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rmal Absorption of Organic Chemical Vapors in Rats and Humans[1]

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Dermal Absorption of Organic Chemical Vapors in Rats and Humans. MCDOUGAL, J. N., EPSON, G. W.. CLEWELL, H. J., III, GARGAS, M. L., AND ANDERSEN, M. E (1990). *Fundam Appl. Toxicol* **14,** 299–308. Quantitation of chemical vapor penetration through skin is necssary for assessment of health hazards involved in some occupational environments. Information on penetration of vapors through human skin is minimal because human exposures are not sanctioned. We have investigated the whole-body dermal penetration of styrene, xylene, toluene, perchloroethylene, benzene, halothane, hexane, and isoflurane in rats and compared the permeability constants with available human studies on vapor penetration. Rats with closely clipped fur were exposed to organic chemical vapors (3000 to 60,000 ppm) while breathing fresh air through a latex mask. Blood concentrations taken during the 4-hr exposures were determined by sampling through indwelling jugular cannulas. A physiologically based pharmacokinetic model was used to predict permeability constants consistent with the experimental blood concentrations. Permeability constants (cm/hr) were estimated by a least-square optimization and ranged from 1.75 cm/hr for styrene to 0.03 cm/hr for isoflurane. Rat permeability constants were uniformly two to four times greater when compared to the human constants which were calculated from the literature. These results indicate that organic vapor permeability constants in rats are a conservative estimate of organic vapor permeability constants in humans and that the consistent differences in permeability constants between these two species may be due to physiological differences in the skin.

nding and quantifying absorption ical vapors through skin is necessary ccurate assessment of health hazards pational environments where respira- otection is provided but the skin sur- mains exposed. Until the early 1900s, was considered an effective barrier to etration of liquids and vapors. Now it is recognized that chemicals penetrate the skin by passive diffusion and that the rates of penetration are related to lipid solubility of the penetrant (see reviews by Scheuplein and Blank, 1971 and Schaefer et *al.*, 1982). A suitable *in* vivo animal model for predicting rates **of** penetration of vapors through human skin would provide valuable risk assessment information (Clewell and Andersen, 1985). For example, if a safe level in the environment has been set based on inhalation of a chemical, it would be useful to know how respiratory protection extends the range of safe exposure concentrations where skin vapor penetration is still possible.

The literature contains several reports of quantitation of organic chemical vapor penetration through skin of human volunteers.

animals used in this study were handled in accor- with the principles stated in the *Guide for the Care of Laboratory Animals,* prepared by the Com- on Care and Uses of Laboratory Animals of the of Laboratory Resources, National Research DHHA, National Institute of Health Publica- 85-23, 1985, and the Animal Welfare Act of amended.

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Benzene (Hanke *et al.*, 1961) and aniline (Dutkiewicz and Piotrowski, 1961) vapor penetration was studied in Poland in the 1960s. More recently, Riihimaki and Pfaffli (1978) studied dermal penetration of xylene, styrene. toluene, 1,1,1-trichloroethane and tetrachloroethylene (perchloroethylene) vapors. Wieczorek (1985) measured dermal penetration of styrene vapors. Although little information is available about dermal penetration of chemical vapors, more is known about the penetration of these industrially important solvents in liquid form, through guinea pig skin (Jakobson *et* al., 1982) and human skin (Stewart and Dodd, 1964; Dutkiewicz and Tyras, 1967, 1968, 1969; Aitio et al., 1984; Berode *et* al., 1985). Since concentrations are far greater in the pure liquid than in the vapor form, flux across the skin from the liquid form of the chemical will be greater than that from the vapor form (Hanke *et al.*, 1961; Wieczorek, 1985). Factors which determine the rate of penetration of a chemical across the skin are concentration at the skin surface, the surface area exposed, and solubility of chemical in the skin. Solubility of chemical in the skin is affected by chemical characteristics, i.e., molecular weight and charge. The physical form of the chemical, i.e., liquid or vapor, will affect the concentration at the skin surface but should not affect the solubility of a chemical once it is in the skin unless the liquid physically or chemically alters the skin barrier. Temperature and relative humidity may affect blood flow to the skin, but with most organic chemicals which have good solubility in the blood, diffusion through the skin is the limiting factor rather than removal from the skin by the blood.

