

Percutaneous absorption of solvent vapors in man

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RIIHIMÄKI, V. and PFÄFFLI, P. Percutaneous absorption of solvent vapors in man. *Scand. j. work environ. & health* 4 (1978) 73—85. It is known from industrial experience and experimental studies that percutaneous absorption of concentrated liquid solvents may be considerable and even hazardous if large enough areas of skin are exposed for long periods of time. Percutaneous penetration of xylene, styrene, toluene, 1,1,1-trichloroethane and tetrachloroethylene vapors at ambient air concentrations of 600 ppm for 3.5 h was studied in a dynamic exposure chamber with a restricted number of human volunteers. Although the small number of exposed persons precluded conclusive quantitation of absorption and valid intercompound comparisons, aromatic solvents and tetrachloroethylene appear to penetrate skin much more readily than 1,1,1-trichloroethane. Skin penetrating properties of solvents seem, under the circumstances, to be associated primarily with lipid solubility. It was approximated that percutaneous exposure (total body surface) to 600 ppm of xylene vapor for 3.5 h corresponded to an equally long inhalation exposure of less than 10 ppm. Similar percutaneous exposure to 1,1,1-trichloroethane corresponded to an inhalation exposure of only 0.6 ppm. Disease-affected skin may display altered permeability characteristics, and one volunteer with atopic dermatitis exhibited a more than three times larger absorption of xylene vapor when compared to subjects with normal skin. It may be concluded that in the work environment percutaneous absorption of solvent vapors from the surrounding air through undamaged skin is likely to be insignificant.

Key words: human exposure, m-xylene, percutaneous absorption, styrene, tetrachloroethylene, toluene, 1,1,1-trichloroethane, vapor.

In recent years a number of comprehensive reviews on the percutaneous absorption of drugs and chemicals have been published (3, 11, 18, 24, 26, 27). Interest has primarily been focused on the absorption of topically applied compounds in variable concentrations and media (solvents, vehicles) or on absorption after immersion of the skin in concentrated liquids. Few data are available for the assessment of the practical significance of percutaneous absorption of chemicals in vapor or gas form.

In the occupational environment skin is exposed most of the time to small or moderate vapor concentrations in the surrounding air; it much less frequently comes in direct contact with the volatile compounds in liquid form. We therefore wanted to investigate the percutaneous penetration of moderate vapor concentration of some common industrial solvents through human skin in vivo under conditions that would enhance percutaneous absorption.

The penetration of some liquid solvents through human skin has been studied in vivo, e.g., that of chlorinated hydrocarbons (23), 1,1,1-trichloroethane (10), ethylbenzene (4), and the common aromatics toluene, styrene and xylene (5, 7). The penetration of pure liquid solvents has, in many cases,

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proved to be considerable. Percutaneous absorption during and after the immersion of both hands in xylene for 15 min was roughly the same as pulmonary absorption during exposure to a concentration of 100 ppm in the inhaled air for an equally long period (7). For 1,1,1-trichloroethane percutaneous absorption was estimated to be approximately ten times less under rather similar conditions (10).

Permanent gases like carbon dioxide, oxygen, nitrogen and helium penetrate the skin at a rate of 0.1–1.0 μ mole per square centimeter per hour. Diffusion of these gases within the skin is rapid, but the rate of penetration is limited by the modest solubility in the stratum corneum and the low molecular concentrations. Thus the total quantity of material transported is not greater for gases than for pure liquids or dilute aqueous solutions (18).

In studies on the percutaneous absorption of water and water vapor, water has been found to be absorbed from the surrounding liquid water at a rate of 11 μ mole per square centimeter per hour, and water vapor, at a high relative humidity, had approximately the same permeability constant and therefore an equally effective absorption (18).

Alcohol and alkane hydrocarbon vapors are frequently very soluble and produce high surface concentrations in the stratum corneum, but their diffusion constants are small when compared to those of permanent gases. The skin penetration rates of alcohol and hydrocarbon vapors on one hand and permanent gases on the other have been judged not to be very different, however (18).

SUBJECTS

The study was performed with 10 healthy male volunteers, aged 20–35 years, who were employees of the laboratory or other departments of our institute. Each subject gave his informed consent and, prior to the study, underwent a routine medical examination with essentially no abnormal findings.

The status of the skin was carefully examined and was found to be free of

Table 1. Anthropometric measures of the volunteers who participated in the exposures.

Subject	Height (cm)	Weight (kg)	Skin surface area (m ²)
Y.P.	167	59	1.66
V.R.	180	70	1.83
H.H.	170	76	1.87
P.K.	173	72	1.85
J.J.	182	85	2.06
K.A.	189	90	2.17
A.Z.	180	80	1.99
J.P.	174	57	1.68
S.L.	172	64.5	1.76
L.S.	176	73	1.88

cuts, abrasions and other disorders in all but one subject. This person (J.J.) had had atopic dermatitis from childhood, and, although the condition was under control with the occasional application of local steroids, the skin was found to be thickened with some abrasions due to scratching. The greatest changes were observed in the upper extremities and the face. He, unlike all the others, also had a small Van Dyke beard which was restricted to the tip of the lower jaw.

