Penetration rates of both pathways are directly related *to* solubility of the chemical in water and lipids, and indirectly to molecular weight. The penetration rate, referred to as flux, can be considered as an index of dermal absorption potential.

Flux can be experimentally determined. but the outcome of the measurements depends on the experimental setting. Flux can be determined either *in vitro* by measuring the diffusion rate across an excised layer of stratum corneum [Dugard et **al.,** 1984; Tsuruta, 1977], or *in vivo,* by measuring losses of the chemical that had been hermetically applied on a defined area of skin over a certain period of time [Dutkewicz and Tyras, 1968]. The absorption rate *in vivo* can be evaluated by measuring the elimination of the chemical and its metabolite(s) after a defined dermal exposure [Berode et al.. 1985; Flek and Sedivec. 1978; Nakaaki et al.. 1985; Sato and Nakajma. 1978; Stewart and Dodd. 1964]. Since the absorption rate depends on the thickness and hydration of the stratum corneum [Scheuplein and Blank. 1971] and on the perfusion rate of the dermis [Fiserova-Bergerova. in preparation]. the outcome of the measurements depends on the source of the tested skin. There are significant differences in measurements among animal species [Wester and Maibach. 1977] and among measurements obtained by exposing skin from different parts of the body [Scheuplein and Blauk, 1971]. The outcome of the measurements also depends on the form in which the chemical is applied (liquid. vapor. solution. or particulates). **on** the concentration and solubility of the chemical in the vehicle. and on effects of the vehicle on the physiological status of the skin [Dutkieu icz and Tyras. 1967: Fiserova-Bergerova. in preparation; Scheuplein and Blank. 1971; Wester and Maibach, 1977]. Since dermal absorption is a kinetic process. the outcome of the measurements depends on exposure duration and sampling time. The effects of these circumstantial factors account for the differences of dermal absorption rates reported in the literature. For example. the following dermal absorption rates are reported for styrene: 0.03 mg/cm^2/hr (measured *in vitro* in rat [Tsuruta. 1982]) and 0.06 mg/cm^2/hr [Berode et al.. 1985] and 12 mg/cm^2/hr (range9–15) [Dutkiewicz and Tyras. 1968], both measured in volunteers. A similar range of values was reported for xylene: 0.006 mg/cm^2/hr measured *in vitro* in rats [Tsuruta. 1982]: 0.13 mg/cm^2/hr [Riihimaki, 1979] and 7 mg/cm^2 hr (range 4.5–9.6) [Dutkiewicz and Tyras. 1968] measured in volunteers.

Theoretical models relate **flus** to diffusibility of chemicals through a hypothetical reference skin. the parameters of which (thickness. diffusion channels. and diffusion constants) are compiled as mean values for human skin [Berner and Cooper. 1987].

The evaluation of systemic health effects of dermal absorption can be based either on toxicological studies. or on pharmacokinetic studies by comparing biological levels or internal doses resulting from **dermal** and inhalation exposures. There are three similarities in the toxicokinetic 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) the absorbed amount is equally dispersed in the entire cardiac output prior to entering the systemic circulation: and *3)* in an industrial setting. both exposures are enduring. the body exposure tending to reach a steady state.

The purpose of this study **is** to define the significance of dermal absorption potential of industrial chemicals and suggest guidelines for a skin notation. To meer this objective. dermal absorption potential. defined by flux predicted from physical properties of the chemical. is compared with the threshold values. referred to as critical flux. Critical flux is defined as a hypothetical penetration rate through the stratum corneum. which causes the biological levels to increase above those reached during inhalation exposure to a TLV–TWA [Threshold Limit Values and Biological Exposure Indices. 1988]. Critical flux is determined by comparing the dermal uptake rate under specified exposure conditions with the pulmonary uptake rate during exposure to TLV–TWA at steady state.

Considerations in the Selection of Criteria for Skin Notation

To select a criteria for skin notation. the endpoint (further referred to as critical effect). the exposure condition. and the method for obtaining the information must be defined.

Selection of method. In this study. values of flux obtained by a model are preferred over the measured data for the following reasons: 1) measured data exhibit large variability. for reasons discussed above: 2) fluxes. predicted by the theoretical el. proved to fit in the range of experimental data [Fiserova-Bergerova and Pierce, 1989]; *3)* the calculation of flux by the suggested model is simple and requires only physicochemical constants that are readily available: and 4) the theoretical basis of the model provides grounds for understanding the effects of variable exposure factors.

Critical effect. A "critical effect" for skin notation can be: 1) the appearance of the chemical in a biological specimen obtained from dermally exposed subjects: 2) the increase of biological level of the chemical above the noneffect level: 3) biochemical changes: and 4) acute or chronic systemic toxic effect.

In this study. an increase of the biological level above the noneffect level is considered to be a critical effect. **A** dose or arterial blood concentration resulting from occupational inhalation exposure to a **TLV–TWA** will be considered as the noneffect level. The effect of dermal absorption will be evaluated at two biologically significant levels: 1) the dermal absorption potential will be considered to be significant if the dermal penetration rate of nonvolatile chemicals exceeds **30%** of the pulmonary uptake rate during an occupational inhalation exposure to TLV–TWA. or if dermal absorption **of** volatile chemicals increases the arterial blood concentration **30%** above the concentration most likely reached during occupational inhalation exposure to TLV–TWA; and **2)** potential for systemic toxicity induced by dermal exposure will be considered significant if the biological levels triple compared with the biological levels resulting from inhalation exposure to a TLV–TWA. The chemical should carry a skin notation if the potential for dermal absorption and toxicity. under the exposure conditions defined below, is significant.

Exposure conditions in industrial settings. The extent of dermal absorption is directly related to exposure duration and surface area of the exposed skin. and is affected by the form of the chemical contacting the skin. Since dermal and pulmonary

absorptions are pharmacokinetic processes. the absorption rates are a function of time. Moreover. dermal absorption is affected by the physical activity of the worker and the skin temperature [Burton, 1968], namely by increased perfusion of the dermis in the exposed area of the skin.

In this study, the critical flux is calculated for exposures of 2% of the body surface area (equivalent to stretched palms and fingers) to a saturated aqueous solution of the chemical. The calculations are made for the apparent steady state conditions using physiological parameters of a worker performing light physical work [Astrand, 1983]. Possible biochemical changes in the skin are not taken into account.

MATERIALS AND METHODS

One hundred seventy-six chemicals that appear in the TLV booklet were studied [Threshold Limit Values and Biological Exposure Indices, 1988]. Sixty-six (38%) of these chemicals carry skin notation. Seventy-two chemicals (41%), further referred to as volatile chemicals. had a saturated vapor pressure greater than 5 torrs. For simplicity. chemicals with a saturated vapor pressure below 5 torrs will be called nonvolatile.

Calculation of Flux

A two parallel pathway model. proposed by Berner and Cooper [1987] for the evaluation of dermal absoprtion of drugs. is used in this study for the calculation of flux. The model is described by equation I. For details and definitions. see Appendix.

$$Fl = \frac{c_{sat}}{15} (0.038 + 0.153\ P)\ e^{-0.016\ MW} \qquad (I)$$

Calculation of Critical Flux

The critical flux was calculated by comparing either pulmonary and dermal uptake rates of nonvolatile chemicals or concentrations of volatile chemicals in arterial blood resulting from inhalation exposure to TLV. and dermal exposure.