We previously developed a chamber system to investigate whole-body dermal vapor absorption in rats (McDougal *et al.*, 1985). In this system, masks provide respiratory protection and sampling ports facilitate blood sampling during a whole-body exposure to high vapor concentrations of volatile chemicals. The flux of chemical across the skin and permeability constants can be determined based on the concentrations of chemical in the blood during the exposures using an appropriate physiologically based pharmacokinetic (PB-PK) model to describe the distribution, metabolism, and elimination of the chemical which has penetrated the skin (McDougal et al., 1986). In this paper, we describe the transdermal kinetics of eight organic chemical vapors (styrene, *m*-xylene, toluene, perchloroethylene, benzene, halothane, hexane, and isoflurane) in rats and compare these estimated permeability constants with published information on penetration of chemical vapors in human volunteers.

MATERIALS AND METHODS

Animals Male Fischer-344 rats weighing 205 to 273 g used in these studies were obtained from Charles River Breeding Laboratories, Inc. (Wilmington, MA). They were housed three to a cage in a Bioclean laminar flow unit at 22°C and a relative humidity of between 40 and 60% with a 12-hr light/dark cycle starting at 0600.

Chemicals. Styrene (99.8% purity), *m*-xylene (99.8% purity), toluene (99.0% purity), benzene (99.0% purity), and hexane (99.0% purity) were obtained from Fisher Scientific Co. (Fair Lawn, NJ). Perchloroethylene (99+% punty) was obtained from Aldrich Chemical Co. (Milwaukee, WI). Halothane (99.9% purity) was obtained from Halocarbon Laboratories, Inc. (Hackensack, NJ). Isoflurane (99.5% punty) was obtained from Ohio Medical Anesthetics (Madison, WI).

Dermal vapor exposures Rats were exposed to volatile organic chemicals in a custom built chamber designed to allow controlled vapor exposures over the entire body surface of rats whose fur was closely clipped. Operation of this chamber, analytical procedures, and handling of the rats has been previously described (McDougal *et al.*, 1985). Briefly, rats were acclimated to a latex face mask by at least three 8-hr training periods. On the day before exposure, fur of the rats was carefully clipped, to avoid injury to the skin, with electric clippers and indwelling jugular cannulas were implanted under ketamine/xylazine anesthesia. Six rats were placed in the exposure chamber, provided with clean breathing air through the latex masks, and had blood samples (0.1 ml) drawn from cannulas routed to the exterior of the chamber during the 4-hr exposures. Concentration of the effluent air was monitored every 5 min by flame ionization detection on a gas chromatograph and was maintained at the desired concentration by manual operation of needle valves controlling airflow through the chemical bubbler.

Blood samples (0.1 ml) were drawn (after drawing and discarding 0.2 ml which is approximately twice the ca-

TABLE 1

PARAMETERS USED FOR THE ANALYSIS OF ORGANIC CHEMICALS IN BLOOD

Chemical	Blood extraction solvent (blood:solvent)	Oven temperature (°C)	GC detector
Styrene	Carbon disulfide (1:10)	150	Flame ionization
m-Xylene	Methylene chloride (1:1)	100	Flame ionization
Toluene	n-Hexane (1:1)	75	Flame ionization
Perchloroethylene	n-Hexane (1:10)	85	Electron capture
Benzene	m-Xylene (1:1)	70	Flame ionization
Halothane	n-Hexane (1:10)	80	Electron capture
Hexane	Benzene (1:1)	75	Flame ionization
Isoflurane	n-Hexane (1:10)	80	Electron capture

dead space) and total volume drawn was replaced 10% heparin-saline, via the indwelling jugular cannior to exposure and at 0.5, 1.0, 2.0, 3.0, and 4.0 er the start of exposure. These samples were ex- with either 0.1 or 1.0 ml of solvent (Table I). es of the extracts (1 μl) were analyzed with the apiate detector (Table 1) after injection on a 10-ft 10% on Chromosorb W-HP (80-100) in astainless-steel n at the temperature shown in Table 1. With perethylene the extraction efficiency from blood was nd the blood concentrations were corrected for ncy. Extraction efficiencies for the other chemicals essentially 100%.