All the volunteers except two (those exposed to styrene) were nonsmokers, and their body constitutions were roughly similar. Their anthropometric measures are given in table 1.

The subjects were exposed two or three at a time in each experiment.

EXPOSURE

The exposures were conducted in a 15 m³ dynamic exposure chamber in which the air was changed ten times per hour. Solvent vapor was produced with a saturator and diluted with carrier air to create the desired atmosphere. The chamber concentration was continuously monitored by an infrared analyzer (Miran I A, Wilks Scientific Corporation, U.S.A.) and automatically controlled by an Eurotherm 070 (Eurotherm Ltd., England) industrial processor. The concentration was maintained within 5 % of the desired value. The temperature was kept at $25 \pm 1^\circ\text{C}$, and the relative humidity at $50 \pm 10\%$.

The subjects were exposed with respiratory protection for 3.5 h to 300 and 600 ppm of m-xylene (laboratory grade, Merck, FRG) and to 600 ppm of each of the following: styrene (commercial styrene obtained from a local polystyrene manufacturer, Stymer Ltd., and found to be 99.9 % pure), toluene (laboratory grade, Merck, FRG), 1,1,1-trichloroethane (laboratory grade, Fluka, Switzerland) and tetrachloroethylene (commercial grade, Kymi-Kymmene Ltd., Finland, found to be more than 99 % pure) in the ambient air. In two experiments, also 3.5 h in duration, the subjects were exposed without respiratory protection to 20 ppm of xylene and 10 ppm of styrene, respectively.

In order to prevent pulmonary absorption of the solvent vapors, the volunteers wore full facepiece respirators (Dräger, supplied air) which were adjusted to operate on overpressure that allowed air to flow continuously into the mask with full inflow on demand. We continuously monitored the efficiency of the protection provided by the respirator by recording the slightest sense of smell the subjects had of the solvents. Furthermore, on two occasions a subject wearing a fullbody rubber suit and the respirator proved that only trace amounts of solvents were absorbed into the body.

To keep the skin practically unprotected, the subjects wore pyjamas made of thin cloth and socks.

An outline of the skin exposure experiments is presented in fig. 1. Once during each full hour of exposure (at midhour) the volunteers cycled on a bicycle ergometer (Monark, Sweden) at 100 W for 10

min; they remained sedentary the rest of the time. This exercise was sufficient to make the skin perspire for approximately 15 min. Breast skin temperature varied between 29 and 30.5°C and was temporarily raised during the exercise by 0.5°C. The periodic exercise was employed to simulate work conditions in which hydration of the skin from sweating and fairly high skin temperatures enhance percutaneous absorption (18).

In the two inhalation exposures the subjects were sedentary throughout the experiment.

METHODS

Collection of samples

Venous blood samples were collected through a teflon catheter (Stille Tefnyl 55 × 1.45 mm) inserted into a large vein in the left arm. No tourniquet was applied during the sample taking.

Exhaled air samples were collected in 250-ml polyester-lined polyethylene bags. The subjects exhaled as totally as possible through the bag, in which the last part of the forced expiration (alveolar air) remained for analysis.

Postexposure urine samples were collected at freely chosen intervals for 24 h.

Analysis of samples

The *venous blood samples* were analyzed with gas chromatography (GLC) by the head space method (16). One milliliter of blood was used for each assay. The sample was incubated at 60°C for 30 min prior to the analysis. External standards were prepared in mixed human blood. The analytical details are presented in table 2. The coefficient of variation of the standard assays for each compound was smaller than ± 6 % at a concentration level of 1 μ mole/dl.

The *exhaled air samples* were analyzed with GLC using a gas sampling loop of 10 ml in volume. External vapor standards were prepared in polyester-lined polyethyl-

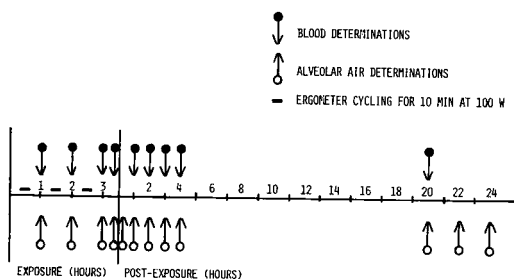


Fig. 1. General outline of the experimental program.

Table 2. Details of the gas chromatographic analyses with a Hewlett Packard 5750 G (HP) and a Perkin Elmer F 11 (PE) apparatus.