Two simplified equations were derived as criteria for skin notation of liquids (see Appendix).

Critical flux for dermal absorption potential

$$Fl^* = \frac{3}{3} TLV \qquad (II)$$

Critical flux for dermal toxicity potential

$$Fl^{**} = 3\ TLV \qquad (III)$$

Critical flux for volatile and nonvolatile chemicals is the same (see Appendix). However. dermal absorption causes a significant reduction in pulmonary uptake of volatile chemicals with relatively large pulmonary retention. and supresses pulmonary uptake and induces exhalation of dermally absorbed volatile chemicals with relatively small pulmonary retention.

Similar criteria were calculated for vapors

$$Fl^{*}_{vap} = 15 \frac{c_{sat}}{\lambda} \quad \text{(IV)}$$

$$Fl^{**}_{vap} = 100 \frac{c_{sat}}{\lambda} \quad \text{(V)}$$

Calculation of Aqueous Solubility

Calculation of aqueous solubility of organic nonelectrolytes using melting point (MP) and hydrophobic constant (P) was suggested by Yalkowsky [1981; Yalkowsky and Valvani, 1980].

$$\log c = -\log P - 0.01\ MP - 0.69 \quad \text{(VI)}$$

For poorly soluble chemicals ($c < 0.01$ mM), an adjustment for the molarity of water is necessary [Yalkowsky and Valvani. 1980]. Thus the concentration of saturated aqueous solution. expressed in mg/ml. is given by equation VII

$$c_{sat} = \frac{55.5 \cdot MW}{P} \exp(-0.01\ MP - 0.69) \quad \text{(VII)}$$

For more soluble chemicals. an adjustment for the volume of displaced water is recommended [Yalkowsky and Valvani. 1980].

$$c_{sat} = \frac{1.000 \cdot MW}{P} \cdot \frac{\exp(-0.01\ MP - 0.69)}{18 + (MW - 18) \cdot \exp(-\log P - 0.01\ MP - 0.69)} \quad \text{(VIII)}$$

If the chemical exists at room temperature as a liquid, 25 was substituted for MP [Yalkowsky and Valvani, 1980]. Berner and Cooper [1987] proposed a similar equation for nonelectrolytes with log $p > 1$.

'Equations VII and VIII were used to calculate aqueous solubility, and the calculated values were compared with measured values using regression log c_{sat} measured versus log c_{sat} calculated.

RESULTS AND DISCUSSION

Calculated and experimental solubilities for 176 chemicals were compared (Fig. 1), and 44 chemicals were not included in further study since the calculated and experimentally determined solubilities differed in multiples larger than 5. Flux. and the ratio of critical flux to flux calculated for aqueous solutions of the remaining 71 nonvolatile chemicals. using equations I and II, are shown in Table I: flux. and the ratio of critical flux to flux calculated for aqueous solutions and vapors of the remaining 61 volatile chemicals, using equations I. 11, and IV, are shown in Table II.

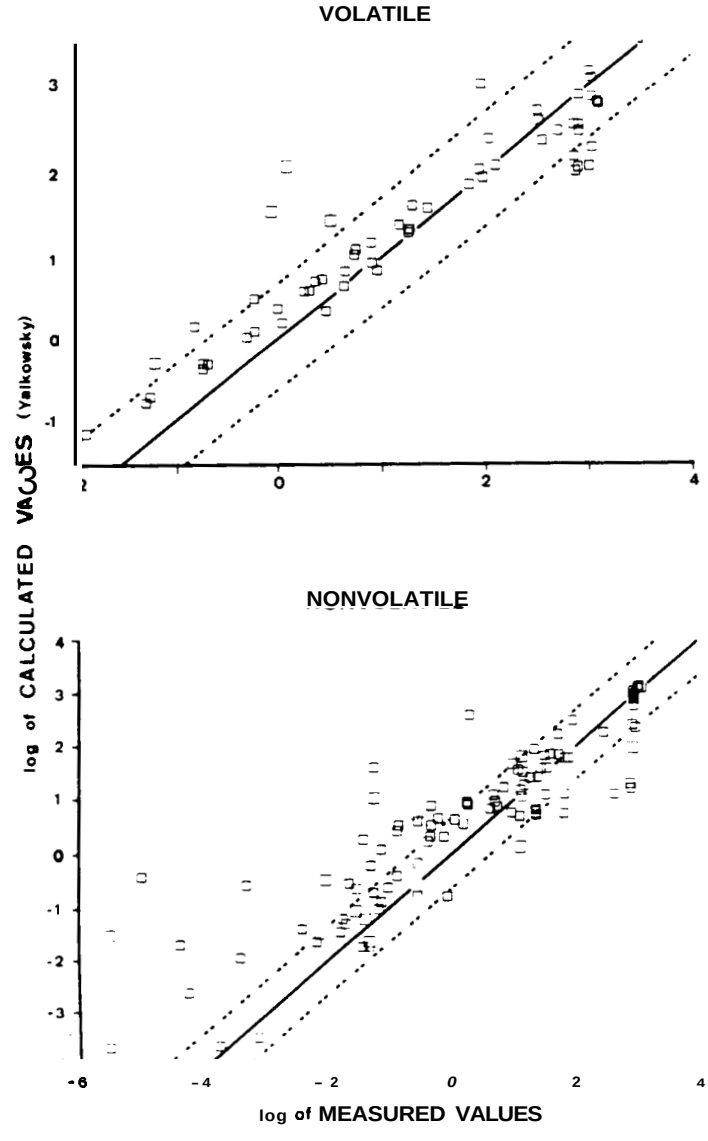

Fig. 1. Correlation between measured and calculated **aqueous** solubility of 176 industrial chemicals. The solubilities are expressed as a logarithm of a saturated solution in water (mg/ml): the solid line indicates the ideal situation when **measured** and calculated values **would** be the same: the broken line indicates the borderline between acceptable and unacceptable **values.**

When $Fl^*/Fl < 1$, the dermal absorption potential is considered significant. Under such circumstances. dermal absorption is expected to raise the biological levels 30% above those occurring during inhalation exposure to TLV. The significant dermal absorption potential is indicated by ''O'' on the left side of the tables. When biological levels triple compared with levels reached during exposure to TLV only (that is. $Fl^{**}/Fl < 1$ or $Fl^*/Fl < 0.15$). the chemical is considered to have the potential for

TABLE 1. Constants Used for the Calculation of Flux and Critical Flux of Nonvolatile Chemicals (SVP < 5 Torrs)*