permeability calculations. Organic vapor permewas analyzed by simulation with a physiologically pharmacokinetic model (Ramsey and Andersen,) with an added skin compartment (McDougal *et* 1986). Briefly, a mathematical description with five omical compartments, each having characteristic flow, volume, and partition coefficients, was used cribe the pharmacokinetics. Partition coefficients e 2) were measured by the vial equilibration od of Gargas (Gargas et *al.*, 1989). Metabolic constants (Table 3) were determined for most chemicals by gas uptake techniques. For modeling purposes, permeability constants were fit both visually and by statistical parameter estimation techniques with similar results. Visually determined permeability constants were used as a starting point for a statistical software program (SIMUSOLV, Dow Chemical Co., Midland, MI) which provided a maximum likelihood estimate of the skin permeability constant in the model by fitting model predictions of blood concentrations to experimental observations.

Human permeability calculations. The permeability constant (P) was calculated for each published human study according to

$$P = \frac{\text{ABS}}{\text{A,} \times C_s \times t}, \quad (1)$$

where ABS is the total absorbed in milligrams, A, is the surface area exposed in square centimeters, t is time in hours. and C_s is the exposure concentration in milligrams per cubic centimeter. The resulting permeability constant (cm/hr) is concentration independent, can easily be scaled for the exposed surface area, and can be compared

TABLE 2

PARTITION COEFFICIENTS USED IN THE PHYSIOLOGICAL MODEL[a]

Chemical	Blood/air	Fat/air	Muscle/air	Liver/air
Styrene	40.2	3476	46.7	140.7
m-Xylene	46.0	1859	41.9	92.0
Toluene	18.0	1021	27.7	82.8
Perchloroethylene	18.9	1638	20.0	69.9
Benzene	17.8	499	10.3	17.8
Halothane	5 3	182	4.5	7.6
Hexane	2.3	159	2 9	12.0
Isoflurane	1.8	98	1.6	4 1

[a] Partition coefficients from Gargas *et al* (1989).

TABLE 3

METABOLIC CONSTANTS USED IN THE PHYSIOLOGICAL MODEL

Chemical	V_{max} (mg/kg/hr)	K_m (mg/liter)	K_{fo} (kg^{-1} hr^{-1})
Styrene[a]	8.4	0.4	0.0
m-Xylene[b]	4.2	0.4	2.0
Toluene[c]	4.7	1.0	0.0
Perchloroethylene[c]	0.0	0.0	0.3
Benzene[c]	3.3	0.6	0.0
Halothane[d]	7.0	0.2	0.0
Hexane[c]	6.0	0.4	3.4
Isoflurane[c]	0.0	0.4	3.0

[a] Ramsey and Andersen, 1984.
[b] Sato and Nakajima, 1979.
[c] Gargas *et al.*, 1986.
[d] Gargas *et al.*, 1982.

with the estimated permeabilities determined in the rat exposures.

Uptake during mixed exposures. In an exposure where respiratory protection is not present, potential absorption of organic vapors could be both through the respiratory tract and through skin. The ratio of the body burden which would be due to dermal absorption during an exposure where the respiratory tract was not protected was calculated by the relationship

$$\text{skin uptake ratio} = \frac{PA_s}{PA_s + Q_p}, \qquad (2)$$

where Q_p is the alveolar ventilation rate (McDougal *et al.*, 1987). This ratio was calculated for a 210-g rat which has total surface area of 267 cm^2 and alveolar ventilation rate of 4.84 liters/hr. This ratio gives an indication of how much protection a respirator would provide in a mixed whole-body exposure. Clothing would be expected to provide some protection from vapor penetration through the skin.

RESULTS

Blood concentration profiles and permeability constants determined from them in these studies were qualitatively similar to those in our previous studies with dihalomethanes (McDougal *et al.*, 1985, 1986). Blood concentrations rose rapidly at first and then more slowly. This behavior was predicted from a permeability constant which did not change during the 4-hr exposure and reflects the process of distribution.