Solvent	Apparatus	Column no. ^a	Column temperature	Detector ^b
M-xylene				
Air	PE	1	140°C	FID
	HP	4	60°C	FID
Blood	PE	1	140°C	FID
Urine	HP	2	190°C	FID
Toluene				
Air	HP	1	80°C	FID
Blood	PE	3	80°C	FID
Styrene				
Air	PE	4	80°C	FID
	HP	1	130°C	FID
Blood	PE	4	80°C	FID
	PE	1	80°C	FID
Urine	HP	2	190°C	FID
1,1,1-Trichloroethane				
Air	HP	3	60°C	ECD, pulse 5
Blood	PE	3	50°C	ECD, pulse 5
Tetrachloroethylene				
Air	HP	3	80°C	ECD, pulse 5
Blood	HP	3	80°C	ECD, pulse 5

^a 1 = Carbowax 20 M, 10 % on Chromosorb P 80/100 mesh, 2 m Ø 3 mm, glas; 2 = OV 17, 10 % on Varaport 30 80/100 mesh, 2 m Ø 3 mm, glas; 3 = Squalan, 10 % on Chromosorb WAW 80/100 mesh, 1.5 Ø 3 mm, glas; and 4 = Se 30, 4 % Chromosorb WAW 80/100 mesh, 1.5 m Ø 3 mm, glas.

^b FID = flame ionization detector with nitrogen carrier, 20–25 ml/min; ECD = electron capture detector with argon-methane (5 %) carrier, 20 ml/min.

ene bags of 5 l in volume. The analytical details are presented in table 2. The coefficient of variation of the standard assays for each compound was smaller than $\pm 5\%$ at a concentration level of 0.01 $\mu\text{mole/dl}$.

The urine samples were analyzed for methylhippuric acid according to the method of Engström et al. (6), for mandelic acid according to the procedure of Engström and Rantanen (8), and for phenylglyoxylic acid with the latter method after reduction to mandelic acid. As a small modification, silyl BSTFA (Pierce Chemical Corp., U.S.A.) was used to improve separation and to reduce detector contamination. The external standards were prepared in mixed human urine. The analytical details are presented in table 2. The coefficient of variation of standard assays was $\pm 7\%$ for methylhippuric acid at a concentration

level of 50 mg/l and $\pm 3\%$ for mandelic acid and phenylglyoxylic acid at a concentration level of 100 mg/l.

Calculation of excretion in exhaled air and urine

The elimination of the solvents in exhaled air and the excretion of their metabolites in urine were followed for at least 24 h. During this time the concentrations of the urinary metabolites, as a rule, approached the limits of sensitivity of the methods applied. Similarly, the concentrations of the solvents in exhaled air and blood were generally too small for reliable analysis the next morning (approximately 20 h after the termination of exposure), with tetrachloroethylene as a distinct exception. Using this evidence as a basis, we approximated that (excluding tetrachloro-

ethylene) the urinary metabolites and exhaled solvents measured within 24 h after exposure represent the largest part of the quantity actually absorbed. Total metabolite excretion in the urine was summated from individual samples over 24 h. The total excretion of xylene, styrene, toluene and 1,1,1-trichloroethane in the exhaled air was estimated on the assumption that the quantitatively significant expiration followed a two-phase elimination curve with a rapid half-time of 1 h during the first two postexposure hours and a slower one of 10 h thereafter (figs. 2, 3, 4). Tetrachloroethylene exhalation displayed three apparent half-times: 1 h (first 2 h of postexposure), 6 h (3–8 h of postexposure) and 72 h (after 8 h) (fig. 5).

The sum of the quantities exhaled in the different phases was calculated according to Sherwood's equation (20):

$$Q = \frac{R_1 - R_2}{\lambda_1} + \frac{R_2 - R_3}{\lambda_2} + \frac{R_3}{\lambda_3}, \quad (1)$$

where R_1 is the initial elimination rate ($\mu\text{mole/h}$); R_2 is the rate at the end of the first phase and at the beginning of

the second; R_3 is the rate at the end of the second phase and at the beginning of the third; and λ_1 , λ_2 , λ_3 are elimination constants calculated from the formula

$$T_{1/2} = \frac{0.693}{\lambda}.$$

For two half-times equation 1 is reduced to

$$Q = \frac{R_1 - R_2}{\lambda_1} + \frac{R_2}{\lambda_2}. \quad (2)$$

Exhalation of the solvents was monitored via forced end-expiration (alveolar air) samples. Average tidal air will, in the elimination phase, exhibit considerably smaller concentrations than alveolar air due to the diluting effect of pulmonary dead space. The alveolar air concentrations were reduced by a factor of 1.5 so that the approximate tidal air concentrations could be obtained in analogy with Sherwood's findings on benzene (20). An average ventilation of 10 l/min was postulated for all subjects over the whole postexposure period.