	Chemical	TLV	MW	MP	WS	log p	H	FI* H
e	Acetylsalicylic acid	0.0050	180.1	I31	10.000	1.23	0.0984	0.04
e	2-Aminopyridinr	0.00'0	Y1.1	58	55.000	0.54	0.4625	0.00
o	n-Amyl acetate	0.5250	130.2	−70	2.000	*2.26*	0.4629	0.85
e	Aniline skin	0.0100	93.1	−6	34.000	0.90	0.6405	0.01
o	Atrazine	0.0050	215.7	I76	0.070	2.63	0.0097	0.39
e	Biphenyl	**0.0015**	154.2	71	0.008	4.04	0.0759	0.01
e	n-Butanol skin	0.1500	74.1	−90	77.000	0.88	1.8801	0.06
o	n-Butyl acetate	0.7100	116.2	−77	14.000	1.73	1.2003	0 44
e	n-Butyl acrylate	0.0550	128.2	−64	1.600	2 36	0.4815	0.09
o	p-ter-Butyltoluenr	0.0600	148.0	−.-ci	0.007	4.60	0.2663	0.17
e	o-Cresol skin	0.0220	108.1	31	25.000	2.00	4.5338	0.00
e	m-Cresol skin	0.0220	108.1	I2	23.500	2 00	4.2618	0.00
e	p-Cresol skin	0.0220	108.1	35	24.000	1.93	3.7061	0.00
e	Cyclohexanol skin	0.2000	100.8	24	36.000	1.23	**1.2612**	0.I2
c	Cyclohexanone skin	0.1000	98.1	−31	23.000	0.81	**0.3271**	0.23
o	o-Dichlorobenzene	0.3000	147.0	−18	*0.*100	3.38	0.2329	**0.97**
	p-Dichlorobenzene	0.4500	147.0	53	**0.079**	3.38	0.1840	1.83
e	Dichloroethyl ether skin	0.0300	143.0	−50	**10.200**	**1.29**	0.2085	0.11
e	Dicyclopentadiene	0.0300	132.2	34	0.050	**4.10**	1.5448	0.01
e	Dieldrin skin	0.0003	380.9	I76	0.000	**5.48**	0.0013	0.14
e	Diethanolamine	0.0150	105.1	28	954.000	**−1.43**	0.5I67	*0.02*
e	2-Diethylaminoethanol skin	0.0500	117.2	25	885.000	0.35	3.4428	0.01
e	Diethylene triamine skin	0.0040	103.2	−39	959.000	−1.40	0.5410	0.01
	Diethyl ketone	0.7050	86.1	−42	47.000	0.79	0.7755	0.68
e	N,N-dimethyl aniline skin	0.0250	121.2	3	1.120	2 31	0.3359	0.06
e	Dimethyl phthalate	0.0050	191.2	0	5.000	2.00	0.2287	0.02
e	Diphenylamine	0.0100	169.2	53	0.300	*3.50*	0.6455	0.01
o	Diuron	0.0100	233.1	I58	**0.042**	3.00	0.0103	0.73
e	DMAC skin	0.0350	87.1	**−20**	943.000	−0.77	0.9980	0.03
e	DMF skin	0.0300	**73.1**	−61	944.000	−1.01	1.0347	*0.02*
e	Ethanolamine	0.0080	61.1	I0	1018.000	−1.31	1.1619	0.01
e	2-Ethoxyethanol skin	0.0190	90.1	−70	931.000	**−0.54**	1.2054	0.01
e	Ethyl butyl ketone	0.2300	114.2	−39	14.300	1.80	1.4865	0.12
e	Ethylene glycol	0.1250	62.1	−13	**1113.000**	**−1.93**	1.0938	0.09
e	Formaldehyde	0.0015	30.0	−92	300.000	0.00	2.3626	0.00
e	Formamide skin	0.0150	**45.0**	**3**	1133.000	−1.65	1.5221	0.01
e	Furfural skin	0.0080	96.1	−37	83.000	0.99	1.8231	0.00
e	Glycerin	0.0100	92.1	**18**	**1264.000**	−2.56	0.7419	0.01
o	Hexachloroethane	0.0100	236.7	I87	0.050	3.30	0.0230	0.33
e	Hexylene glycol	0.1250	118.2	**−40**	923.000	−0.14	1.3826	0.07
o	Isoamyl alcohol	0.3600	88.2	−117	30.000	1.28	**1.4415**	0.19
e	Lindane skin	0.0005	290.9	**I12**	0.017	3.72	0.0087	0.04
o	Methoxychlor	0.0100	345.7	98	**0.040**	4.03	0.0173	0.43
e	2-Methoxyethanol skin	0.0160	76.1	*25*	966.000	0.00	3.6402	0.00
e	4-Methoxyphenol	0.0050	124.2	53	**16.000**	1.34	0.4954	0.01
c	Methyl n-amyl ketone	**0.2350**	114.2	−30	4.300	**2.03**	0.7580	0.23
e	n-Methyl aniline skin	0.0020	107.2	−57	34.000	1.74	3.4473	0.00
e	Methyl n-butyl ketone	0.0200	100.2	−60	26.000	1.38	1.2944	0.01
c	Methyl isoamyl ketone	**0.2400**	114.2	−74	5.400	1.88	0.6712	0.27
o	Methyl isobutyl ketone	*0.2050*	100.2	−74	19.000	1.38	0.9459	**0.16**
c	Metribuzin	0.0050	**214.3**	**I25**	1.200	1.52	0.0132	0.28
e	Morpholine skin	0.0700	87.1	−5	1007.000	**−1.08**	0.8449	0.06
o	Naphthalene	0.0500	**128.2**	80	0.030	3.37	0.0923	0.41

(continued)

TABLE I. Constants Used for the Calculation of Flux and Critical Flux of Nonvolatile Chemicals (SVP < 5 Torrs)* (Continued)

Chemical	TLV	MW	MP	WS	log p	Fl	Fl*/Fl
e p-Nitroaniline skin	0.0030	138.1	148	0.800	1.39	0.0222	0.10
e p-Nitrotoluene skin	0.0110	137.1	55	0.440	2.40	0.1258	0.07
● PCP skin	0.0005	266.4	190	0.001	5.01	0.0118	0.03
o Pentaerythritol	0.0100	136.1	261	55.600	−1.70	0.0172	0.44
e p-Phenylene diamine skin	0.0001	108.1	147	41.500	−0.26	0.0599	0.00
● Phenyl ether	0.0070	170.2	28	0.021	4.28	0.2680	0.02
● Phenyl mercaptan	0.0020	110.2	−15	0.470	2.52	0.2726	0.01
● Propoxur	0.0005	209.2	92	2.000	1.58	0.0275	0.01
● Ronnel	0.0100	321.6	41	0.040	4.88	0.1804	0.04
o Strychnine	0.0002	334.4	270	0.143	1.93	0.0006	0.19
o Styrene skin	0.2150	104.0	−31	0.300	2.95	0.5166	0.31
● o-Toluidine skin	0.0090	107.2.	−10	15.000	1.30	0.5566	0.01
e p-Toluidine skin	0.0090	107.1	44	7.400	1.40	0.3448	0.02
e Tributyl phosphate	0.0025	266.3	−80	5.900	2.36	0.1947	0.01
● Trichloroacetic acid	0.0070	163.4	58	13.000	1.13	0.1334	0.04
3 1,2,4-Trichlorobenzene	0.0400	181.5	17	0.019	4.23	0.1804	0.17
Trichlorofluoromethane	5.600	137.4	− 111	1.100	2.53	0.4222	9.95
ɔ Trimethyl benzene	0.1250	120.2	−44	0.060	3.60	0.3561	0.26

TLV, TLV–TWA (mg L); MW, molecular weight; MP, melting point (°C); WS, solubility in water (mg/ml at room temperature); log p, decadic logarithm of octanol–water partition coefficient; Fl, flux, calculated for a saturated aqueous solution using equation 4 (mg/cm² hr); Fl, critical flux calculated for aqueous solution using equation 9 (mg/cm²/hr); ɔ, potential for dermal absorption (0.15 < Fl* Fl < 1); ●, potential tor dermal toxicity (Fl* Fl < 0.13).

dermal toxicity. Potential for dermal toxicity is indicated by "●" on the left side of the tables. Predicted significant absorption of vapors is indicated by "X" on the left hand side of the table. Tables III–VI list tho studied chemicals with dermal toxicity potential. with dermal absorption potential only. with no significant dermal absorption. and outsiders. Skin notation as shown in the TLV-BEI booklet is also indicated [Threshold Limit Values and Biological Exposure Indices, 1988].