Organic Chemical Blood Concentrations

At a styrene exposure concentration of 3000 ppm (Fig. 1a), mean styrene blood concentrations in five rats (226 ± 5 grams) were about 3 μg/ml at ½ hr and rose steadily to reach about 10 μg/ml at 4 hr. This continued increase in blood styrene concentrations was the most pronounced of the chemicals studied and indicated that steady state was not reached during the exposure period.

Xylene blood concentrations in six rats (273 ± 3 g) also rose steadily during the first hr at an exposure concentration of 5000 ppm (Fig. 1b) and appeared to level off at around 10 μg/ml during the last 2 hr.

Toluene blood concentrations in six rats (216 ± 3 g) exposed to 8000 ppm rose steadily from about 3 μg/ml at ½ hr to 8 μg/ml at 4 hr (Fig. 1c).

At a perchloroethylene exposure concentration of 12,500 ppm (Fig. 1d), mean blood concentrations in four rats (233 ± 4 g) ranged from 10 μg/ml at ½ hr to 30 μg/ml at 4 hr.

Benzene blood concentrations at 4000 ppm exposure concentration were 8 μg/ml at ½ hr and rose slowly to 11 μg/ml during the remainder of the exposure (Fig. 1e) in five rats (232 ± 2 g).

Halothane blood concentrations at 500 ppm in four rats (230 ± 4 g) were 1.6 μg/ml at ½ hr and about 3.5 μg/ml at 2 hr and remained there until 4 hr (Fig. 1f).

At 60,000 ppm hexane (Fig. 1g), blood concentrations ranged from 0.5 to 0.8 μg/ml in five rats (231 ± 6 g). This was approximately the minimum detectable level of the hexane assay and the data showed considerably more scatter than with the other chemicals.

Mean blood concentrations in six rats (2 ± 4 g) after exposure to 50,000 ppm isoflurane reached 1.8 μg/ml at 2 and 3 hr and dropped slightly at 4 hr (Fig. 1h).

Although there was considerable variation in data with these eight chemicals, blood co

centrations from individual rats, for most chemicals, tracked very consistently throughout the entire exposure. This indicates that variability was probably due to individual rat differences rather than analytical variability.

Dermal Penetration Measurements

Calculated flux (Table 4) was greatest for the perchloroethylene exposure and lowest for the hexane exposure. Estimated permeability constants ranged from 1.75 cm/hr for styrene to 0.026 cm/hr for isoflurane. Simulated blood concentrations based on estimated permeability constants and the measured blood concentrations are shown in Figs. 1a–1h. The percentage of chemical which would be absorbed due to dermal absorption in a mixed dermal and inhalation exposure in rats was determined to be less than 10% in the chemicals studied (Table 4).

DISCUSSION

The permeability constants for this set of organic chemicals generally decrease as solubility in fat decreases (Table 2) showing the expected relationship to lipid solubility (r^2 = 0.958). Styrene, with fat solubility more than 35 times greater than that of hexane, has a permeability constant approximately 67 times greater. Solubility in muscle tissue also decreases as the permeability constant decreases (r^2 = 0.827). Skin partition coefficients would be expected to be the best predictor of the permeability constant; however, due to the difficulty of homogenizing skin, we have been unable to measure reliable skin partition coefficients.

Determination of these permeability constants extends the range of values we previously reported for dibromomethane (1.32 cm/hr), bromochloromethane (0.79 cm/hr), and dichloromethane (0.28 cm/hr) in rats (McDougal *et al.*, 1986). The permeability values for the dihalomethanes were shown to be consistent over a three order of magnitude range of exposure concentrations; therefore, only one exposure concentration was examined in these studies. Our experience suggests that permeability constants are not dose dependent with vapor studies. Dose-dependent permeability constants may result when liquid is in contact with the skin at high concentrations.

Quantitative information on organic vapor exposures in volunteers is minimal (Table 5). For comparison with our rat data, permeabilities (P) have been calculated for these chemicals by using Eq. (1), where the estimate of the total amount of chemical absorbed was that reported in the human study and A_s was estimated to be 19,000 cm^2. The calculated human permeability values in this table are based on a wide variety of experimental methods used to determine the amount of chemical absorbed and the individual studies contain very few subjects.