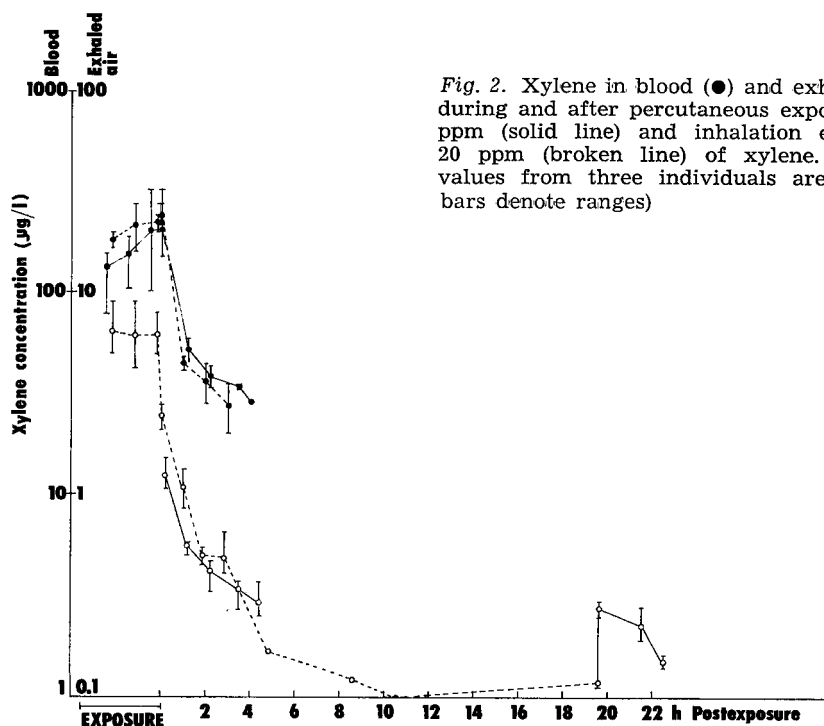


Fig. 2. Xylene in blood (●) and exhaled air (○) during and after percutaneous exposure to 600 ppm (solid line) and inhalation exposure to 20 ppm (broken line) of xylene. (Means of values from three individuals are presented; bars denote ranges)

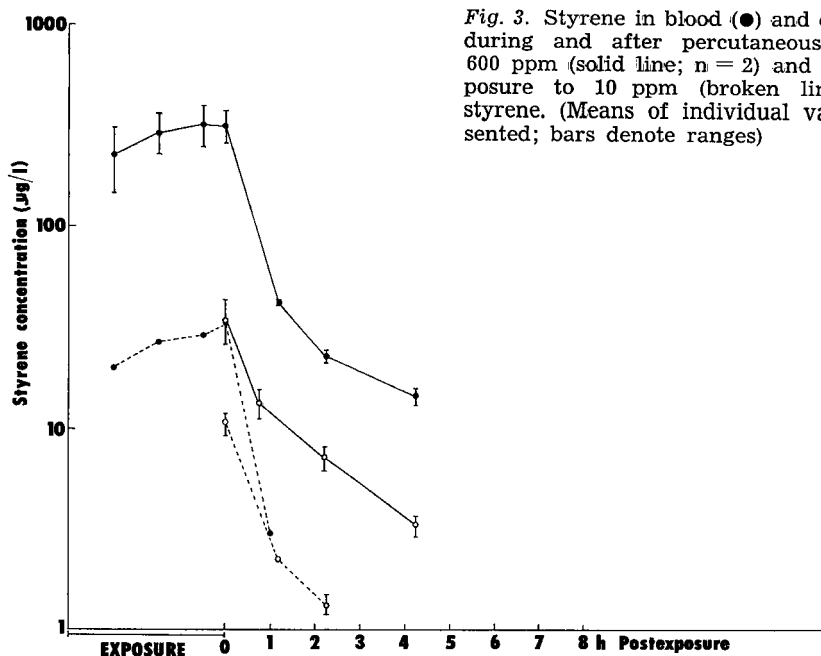


Fig. 3. Styrene in blood (●) and exhaled air (○) during and after percutaneous exposure to 600 ppm (solid line; n = 2) and inhalation exposure to 10 ppm (broken line; n = 3) of styrene. (Means of individual values are presented; bars denote ranges)