Expediency of Calculated Aqueous Solubility

Equation 4 in the Appendix shows that the dermal penetration rate is directly related to aqueous solubility of chemicals. Therefore the accuracy of flus prediction depends. to a large extent. on the accuracy of c_{sat} values. The c_{sat} values of some chemicals vary dependinp on the source of information: for some important chemicals. the values were not found. (This is especially true for chemicals poorly soluble in water). An existing model [Yalkowsky and Valvani. 1980] was employed to predict aqueous solubility of the studied chemicals (equations VII and VIII). Large differences between calculated and tabular values were found tor 44 chemicals (Fig. 1). These outsiders are mainly poorly soluble chemicals whose solubility is difficult to measure. or acids and bases with solubility dependent on pH. The correlation between calculated and tabular values for the remaining 132 chemicals was in the expected range (for correlation of log–log values. r = **0.886).** and the tabular values were used for calculation of flux. A disagreement between calculated and tabular values of solubility can be considered as an indicator that one or both values of log P and c_{sat} are incorrect or that additional molecular properties. such as polar-

TABLE II. Constants Used for the Calculation of Flux and Critidl Flux of Volatile Chemicals (SVP > 5 Torrs)*

Chemical	TLV	MW	MP	WS	PC	log p	Fl	Fl* Fl	Fl*vap Fl
● .Acetic acid	0.0250	60.1	1-	1049 000	500.00	−0 24	3.37	0.01	9.34
○ Acetone	1.7800	58 1	−94	778 000	395.00	−0.24	15 x	0.52	11.45
● Acetonitrile skin	0.0700	41.1	−43	783 000	1000 00	−0.34	2 92	0 02	4 02
● Allylalcohol skin	0.0050	58 1	−129	854 000	2000 00	0.17	5.94	0.00	1.os
● Benzene	0 0300	7X.1	h	1 7x0	2.80	2.13	**0.70**	0.03	13.56
○ 1.3-Butadiene	0.2200	4x.o	−109	0 735	0.50	1.YY	0.34	0 48	64 71
● Sec butanol	0 3050	74 1	−100	125 000	200.00	0 61	1.68	0.14	5.57
● n-Butylamine skin	0.0150	73.1	−50	733 000	50.00	−1.22	0 72	0 02	306.Y3
● Carbon disulfide skin	0.0300	7h. 1	− 112	2 940	0.80	2.00	0 89	0.03	61.96
● Carbon tetrachloride skin	0.0301	153 X	−23	1.000	0.25	2 83	0 59	0.04	101 88
Chlorobenzene	0 3500	1 12.h	−45	0 500	4.10	2 46	0.24	1.0X	7 53
● Chloroform	0.0500	119 4	−64	8.150	4.00	1 97	1.15	0.03	26.54
● Chloropicrins	0 0007	164 4	−64	2.000	10 00	2 44	0 41	0.00	7 40
○ Cumene skin	0.2450	120.2	−Yh	0.050	1 40	3 bb	0.34	0.54	157
Cyclohexane	1.0500	84 2		0 055	0 YO	3 14	0 40	1.96	2 28
Cyclohexene	1.0100	82 1	−104	0.213	5 00	2.86	0.42	1.79	1.51
○ 1.1-Dichloroethane	0.8100	YY.O	−97	5.500	2.70	1.79	0.71	0.85	42 86
1.2-Dichloroethylene	0.7900	Yh Y	−80	Y 000	2.50	1.48	0.59	1.00	91.13
● Diisopropylamine shin	0.0200	101.2	− Yh	8.000	10.00	1.66	0.74	0.02	16.16
● Dioxane shin	0.0900	88.1	10	1033.000	500.00	−0.42	1.62	0.04	19 16
○ Enflurane	0.5750	184.5	0	10.000	0.80	2.10	0.67	0.64	278.99
○ Ethanol	1.9000	46. 1	−114	789.000	1906.00	−0.31	2.84	0.50	2.19
○ ' acetate	1.400	xx. 1	−83	x7.000	193.00	0.70	1.14	0.92	5.93
● ..ₚ lamine	0 0180	45.1	−81	684.000	2000.00	−0.13	3.36	0.00	1.53
○ Ethyl hcnzene	0.4350	106.2	−95	0 200	1.70	3.15	0.53	0.62	3.35
Ethylchloride	2.6000	b4.5	−139	10 000	1.20	1.43	0.99	1.98	126.62
○ Ethyl ether	1.2000	74.1	−116	69.000	5.00	0.83	1.51	0.60	137.37
○ Ethyl formate	0.3000	74.1	−X0	110 000	5.00	0.26	0.71	0 32	465.43
● Ethyl mercaptane	0.0010	62. 1	−147	10 000	1.00	1.17	0.57	0.00	26410
● Formic acid	0.0090	46 0	8	1220.000	1000.00	−0.54	3 20	0.00	5 72
○ Halothane	0 4000	197.4	0	4.500	0.70	2.30	0.39	0.77	247.47
○ n-Heptane	1.6000	100.2	−91	2.400	0.50	2.70	2.47	0.49	29. I5
○ n-Hexane (X)	0.1800	86.2	−95	0.014	1.10	3.94	0.31	0.43	0.61
● Hydrazine skin	0.0001	32.0	2	1004.000	500.00	−1.23	1.88	0.00	15.99
● Isobutyl alcohol (X)	0.1500	74.1	−108	95.000	2000.00	0.76	1.78	0.06	0.40
○ Isopropyl alcohol	0.9800	60.1	−89	785.000	1000.00	0.05	4.20	0.18	2.81
● Isopropylamine	0.0120	59.1	−101	694.000	3.00	−0.03	3.15	0.00	1067.97
● Mesityl oxide	0.0600	9x.1	−59	28.000	10.00	1.24	1.05	0.04	40.11
● Methanol skin	0.2600	32.0	−98	791.000	1900.00	−0.77	2.02	0.10	3.09
○ Methyl acetate	0.6100	74. 1	−98	319.000	100.00	0.18	1.75	0.26	27.32
Methylal	3.1000	76.1	−105	330.000	10.00	0.00	1.24	1.87	398.06
● Methylamine	0.0120	31.1	−94	1213.000	1.00	−0.57	3.89	0.00	4673.79
● Methyl chloride	0.1050	50.5	−97	88.000	0.20	0.91	3.35	0.02	1969.24
○ Methyl chloroform	1.9000	133.4	−33	4.400	0.93	2.49	1.64	0.87	43.21
● Methylene chloride	0.1750	84.9	−97	20.000	7.20	1.25	0.95	0.14	44.06
○ Methyl ethyl ketone	0.5900	72 1	−86	353.000	254.00	0.28	2.45	0.18	8.52
● Methyl iodide skin (X1	0.0100	142.0	−h7	18.000	300.00	1.hY	0.93	0.01	0 97
○ Methyl propyl ketone	0.7000	86.2	−78	43.000	181.00	O.Y1	0.93	0.57	3 85
○ Nitromethane	0.2500	61.0	−29	107.000	400.00	0.08	0.60	0.31	6.73
○ n-Propyl acetate	0.8400	102.1	−93	18.900	50.00	1.50	1.20	0.53	4.73
● n-Propyl alcohol skin	0.5000	60.1	−127	505.000	1000.00	0.25	3.99	0.09	1.90
○ Propylene dichloride	0.3500	113.0	−100	2.700	6.00	2.14	0.62	0.42	10.81
● 1 1 2,2-Tetrachloroethane skin	0.0070	1h7.Y	−44	2.900	36.00	2.70	1.01	0.01	1.20