Wieczorek (1985) studied styrene absorption through the skin at two exposure concentrations 3250 mg/m^3 (one volunteer) and 1370 mg/m^3 (three volunteers). Volunteers, clothed only in shorts, were placed in a chamber maintained at 23–25°C and 33–36% relative humidity wearing respirators connected to fresh breathing air outside the chamber during a 2-hr exposure. Urine was collected half-way through the exposure and at intervals of several hours for 24 hr after exposure. Wieczorek estimated the amount of styrene absorbed to be 175 mg in one subject at the high concentration and an average of 45 mg in the subjects exposed to the low concentration using

$$Y = 0.64X + 4.8, \qquad (3)$$

where Y is the excretion of mandelic and phenylglyoxylic acids in 24 hr and X is the dose absorbed as determined from inhalation studies. Riihimaki and Pfaffli (1978) exposed two volunteers wearing respirators for respiratory protection and thin pajamas and socks to 600 ppm styrene vapor for 3.5 hr. Once an hour the subjects cycled on a bicycle ergometer at 100 W for 10 min and were sedentary for the remainder of the hour. Venous blood and exhaled air samples were taken four

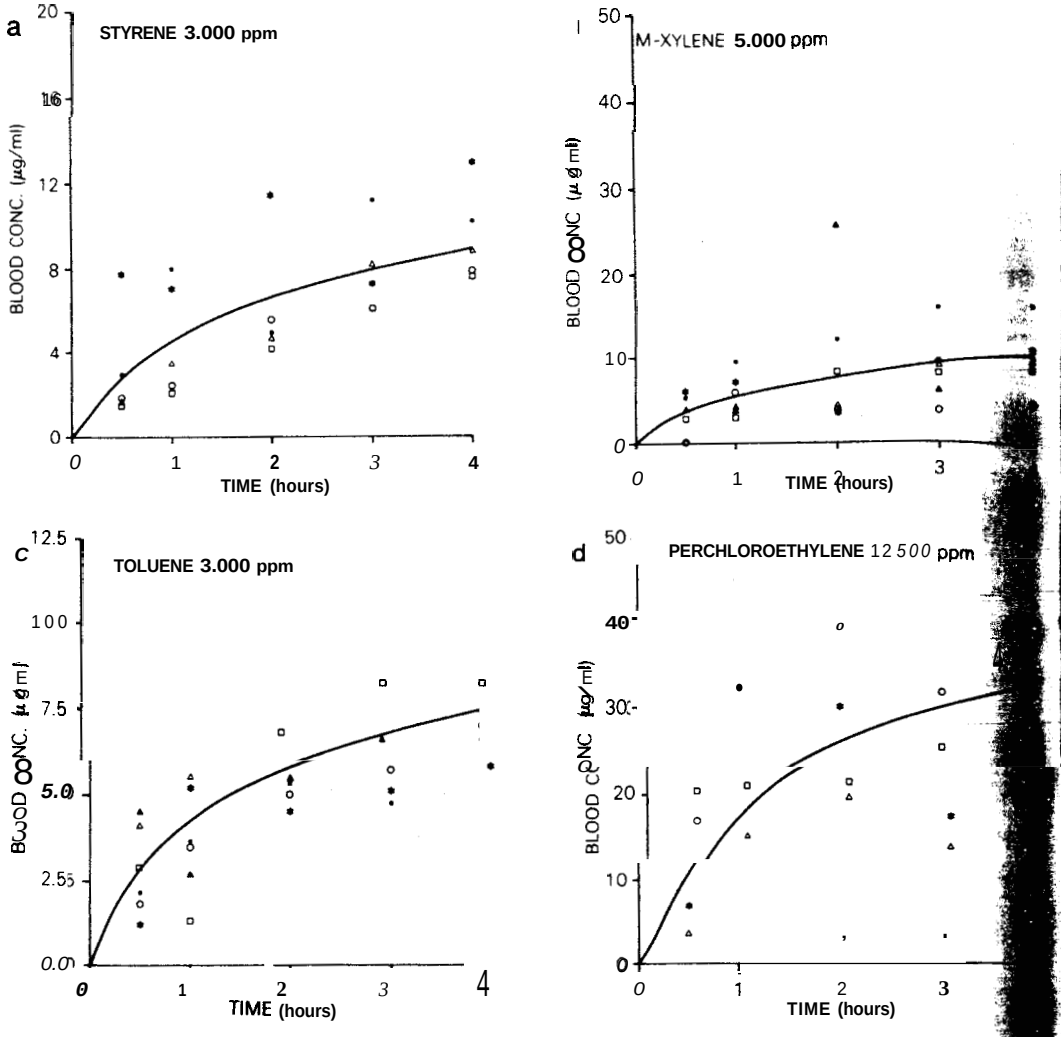

FIG. 1. Fits of simulated blood concentrations using optimized permeability constants to experimental blood concentrations (various symbols) during 4-hr exposures to styrene ($n = 5$) (a), *m*-xylene ($n = 6$) (b), toluene ($n = 6$) (c), perchloroethylene ($n = 4$) (d), benzene ($n = 5$) (e), halothane ($n = 4$) (f), hexane ($n = 4$) (g), and isoflurane ($n = 6$) (h). Exposure concentrations and blood collections are described under Materials and Methods and Results. In each graph the solid line is the best-fit curve for the entire data set.

times during the exposure and four times postexposure. Postexposure urine samples were collected for 24 hr. They estimated that 60.1 mg of styrene was absorbed during the experiment. Giving equal weight to the three studies with styrene indicate a human permeability constant of approximately 0.9 cm/hr.

Riihimaki and Pfaffli (1978) exposed two volunteers to 300 and three volunteers to 600 ppm *m*-xylene using the same experimental design as with styrene. On the basis of urinary metabolite and expired air concentrations they calculated that 20.8 and 44.5 g, respectively, were absorbed during the 3.5-hr exposures. Permeability constants calculated from these amounts absorbed averaged 0.6 cm/hr.

Riihimaki and Pfaffli (1978) also exposed volunteers to toluene using the same experimental design as with styrene. They estimated