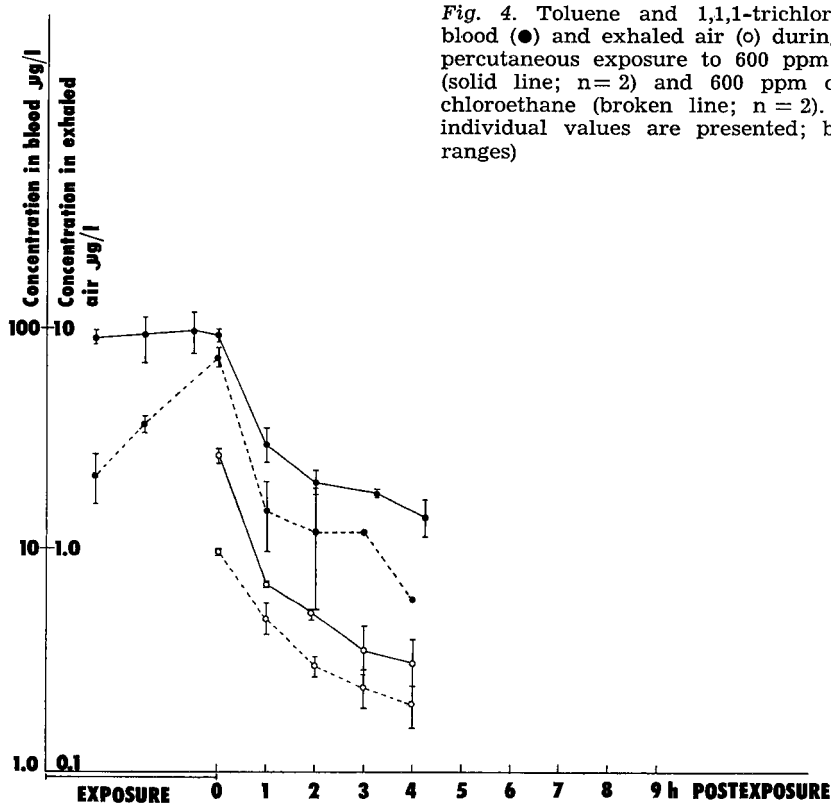


Fig. 4. Toluene and 1,1,1-trichloroethane in blood (●) and exhaled air (○) during and after percutaneous exposure to 600 ppm of toluene (solid line; n = 2) and 600 ppm of 1,1,1-trichloroethane (broken line; n = 2). (Means of individual values are presented; bars denote ranges)

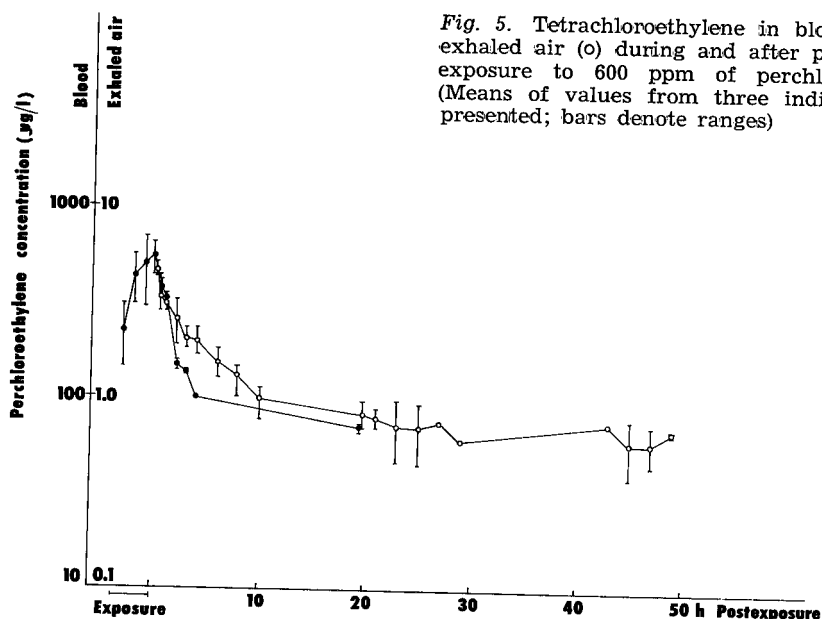


Fig. 5. Tetrachloroethylene in blood (●) and exhaled air (○) during and after percutaneous exposure to 600 ppm of perchloroethylene. (Means of values from three individuals are presented; bars denote ranges)

Theoretical calculation of pulmonary absorption

For the comparison of percutaneous absorption with postulated absorption via the respiratory tract at the same concentration, the following approximations were made in the computation of theoretical pulmonary uptake: (a) experimental subjects ventilate at 10 l/min (light work); (b) the average pulmonary retention of xylene, styrene and toluene is 60 % (1); and (c) the average pulmonary retention of 1,1,1-trichloroethane is 40 % (2), and that of tetrachloroethylene 50 % (9). Uptake was calculated as the product of (inhaled air concentration — exhaled air concentration) x ventilation x length of exposure.

It must be admitted that the retained fractions computed for chlorinated hydrocarbons, in particular, are to some extent uncertain. The authors referred to have actually measured alveolar air concentrations from which tidal air concentrations can only be approximated by multiplication with a factor of 1.5. Changes of uptake during a period of time are not considered; retention represents the average over the whole (theoretical) exposure period. It can be expected that retention is largest for aromatic solvents which display good solubility in the blood and tissues and exten-

sive metabolic turnover in contrast to modestly soluble and nonmetabolized 1,1,1-trichloroethane.

RESULTS

Compiled data on the percutaneous absorption of xylene, styrene, toluene, 1,1,1-trichloroethane and tetrachloroethane vapors are presented in table 3. During exposure to moderate concentrations (300 and 600 ppm) percutaneous penetration corresponds to approximately 0.1 to 2 % of the amount estimated to be absorbed from the respiratory tract. There seems to be a clear difference in the penetrating efficiency of 1,1,1-trichloroethane and the other solvents studied.