(continued)

TABLE II. Constants Used for the Calculation of Flux and Critical Flux of Volatile Chemicals (SVP > 5 Torrs)* (Continued)

Chemical	TLV	MW	MP	WS	PC	log p	Fl	Fl*/Fl	Fl*vap/Fl
● Thioglycolic acid skin	0.0040	92.1	−17	1325.000	2000.00	0.09	4.58	0.00	2.17
○ Toluene	0.3750	92.1	−Y5	0.600	1.10	2.69	0.69	0.41	5.95
● 1,1,2-Trichloroethane skin	0.0450	133.4	−37	4.500	17 10	2.12	0.72	0.05	5.50
○ Trichloroethylene	0.2700	131.5	−87	1.100	1.50	2.29	0.27	0.76	41.17
● Tnerhylamine	0.0400	101.2	−115	15.000	5.00	1.35	0.69	0.04	65.61
○ o-Xylene	0.4350	106.2	−25	0.180	2.60	3.14	0.46	0.70	2.24
○ m-Xylene	0.4350	106.2	−47	0.180	1.70	3.20	0.53	0.61	2.98
○ p-Xylene	0.4350	106.2	13	0.200	1.60	3.15	0.53	0.62	3.56

*PC, water–gas partition coefficient at body temperature: Fl^*_{vap}, critical flux calculated for vapors using equation 14 (mg/cm²/hr); (X), significant dermal absorption of vapors ($Fl^*_{vap}/Fl < 1$); other symbols are the same as in Table I.

izability or decomposition affect the solubility and possibly. dermal absorption. Flux for these outsiders is not reported (Table **VI).**

Comparison of Predicted Dermal Absorption With Skin Notation

A dermal absorption potential is predicted for 122 chemicals. of which only 43 (35%)can-y a skin notation. **A** significant dermal toxicity potential is indicated for 77 chemicals. of which 40 ***(52%)*** carry skin notations. **A** dermal absorption potential. but not **a** toxicity potential. was predicted for three chemicals carrying the skin notation (cumene. cyclohexanone. and styrene).

In most instances. a skin notation is lacking for chemicals with TLVs designed to protect against irritation. Since the threshold for systemic toxicity of irritants is usually larger than the threshold for irritation. the critical flux for irritants is likely underestimated. Examples are acetic and formic acids. acetone. chloropicrin, methyl acetate. and some amines, ketones. and alcohols. It is probably justified that these irritants do not carry a skin notation. although dermal absorption of some of these irritants was predicted and documented [Schaefer et al.. 1982]. The absence **of a** skin notation for nonirritants with predicted significant dermal absorption was further investigated. and the following causes were indicated.

1. **The** absence of **skin** notation can be the result of the lack of information. Biological effects of the majority of chemicals included in this category were insufficiently studied. and their TLVs are based on a relatively small amount of information [Documentation of the Threshold Limit Values and Biological Exposure Indices. 1986]. Examples are p-ter-butyl toluene. dicyclopentadiene. ethyl butyl ketone. and metribuzin.
2. Lack of cognizance of information can be another reason for absence of skin notation. For example. dermal absorption of aspirin [Schaefer et al.. 1982; Wester and Maibach. 1977], benzene [Tsuruta. 1982], n-butyl acrylate [Carpenter et al., 1974], ethylbenzene [Dutkiewicz and Tyras. 1967: Tsuruta. 1982], methyl chloroform [Fukabori et al.. **1977:** Stewart and Dodd. 1964], methylene chloride and perchloroethylene [Stewart and Dodd. 1964], phenylmercaptan (Fairchild and Stokinger, 1958: Schafer, 1972], o-dichlorobenzene [Documentation of ***the*** Threshold Limit Values and Biological Exposure indices, 1986], toluene [Sato

TABLE 111. Chemicals With Dermal Toxicity Potential

Acetic acid	Ethyl mercaptane
Acetonitrile"	Formaldehyde
Acetylsalicylic acid	Formamide"
Allylalcohol"	Formic acid
2-Aminopyridine	Furfural"
Aniline"	Glycerin
Benzene	Hexylene glycol
Biphenyl	Hydrazine"
n-Butanol"	Isobutyl alcohol
sec-Butanol	Isopropylamine
n-Butyl acrylate	Lindane"
n-Butylamine"	Mesityl oxide
Carbon disulfide[a]	Methanol"
Carbon tetrachloride"	2-Methoxyethanol[a]
Chloroform	4-Methoxyphenol
Chloropicrine	Methylamine
o-Cresol[a]	n-Methyl aniline"
m-Cresol	Methyl n-butyl ketone
p-Cresol[a]	Methyl chloride
Cyclohexanol[a]	Methylene chloride
Dichloroethyl ether"	Methyl iodide[a]
Dicyclopentadiene	Morpholine[a]
Dieldrin"	p-Nitroaniline"
Diethanolamine	p-Nitrotoluene"
2-Diethylaminoethanol'	PCP[a]
Diethylene triamine"	p-Phenylene diamine"
Diisopropylamine"	Phenyl ether
N,N-dimethyl aniline"	Phenyl mercaptan
Dimenthyl phthalate	Propoxur
Dioxane"	n-Propyl alcohol"
Diphenylamine	Ronnel
DMAC[a]	1,1,2,2-Tetrachloroethane[a]
DMF"	Thioglycolic acid"
Ethanolamine	o-Toluidine"
2-Ethoxyethanol"	p-Toluidine"
Ethylamine	Tributyl phosphate
Ethyl butyl ketone	Trichloroacetic acid
Ethylene glycol	1,1,2-Trichloroethane[a]
	Triethylamine

"Skin notation in **1987–1988** TLV–BEI booklet.

and Nakajma, 1978; Tsuruta, 19821, trichloroethylene [Sato and Nakajima, 1978; Stewart and Dodd, 1964: Tsuruta, 19771, and some alcohols [Schaefer et al.. 19821 was experimentally documented. but the information is not evaluated in the TLV-documentations [Documentation of the Threshold Limit Values and Biological Exposure Indices, 19861.