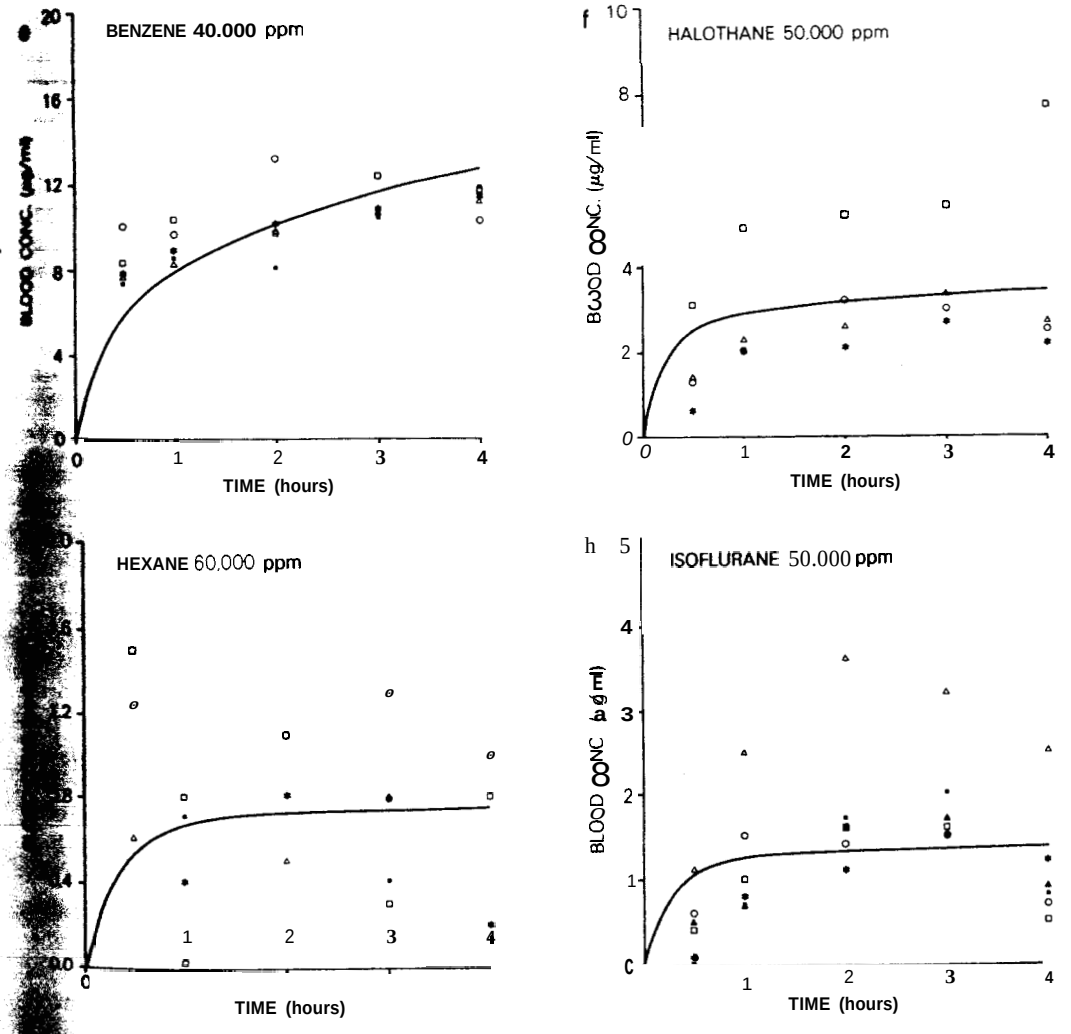

FIG. 1—*Continued*

mg was absorbed during the exposure on the basis of exhaled breath concentrations of toluene, assuming that 16% of the absorbed toluene was exhaled. From their data we calculate a permeability constant of 0.18 cm/hr.

In vapor penetration studies with perchloroethylene (Riihimaki and Pfaffli, 1978) 47.1 mg was absorbed during the exposure, which gives a permeability constant of 0.17 cm/hr.

Hanke and co-workers (1961) exposed two nude volunteers (provided with fresh breathing air through a mask) to 1 mg/liter of benzene vapor for 7 hr and collected urine for 24 hr following exposure. On the basis of the amount of phenol recovered from the urine, they estimated that approximately 10 mg of benzene was absorbed because 30% of the benzene absorbed is excreted as phenol in addition to the physiological amount of phenol which is normally in urine. The calculated human permeability constant in these exposures is 0.08 cm/hr.

Absorption of aniline vapor through the skin was studied in an unspecified number of volunteers (Dutkiewicz and Piotrowski, 1961) who were placed in a chamber maintained at a minimum 25°C and at least 35% relative humidity by determining the amount of *p*-

TABLE 4

DERMAL VAPOR ABSORPTION MEASUREMENTS AND CALCULATIONS[a]