Kinetics of xylene

The kinetics of xylene was studied in percutaneous exposure to 300 and 600 ppm and in inhalation exposure to 20 ppm, which was estimated to be nearly equivalent in terms of absorbed dose (table 4). The proportional excretion of xylene in exhaled air and methylhippuric acid in the urine were very similar in all exposures, and percutaneous absorption appeared to be directly dependent on concen-

Table 3. Comparative presentation of the kinetic features observed and estimated after percutaneous exposure of human volunteers to some aromatic and chlorinated aliphatic solvent vapors. (Means and ranges of individual values are given)

Exposure	a Urinary metabolite (s) (μ mole)	b Expired (μ mole)	a + b = c Calculated percutaneous absorption (μ mole)	$\frac{a}{c}$ %	$\frac{b}{c}$ %	d Estimated ^a pulmonary absorption (μ mole)	$\frac{c}{d}$ %
Xylene (300 ppm), n = 2	173.0 (163.8—182.3)	22.7 (20.1—25.2)	195.7 (183.9—207.5)	88.4	11.6	15 489	1.3
Xylene (600 ppm), n = 3	390.6 (333.4—461.3)	28.5 (24.0—32.1)	419.1 (357.4—493.4)	93.2	6.8	30 978	1.4
Styrene (600 ppm), n = 2	521.3 (444.7—597.9)	54.8 (44.7—64.8)	576.1 (489.4—662.7)	90.5	9.5	30 490	1.9
Toluene (600 ppm), n = 2		45.9 (37.9—53.9)	286.9 ^b		16.0 ^b	30 772	0.9
1,1,1-Trichloro- ethane (600 ppm), n = 2		15.7 (14.5—16.9)	15.9 ^c		99.0 ^c	20 399	0.08
Tetrachloroethylene (600 ppm), n = 3		281.2 (231.7—325.8)	286.9 ^d		98.0 ^d	25 451	1.1

^a Estimation based on the assumption that the retention of xylene, styrene and toluene is 60 %; that of 1,1,1-trichloroethane 40 %; and that of tetrachloroethylene 50 %.

^b Based on the assumption that 16 % of the absorbed toluene is exhaled.

^c Based on the assumption that 99 % of the absorbed 1,1,1-trichloroethane is exhaled.

^d Based on the assumption that 98 % of the absorbed tetrachloroethylene is exhaled.

Table 4. Kinetics of xylene in human volunteers after percutaneous (300 and 600 ppm in ambient air) and pulmonary exposure (20 ppm). (Means and ranges of individual values are given)

Xylene exposure	a Urinary methylhippuric acid (μ mole)	b Expired xylene (μ mole)	a + b = c Calculated absorption (μ mole)	$\frac{a}{c}$ %	$\frac{b}{c}$ %	d Estimated pulmonary absorption (μ mole)	$\frac{c}{d}$ %
<i>Percutaneous</i>							
300 ppm, n = 2	173.0 (163.8—182.3)	22.7 (20.1—25.2)	195.7 (183.9—207.5)	88.4	11.6	15 489	1.3
600 ppm, n = 3	390.6 (333.4—461.3)	28.5 (24.0—32.1)	419.1 (357.4—493.4)	93.2	6.8	30 978	1.4
<i>Inhalation</i>							
20 ppm, n = 3	318.8 (261.6—406.9)	38.4 (36.1—40.8)	357.2 (297.7—447.7)	89.2	10.8	619.6 ^a	57.7

^a Sedentary volunteers ventilated at an approximate rate of 7 l/min; 60 % retention assumed.

tration. It must be noted, however, that (in inhalation exposure to 20 ppm) only 58 % of the estimated absorbed dose was detected in the expired air or in the form of a urinary metabolite within approximately 24 h. Interindividual variability in the results was also quite marked.

Urinary excretion of methylhippuric acid (figs. 6, 7) indicates a basically similar course of excretion after percutaneous and inhalation exposure. A closer examination suggests that in the context of percutaneous absorption excretion is delayed and prolonged by some 2—4 h.

Kinetics of styrene

The kinetics of styrene was studied in percutaneous exposure to 600 ppm and in inhalation exposure to 10 ppm. Elimination via exhaled air and urine is similar in percutaneous and inhalation exposures (table 5). The two metabolites of styrene, mandelic acid and phenylglyoxylic acid, are excreted in equal proportions (approximately 1:1) in both types of exposure (table 6). Likewise, cumulative urinary excretion of mandelic acid and phenylglyoxylic acid does not remarkably differ in the two exposure types, but, again, there is a suggestion of slightly delayed excretion (fig. 8).