3. Skin notation can be based on information related to an inappropriate biological effect. For example, tests showed that dermal absorption of aspirin is too small to produce a therapeutic dose. However. the dose produced by inhalation exposure to TLV–TWA is about 100 times smaller than the minimal therapeutic dose. Another example is hexachloroethane, whose TLV was recently reduced from 0.1 to 0.01 mg/l, based on systemic toxicity [Threshold Limit Values and Biological

TABLE IV. Chemicals With Dermal Absorption Potential Only

Acetone	Isopropyl alcohol
n-Amyl acetate	Methoxychlor
Atrazine	Methyl acetate
1.3-Butadiene	Methyl n-amyl ketone
n-Butyl acetate	Methyl chloroform
p-ter-Butyltoluenc	Methyl ethyl ketone
Cumene"	Methyl isoamyl ketone
Cyclohexanone"	Methyl isobutyl ketone
o-Dichlorobenzene	Methyl propyl ketone
1.1-Dichloroethane	Metribuzin
1,2-Dichloroethylene	Naphthalene
Diethyl ketone	Nitromethane
Diuron	Pentaerythritol
Enflurane	n-Propyl acetate
Ethanol	Propylene dichloride
Ethyl acetate	Strychnine
Ethyl benzene	Styrene"
Ethyl ether	Toluene
Ethyl formate	1.2,4-Trichlorobenzene
Halothane	Trichloroethylene
n-Heptane	Trimethyl benzene
Hexachloroethane	o-Xylene
n-Hexane	rn-Xylene
Isoamyl alcohol	p-Xylene

"Skin notation in 1987–1988 TLV–BEI booklet.

TABLE V. Chemicals Without Significant Dermal Absorption

Chlorobenrene	p-Dichlorobenzene
Cyclohexane	Ethylchloride
Cyclohcxene	Methylal
	Trichlorotluoromethane

Exposure Indices. 1988]. Dermal absorption potential related to the old TLV (based on protection against irritation) was insignificant. but it is significant with respect to the proposed TLV. Another example is benzene. whose TLV **was** reduced tenfold. and therefore a skin notation became appropriate.

Hansen [1982] was the first to **use** a theoretical model to predict **skin** notation. His moaei calls for a **skin** notation for an additional 44 chemicals **in** the TLV table. Our study also calls for additional skin notations. There is a difference in his and our approach in identifying the significance of dermal absorption. Hansen's criteria are based on the swelling of psoriasis scales. while our criteria are toxicologically based. Despite this difference. both studies conclude that the list of chemicals with skin notation is incomplete.

A Reference Value for Flux in an Industrial Setting

In the workplace. the threshold **for** flux can vary depending on the exposed areas. dermal exposure duration. and selected threshold for the biological level. To

TABLE VI. Chemicals Excluded From the Study (Outsiders)

Acrylamide[a]	p-Dinitrobenzene[a]
Acrylic acid	Dinitrotoluene[a]
Acrylonitrile[a]	Fenthion[a]
Aldrin[a]	Hydroquinone
Benzidine[a]	Malathion[a]
n-Butane	Methyl acetylene
2-Butoxy ethanol[a]	Methyl bromide[a]
n-Butyl mercaptan	Methyl parathion[a]
Captan	Nitrobenzene[a]
Carbaryl	Nitroglycerin[a]
Catechol	1-Nitropropane
Chlordane[a]	o-Nitrotoluene[a]
Chlorpyrifos[a]	m-Nitrotoluene[a]
Cyclohexylamine	Nitrous oxide
2,4-D	Parathion[a]
DDT	Perchloroethylene
Diazinon[a]	Phenol[a]
3,3'-Dichlorobenzidine[a]	Picric acid[a]
Dichlorodifluoromethane	Propionic acid
Diethylamine	Pyridine
m-Dinitrobenzene[a]	Resorcinol
o-Dinitrobenzene[a]	Tetrahydrofuran

[a]Skin notation in 1987–1988 TLV–BEI booklet

estimate a reference value (RV) for a dermal exposure existing in the workplace conditions, the following formula can be derived from equation 5 in the Appendix.

$$RV = \frac{\Delta BL\%}{100} \cdot \dot{V}_{alv} \cdot TLV \cdot \frac{100}{EA\% \cdot SA} \cdot \frac{8}{hrs} \qquad (IX)$$

and after substitution

$$RV = 0.4 \frac{\Delta BL\% \cdot TLV}{EA\% \cdot hrs} \qquad (X)$$

where $\Delta BL\%$ denotes the chosen increase of biological levels expressed in percentage of levels reached during exposure to TLV–TWA only, EA% denotes percentage of body surface dermally exposed. hrs denotes duration of dermal exposure in hours, and TLV is TLV–TWA in mg/l.

If predicted flux, calculated by equation I, exceeds the reference value ($FI > RV$), then a dermal overexposure at the selected BL-level is predicted. For practical purposes, two $\Delta BL\%$ are of main interest: 1) levels at which dermal exposure affects the relationship between air monitoring and biological monitoring (usually related to $\Delta BL\% = 30\%$); and 2) levels at which dermal exposure contributes to systemic toxicity (usually related to $\Delta BL\% = 200\%$).

Dermal Absorption of Vapors and Gases

Dermal absorption of vapors and gases is usually considered negligible compared with pulmonary uptake [Riihimaki and Pfaffli. 19781. Critical flux for whole

body exposure to gases and vapors is not affected by exposure concentration (equation 14 in the Appendix). However, its application is restricted to concentrations considerably smaller than the concentrations corresponding to saturated vapor pressure; otherwise. the condensation distorts the prediction of dermal penetration of the vapor. Furfural is an example of how condensation significantly increases **absorption of vapors" [Flek and Sedivec. 1978].

Significant dermal absorption potential for vapors and gases can be predicted by comparing FL^*_{vap} with FI (Table II). Of 61 volatile chemicals, only 3 show a dermal absorption potential for vapors: n-hexane, isobutyl alcohol. and methyl iodide.

CONCLUSIONS

A dermal penetration rate [flux (Fl)], predicted from physical properties of the chemicals, is suggested as an index of the dermal absorption potential of industrial chemicals. The prediction is designed for organic nonelectrolytes. Since published data on log P and aqueous solubility are sometimes inconsistent. it is advisable to test the information on the octanol–water partition coefficient and on aqueous solubility (equations VII and VIII) before using it for the prediction of flux.

Two reference values are recommended as criteria for skin notation.

1 Critical flux (Fl*) for dermal absorption potential relates to dermal absorption raising the dose of nonvolatile chemicals or biological levels of volatile chemicals 30% above those observed during inhalation exposure to TLV–TWA only. If dermal exposure of 2% of body surface to saturated aqueous solution raises the levels by 30% (Fl > Fl*), the chemical should be classified as a chemical with dermal absorption potential and identified as such in the TLV booklet. Biological monitoring of these chemicals is advisable. especially if dermal exposure to a significant fraction of body surface is prolonged. Biological levels of indicators of exposure to these chemicals are not necessarily quantitative indicators of inhalation exposure.

2. Critical flux (FL**) for dermal toxicity potential relates tu dermal absorption. which triples biological levels as compared with levels observed during inhalation exposure to TLV–TWA only. If dermal exposure of 2% of body surface to saturated aqueous solution triples biological levels. the chemical should be classified as a chemical with dermal toxicity potential and should carry a skin notation; biological monitoring. if a method is available. should be instituted. If biological levels persistently exceed BEIs, steps should be taken to reduce dermal exposure. unless other origins of the increased biological levels are indicated (nonoccupational exposure. interference by medication. enzyme induction. etc.).

Absence of a skin notation for chemicals with predicted dermal toxicity potential should be investigated and experimental testing encouraged. Critical flux relates to systemic effect and can be overestimated for chemicals whose TLVs are based on preventing irritation and discomfort.

Critical flux should be lowered if a large area of body surface is exposed to aerosol. particles. liquids. or solutions. Equation X is suggested for the calculation of a reference value for dermal exposure in an industrial setting.