Chemical	Concentration (ppm)	Flux (mg/cm²/hr)	Permeability constant[b] (cm/hr)	Skin uptake in a exposure (%)
Styrene	3,000	0.0211	1.753 ± 0.105	9.4
m-Xylene	5,000	0.0151	0.723 ± 0.003	3.9
Toluene	8,000	0.0206	0.721 ± 0.007	3.7
Perchloroethylene	12,500	0.0541	0.668 ± 0.080	3.5
Benzene	40,000	0.0191	0.152 ± 0.006	0.8
Halothane	50,000	0.0180	0.045 ± 0.005	0.2
Hexane	60,000	0.0065	0.031 ± 0.004	0.1
Isoflurane	50,000	0.0096	0.025 ± 0.004	0.1

[a] Rats with closely clipped fur received whole-body exposures to vapor in the presence of respiratory prote described under Materials and Methods. Flux, permeability, and skin uptake were calculated as describe Materials and Methods.

[b] Permeabilities are expressed as means ± SD, which are calculated by the estimization program. These are not a measure of the variability in the rat population, but reflect the confidence that could be placed on t value for permeability.

aminophenol excreted in the urine for 24 hr after exposure. The amount of aniline vapor absorbed through the skin was suggested to be comparable to the amount which would be absorbed through the respiratory tract in a situation where an individual could be exposed by both routes. The authors reported fluxes, based on exhaled air samples and urinary metabolites (Table 5). The permeability constant calculated on the basis of these fluxes ranged from 0.02 to 0.04 cm/hr.