DISCUSSION

The main objective of the study, estimation of total percutaneously absorbed solvent vapor, is, inherent of the *in vivo* ap-

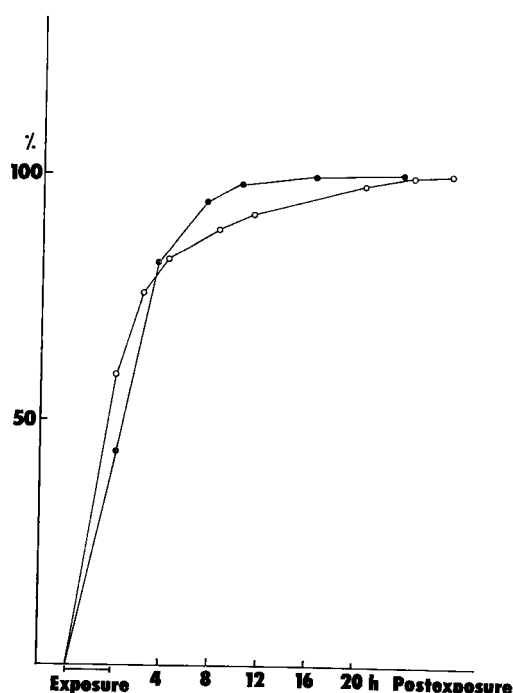


Fig. 7. Cumulative urinary excretion of methylhippuric acid after percutaneous exposure to 600 ppm of xylene (—●—) and inhalation exposure to 20 ppm of xylene (—○—).

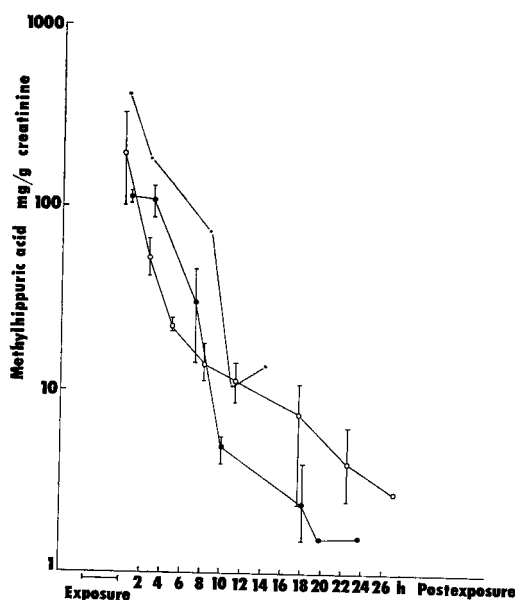


Fig. 6. Urinary excretion of methylhippuric acid after percutaneous exposure to 600 ppm of xylene [—●— (n = 3); —*— (individual with atopic dermatitis)] and inhalation exposure to 20 ppm of xylene [—○— (n = 3)]. (Means of individual values are presented; bars denote ranges)

proach chosen, vulnerable to errors if elimination is not accurately and completely monitored. Crucial in this context is the slow elimination of a compound from bodily stores in analytical threshold concentrations for a long period of time. The application of two standard half-times (1 h and 10 h) for the expiratory elimination of all aromatics and 1,1,1-trichloroethane was based on experimental findings, but it is not necessarily correct. After a large inhalation exposure to xylene, urinary methylhippuric acid excretion exhibits a long "tail" with a half-time of approximately 24 h (19). Against this background the measured total urinary excretion of methylhippuric acid, which extended for 24 h in this study, is likely to underestimate the actual excretion. The overall error, even if on the order of 50 % ("recovery" in the inhalation exposure to 20 ppm of xylene was about 60 %), will not change the results fundamentally, however.

Table 5. Kinetics of styrene in human volunteers after percutaneous (600 ppm in ambient air) and pulmonary exposure (10 ppm). (Means and ranges of individual values are given)

Styrene exposure	a Urinary metabolites (μ mole)	b Expired (μ mole)	a + b = c Calculated absorption (μ mole)	$\frac{a}{c}$ %	$\frac{b}{c}$ %	d Estimated pulmonary absorption (μ mole)	$\frac{c}{d}$ %
<i>Percutaneous</i>							
600 ppm, n = 2	521.3 (444.7—597.9)	54.8 (44.7—64.8)	576.1 (489.4—662.7)	90.5	9.5	30 490	1.9
<i>Inhalation</i>							
10 ppm, n = 3	275.4 (162.6—419.6)	12.7 (11.7—14.1)	288.1 (174.3—433.7)	95.6	4.4	355.7 ^a	81.0

^a Sedentary volunteers ventilated at an approximate rate of 7 l/min; 60 % retention assumed.

Another source of systematic error might be insufficient respiratory protection during the intended percutaneous exposures. Leakage was not subjectively observed, and tests with di-octyl phthalate aerosol under very similar conditions have shown that, when a full facepiece respirator operates on overpressure, even bearded persons with extremely poor face seals exhibit an inward leakage rate of 0.001 % or less (22). Only one of our volunteers had a small Van Dyke beard, which has been shown to impair the face seal slightly in a full facepiece mask (15).