Potential for significant dermal absorption or toxicity of gases or vapors of

volatile chemicals is rare. However. condensation of vapors on the body surface can raise the penetration rate above the predicted flux. Vapors of chemicals with low saturated vapor pressure are more likely to condense .on the body surface than are gases or vapors of highly volatile chemicals.

The proposed formulas are meant for practical use: therefore certain simplifications are made. For example. the calculation of critical flux is based on steady state conditions. not takins into account the raising of biological levels in time or deposition in subcutaneous fat. The biochemical changes in skin induced by the cheniical or by the vehicle are not included in the calculation of flux. nor is the regional variation in skin composition taken into account.

REFERENCES

Albery WJ. Hadgraft J (1979): Percutaneous absorption: Theoretical description. J Pharm Pharmacol 31:129–139.

Astrand I (1983): Effect of physical exercise on uptake. distribution. and elimination of vapors in man In Fiserova-Bergerova V (ed): "Modeling of Inhalation Exposure to Vapors: Uptake. Distribution. and Elimination." Vol. II. Boca Raton. FL: CRC Press. pp 107–130.

Berner B. Cooper ER (1987): Models of skin permeability. In Kydonieu AF. Berner B (eds): "Transdermal Deliver) of Drugs." Vol. II. Boca Raton. FL: CRC Press. pp 41–55.

Berode M. Droz PO. Guillemin M (1985): Human exposure to styrene. VI. Percutaneous absorption in human volunteers. Int Arch Occup Environ Health 55:331–336.

Burton AC (19681: "Physiology and Biophysics of the Circulation." Chicago: Year Book Medical Publishers. Inc., pp 13–22.

Carpenter CP. Weil CS. Smyth HF Jr (1974): Range-finding toxicity data: List VIII. Toxicol Appl Pharmacol 28:313–319.

J JA (ed) (1979):"Lange's Handbook of Chemist? ." ed 12. New York: McGraw-Hill Book Co.

Documentation of the Threshold Limit Values and Biological Exposure Indices (1986): 5th ed and Suppls. 1987 and 1988. Cincinnati. OH: American Conference of Governmental Industrial Hygienists.

Dugard PH (1983): Skin permeability theory in relation to measurements of percutaneous absorption in toxicology. In Marzulli FN. Maibach HI (eds) "Dermatotoxicology." ed 2. Washington. DC: Hemisphere Pub. Corp., pp 95–116.

Dugard PH. Walker M. Mawdsley SJ. Scott RC (1984): Absorption of some glycol ethers through human skin in vitro. Environ Health Perspect 57:193–197.

Dutkiewicz T. Tyras H (1967): A study of the skin absorption of ethylbenzene in man. Br J Ind Med 24:330–332.

Dutkiewicz T. Tyras H (1968): Skin absorption of toluene. styrene. and xylene by man. Br J Ind Med 25:243.

Fairchild EJ, Stokinger HE (1958):Toxicologic studies on organic sulfur compounds. Am Ind Hyg Assoc J 19:171–189.

Fiserova-Bergerova V (1983): Gases and their solubility: A review of fundamentals. In Fiserova-Bergerova V (ed): "Modeling of Inhalation Exposure to Vapors: Uptake. Distribution, and Elimination." Vol. I. Boca Raton. FL: CRC Press. pp 3–28.

Fiserova-Bergerova c': Interaction between inhalation and dermal exposure: Simulation model. (in preparation)

Fiserova-Bergerova (Thomas) V. Pierce JT (1989):Biological monitoring V. Dermal absorption. Appl Ind Hyg 4:F14–F21.

Flek J. Sedivec V (1978): The absorption. metabolism and excretion of furfural in man. Int Arch Occup Environ Health 41:159–168.

Fukabori S. Nakaaki K. Yonemoto J. Tada O (1977): On the cutaneous absorption of 1.1.1-trichloroethane (2). J Sci Labour 53:89–95.

Grandjean P. Berlin A. Gilbert M, Penning W (1988): Preventing percutaneous absorption of industrial chemicals: The "skin" denotation. Am J Ind Med 14:97–107.

Guy RH, Hadgraft J. Maibach HI (1985): Percutaneous absorption in man: A kinetic approach. Toxicol Appl Pharmacol 78:123–129.
Hansch C. Leo A (1979): "Substituent Constants for Correlation Analysis in Chemistry and Biology." New York: Wiley-Interscience Pub.
Hansen CM (1982): "The Absorption of Liquids Into the Skin." Report T3-82. Horsholm. Denmark: Scand Paint Printing Ink Res. Inst.
Kuabota K, Ishizaki T (1986): A calculation of percutaneous drug absorption—I. Theoretical. Comput Biol Med 16:7–19.
Michaels AS. Chandraskaran SK, Shaw JE (1975): Drug permeation through human skin: Theory ana in vitro experimental measurement. AICHE J 21:985–996.
Nakaaki K. Fukabori S. Tada O (1985): An experimental study on percutaneous absorption of mixed organic solvents. J Sci Labour 61:1–10.
Riihimaki V (1979): Percutaneous absorption of m-xylene from a mixture of m-xylene and isobutyl alcohol in man. Scand J Work Environ Health 5:143–150.
Riihimaki V. Pfaffli. P (1978): Percutaneous absorption of solvent vapors in man. Scand J Work Environ Health 4:73–85.
Sato A. Nakajima T (1978): Differences following skin or inhalation exposure in the absorption and excretion kinetics of trichloroethylene and toluene. Br J Ind Med 35:43–49.
Scansetti G, Pilatto G, Rubino GF (1988): Skin notation in the context of workplace exposure standards. Am J Ind Med 14:725–732.
Schaefer H. Zesch A. Stuttgen G (1982): Flux. In: "Skin Permeability." New York: Springer-Verlag, pp 829–831.
Schafer EW (1972): The acute oral toxicity of 369 pesticidal. pharmaceutical and other chemicals to wild birds. Toxicol Appl Pharmacol 21:315–330.
Scheuplein RJ. Blank IH (1971): Permeability of the skin. Physiol Rev 51:702–747.
Stewart RD. Dodd HC (1964): Absorption of carbon tetrachloride. trichloroethylene. tetrachloroethylene. methylene chloride and 1.1.1-trichloroethane through the human skin. Ind Hyg J 25:439–446.
Threshold Limit Values and Biological Exposure Indices for 1988–1989 (1988): Cincinnati. OH: American Conference of Governmental Industrial Hygienists. Inc.
Tsuruta H (1977): Percutaneous absorption of organic solvents. II. A method for measuring the penetration rate of chlorinated solvents through excised rat skin. Ind Health 15:131–139.
Tsuruta H (1982): Percutaneous absorption of organic solvents. 111. On the penetration rates of hydrophobic solvents through the excised rat skin. Ind Health. 20:335–345.
Verschueren K (1983): "Handbook of Environmental Data on Organic Chemicals." ed 2. New York: Van Nostrand Reinhold Co.
Wester RC. Maibach HI (1977): Percutaneous absorption in man and animal: A perspective. In Drill VA, Luznr P (eds): "Cutaneous Toxicity." New York: Academic Press. Inc., pp 111–126.
Windholz M (ed) (1976): "The Merck Index, an Encyclopedia of Chemicals and Drugs." ed 9. Rahway, NJ: Merck & Co., Inc.
Yalkowsky SH (1981): Solubility and solubilization of nonelectrolytes. In Yalkowksy SH fed): "Techniques of Solubilization of Drugs." New York: Marcel Dekker. pp 1–14.
Yalkowsky SH. Valvani SC (1980): Solubility and partitioning. I: Solubility of nonelectrolytes in water. J Pharmaceut Sci 69:912–922.