Of the chemicals which have been studied in humans, methyl chloroform (1,1,1-trichloroethane) was the least permeable. Riihimaki and Pfaffli (1978) reported that 2.1 mg was absorbed in their study with two volunteers exposed to 600 ppm, on the basis of the assumption that 99% of the absorbed methylchloroform is exhaled. The calculated permeability constant was 0.01 cm/hr.

There is good agreement of the relative ranking with chemicals, which were done in both rats and humans. Generally, our experiments show that the permeability constant for each chemical in rats is from two to four times greater than the human permeability constants calculated from the literature data (Table 5). The apparent greater permeability in rats could have at least two explanations. First, rat skin may be more permeable been suggested in comparisons betwe and human skin. Tregear (1964) foun ethylene bromide, paraoxon, and thio lic acid permeability constants for exci skin were approximately twice the perm ity constants for excised human skin naugh and co-workers (1982) found, *in* that rat skin was three times more perm to urea than human skin was, but that ability was about the same for acetylsa acid, and less than human skin for b acid. Wester and Maibach (1983) re that the percentage of testosterone d sorbed, *in vivo,* was 3.6 times greater than humans. Second, experimental ences may also account for differences i etration, e.g., Riihimaki and Pfaffli cl their volunteers with thin pajamas w could have afforded some protection a styrene, xylene, toluene, perchloroeth and methyl chloroform vapor penetr This may be the reason that permeab calculated from Riihimaki and Pfaffli's with styrene are lower than those calc from the studies of Wieczorek (Table 5).

Our study demonstrates that deter tion of rates of penetration of organic v in rats using these methods correlates wi

TABLE 5

CALCULATED HUMAN PERMEABILITY CONSTANTS[a]

Chemical	C_s (mg/cm^3)	t (hr)	ABS (mg)	Flux (mg/cm/hr)	P (cm/hr)
yrene[b]	2.55×10^{-3}	3.5	60.1		0.35
yrene[c]	3.25×10^{-3}	2.0	175.0		1.42
yrene[c]	1.37×10^{-3}	2.0	45.0		0.87
-Xylene[b]	1.30×10^{-3}	3.5	20.8		0.24
-Xylene[b]	2.61×10^{-3}	3.5	44.5		0.26
luene[b]	2.26×10^{-3}	3.5	26.4		0.18
chloroethylene[b]	4.07×10^{-3}	3.5	47.1		0.17
zene[d]	1.00×10^{-3}	7.0	10.0		0.08
line[e]	5.00×10^{-3}	6.0		1.90×10^{-4}	0.04
line[e]	1.00×10^{-2}	6.0		2.50×10^{-4}	0.03
line[e]	2.00×10^{-2}	6.0		4.00×10^{-4}	0.02
hyl chlor[b]	3.27×10^{-3}	3.5	2.1		0.01

[a] Calculated according to Eq. (1) in text.
[b] Riihimaki and Pfaffli, 1978.
[c] Wieczorek, 1985.
[d] Hanke *et al.*, 1961.
[e] Dutkiewicz and Piotrowski, 1961.

imental values obtained in humans and t differences in permeability may be due recognized differences in skin structure. cause the rat permeability constant is her than that of humans, vapor penetra- n data from rats provide a conservative es- nate of the risk to humans exposed to vapor orption via the skin route. Ideally, we uld be able to examine physiological ferences in skin from different species (i.e., ckness, partition coefficients, capillary nsity, and hair follicle density and depth in ratum corneum, epidermal layers, etc.) and trapolate permeability constants from one ecies to another on the basis of those ferences. Styrene inhalation exposures in dents were used to extrapolate in inhala- ion exposures in humans with very good re- lts (Ramsey and Andersen, 1984). Our ethod currently suggests a means to esti- nate human vapor penetration for occupa- ional chemicals which could not be ethically vesti gated in human volunteers. Quantita- ion of the dermal route of absorption in the esence of respiratory protection also pro- ides information about the proportion of chemical absorption which is due to dermal uptake in whole-body exposures.

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