APPENDIX

In the model by Berner and Cooper [1987] the two diffusion pathways. polar and lipophilic. are considered to be independent of each other.

The diffusion constant for both polar and lipophilic pathways (Dp and D_L) have been estimated based on Bueche's free-volume theory for rigid molecules

$$D_P = 3.8\ 10^{-5}\ e^{-0.016\ MW} \quad (1)$$

$$\text{and } D_L = 1.7\ 10^{-5}\ e^{-0.016\ MW} \quad (2)$$

where MW is the molecular weight of the studied chemical. The equation describing **flux** (Fl) is a sum of penetration rates mediated by polar and lipophilic pathways. The difference in availability for diffusion either by polar or lipophilic pathways is defined by the hydrophobic constant. P. which denotes the octanol–water partition coefficient

$$Fl = (A_P \cdot D_P + A_L \cdot D_L \cdot P) \frac{c_{sat}}{l} \quad (3)$$

where c_{sat} denotes the concentration of saturated aqueous solution of the chemical in mg/ml, and l is the thickness of the stratum corneum. which varies from 10 to 40 μm. In this study. it is assumed that l = 15 μm [Berner and Cooper. 1987]. **A,** and **A, in** equation **3** denote area fractions of the polar and lipophilic pathways. respectively. From fitting water penetration data, Berner and Cooper [19871 proposed that the area for the polar pathway accounts for 10% of the total skin area. which means that A_p = 0.1 and **A,** = 0.9. After substituting in equation 3. a simple equation for the calculation of flux is obtained.

$$Fl = \frac{c_{sat}}{15} (0.038 + 0.153\ P)\ e^{-0.016\ MW} \quad (4)$$

The values for c_{sat}, P. and MW were obtained from Dean [1979], Hansch and Leo [1979], Verschueren [1983], and Windholz [19761. When more than one value was reported in the reference sources, the compiled value shown in Tables I and II was used. For chemicals miscible with water, the density of the liquid multiplied by 1,000 was substituted for c_{sat}.

Calculation of Critical Flux

Critical flux (Fl*) can be calculated by comparing inflow and outflow, of the chemical across the lung. **At** steady state

$$\begin{array}{ccc} \text{inflow} & = & \text{outflow} \\ \dot{V}_{alv} \cdot TLV + \dot{Q} \cdot c_{,} + Fl \cdot EA & = & Q \cdot c_{art} + \dot{V}_{alv} \cdot c_{alv} \end{array} \quad (5)$$

where $\dot{V}_{alv}$ is alveolar ventilation (= 900 L/hr), Q is cardiac output. c_{alv} and c_{art} are concentrations (mg/L) in alveolar air and arterial blood. respectively. TLV is TLV–TWA expressed in mg/L. **A** concentration of the chemical in mixed venous blood (c_{vt}) reflects the average concentration in venous blood from all tissues but does not include the amount of chemical absorbed by the dermis under the exposed area. EA is area of body surface (in cm^2) exposed to saturated aqueous solution of the studied chemical, and Fl is predicted flux in $mg/cm^2/hr$.

Critical Flux for Dermal Absorption Potential (Fl*)

Fl* for nonvolatile chemicals. Since nonvolatile chemicals are not exhaled, $V_{alv} \cdot c_{alv} = 0$. In the absence of dermal exposure **EA** = 0, and equation **5** is written

$$\dot{V}_{alv} \cdot TLV = Q \cdot (c_{art} - c_{vt}) \quad (6)$$

In the presence of dermal exposure, which raises c_{art} and c_{vt} by 30%. equation **5** is modified:

$$\dot{V}_{alv} \cdot TLV + Fl \cdot EA = 1.3 \cdot \dot{Q} \cdot (c_{art} - c_{vt}) \quad (7)$$

After substitution from equation 6. equation 7 can be rearranged to calculate critical flux for any exposed area:

$$Fl^* = \frac{0.3\, \dot{V}_{alv} \cdot TLV}{EA} \quad (8)$$

Critical flux calling for dermal absorption potential notation is obtained after substiting the following values: $\dot{V}_{alv} = 900$ L/hr, $EA = 360\ cm^2$

$$Fl^* = \tfrac{3}{4}\, TLV \quad (9)$$

Fl* for volatile chemicals. In the absence of dermal exposure (EA = 0), equation **5** can be written:

$$\dot{V}_{alv} \cdot (TLV - c_{alv}) = \dot{Q} \cdot (c_{art} - c_{vt}) \quad (10)$$

At steady state, all concentrations in venous blood are equilibrated with tissue concentrations.

In the presence of dermal exposure. which raises c_{alv}, c_{art}, and c_{vt} by 30%, equation **5** is modified.

$$\dot{V}_{alv} \cdot (TLV - 1.3 c_{alv}) + Fl \cdot EA = 1.3 \cdot Q \cdot (c_{art} - c_{vt}) \quad (11)$$

After substitution from equation 10, equation 11 can be rearranged **to** calculate the dermal absorption rate.

$$Fl \cdot EA = 0.3 \cdot \dot{V}_{alv} \cdot TLV \quad (12)$$

Critical flux calling for dermal absorption potential is obtained after substituting in equation 12

$$Fl^* = \frac{3}{4}\, TLV \quad (13)$$

Fl^*_{vap} for gases and vapors. Critical flux for dermal absorption potential of vapors and gases is calculated on the assumptions that the whole body is exposed **to** a gas or vapor and that the concentration of the chemical in water of the outside layers of stratum corneum (c_s) is readily equilibrated with the exposure concentration. Under these assumptions. $EA = SA = 18000\ cm^2$ and $c_w = TLV \cdot \lambda$, where A is water-gas partition coefficient. Thus, $Fl \cdot EA$ in equation 12 is replaced by the expression $Fl \cdot (c_w / c_{sat}) \cdot SA$, where c_{sat} denotes an aqueous saturated solution. Critical

flux for dermal exposure to vapors and gases is obtained after substituting for **SA** and $\dot{V}_{alv}$:

$$Fl^{*}_{vap} = \frac{0.3 \cdot \dot{V}_{alv}}{SA} \cdot \frac{c_{sat}}{TLV\lambda} \cdot TLV = 15 \frac{c_{sat}}{\lambda} \qquad (14)$$

Values of partition coefficients are taken from Fiserova-Bergerova [1983] or estimated by the author,.

Critical Flux for Dermal Toxicity Potential (Fl**)

TLV–TWA have incorporated a safety factor that provides for an excursion factor of 3 for concentrations of chemicals in the workplace [Threshold Limit Values and Biological Exposure Indices. 1988]. It can therefore be assumed that it provides a safety factor for tripling biological levels. Therefore the proposed threshold for systemic toxicity potential is associated with flux related to the increase of biological levels by 200%. Such flux for dermal toxicity potential can be calculated using the following equations

$$Fl^{**} = \frac{200}{30} Fl^{*} = 5\ TLV \qquad (15)$$

and for vapors and gases

$$FL^{**}_{vap} = \frac{200}{30} Fl^{*}_{vap} = 100 \frac{c_{sat}}{\lambda} \qquad (16)$$