The study was performed with only a few volunteers per compound, and inter-individual variability was frequently considerable. The restricted number of subjects does not permit conclusive quantitative estimations of percutaneous penetration rates, nor valid intercompound

comparisons. However, we can approximate that the percutaneous penetration rate of 600 ppm of xylene vapor is on the order of 0.006 μ mole per square centimeter per hour (total skin area of subjects having been about 19,000 cm²). Liquid xylene has been shown to penetrate the skin of hands at a rate of 1.13 μ mole per square centimeter per hour (2 μ g per square centimeter per minute) (7), and this rate indicates that, when a nearly 1,700-fold difference in concentration is allowed for, xylene vapor displays a ten times more efficient penetration than concentrated liquid xylene.

In fact, this figure is likely to be an underestimation because regional differences in skin permeability (hands are relatively more permeable) are not taken into account. It is not uncommon, either, that concentrated liquids display impaired

Table 6. Metabolism of styrene to mandelic acid and phenylglyoxylic acid in volunteers after percutaneous and pulmonary exposure to styrene vapor. (Means and ranges of individual values are given)

Styrene exposure	a Mandelic acid in urine (μ mole)	b Phenylglyoxylic acid in urine (μ mole)	a + b (μ mole)	$\frac{a}{b}$
<i>Percutaneous</i>				
600 ppm, n = 2	262.1 (206.4—317.9)	259.2 (238.3—280.0)	521.3 (444.7—597.9)	1.0
<i>Inhalation</i>				
10 ppm, n = 3	142.6 (82.0—199.4)	132.8 (76.6—220.2)	275.4 (162.6—419.6)	1.1

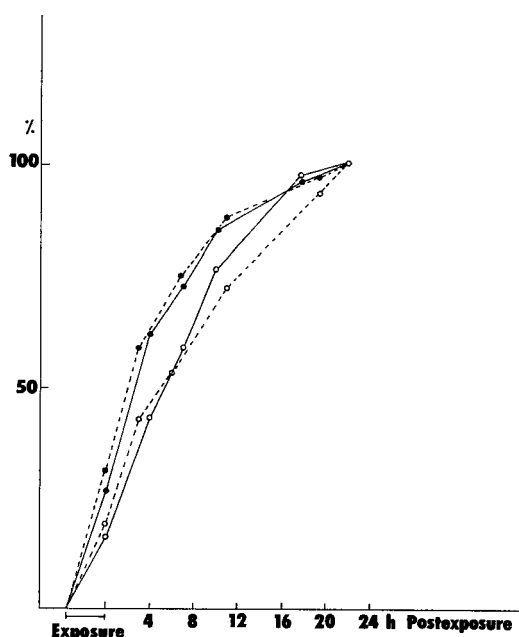


Fig. 8. Cumulative urinary excretion of mandelic acid (●) and phenylglyoxylic acid (○) after percutaneous exposure to 600 ppm of styrene (solid line) and inhalation exposure to 10 ppm of styrene (broken line).

permeability due to, e.g., their dehydrating effect on the stratum corneum (18). On the other hand, percutaneous penetration was enhanced in our study by a rather high skin temperature and repeated sweating.

Permeability constants of gases are considerably larger than respective values for the same penetrants in a solution phase. For instance, the permeability constant of water vapor in small concentrations is approximately 50,000 times greater than that of liquid water. Yet, saturated water vapor displays nearly the same constant as liquid water (18). Absorption rates per unit area of skin are not very different for the same penetrant in gas, vapor and liquid (solution) form because molecular concentrations of gases and vapors are generally much smaller.

Typical for the penetration of gases and vapors is the shorter lag period than that of the penetration of compounds from solution (18). A delay of several minutes was observed in the percutaneous absorp-

tion of liquid toluene (13) and xylene (7) in humans. We did not measure the rapidity with which the examined compounds entered systemic circulation, but the course of events in venous blood was observed at hourly intervals. The buildup of blood concentration had almost reached a steady-state level for xylene (fig. 2), styrene (fig. 3) and toluene (fig. 4) within 1 h, and the blood concentration curves of xylene and styrene ran nearly parallel in the percutaneous and (equivalent) inhalation exposures. The blood concentration of 1,1,1-trichloroethane behaves quite differently, and there is a steady and quantitatively marked increase up to the end of percutaneous exposure (fig. 4). In inhalation exposure blood concentrations of 1,1,1-trichloroethane have been shown to rise rapidly and attain a steady level soon (2, own unpublished observations). The tetrachloroethylene concentration in blood seems to combine features from both of the other types already mentioned (fig. 5). Although xylene vapor obviously penetrates the skin quite rapidly, the observation of delayed methylhippuric acid excretion after percutaneous exposure (fig. 6) would indicate that there is a further release of the compound from skin for some hours after the termination of exposure. The blood concentration of xylene also declines more slowly after percutaneous exposure than after inhalation exposure (fig. 2). A similar phenomenon of continued absorption of xylene from skin up to 5 h into the postexposure period was detected in hand immersion studies (7).

The observation that only small amounts of 1,1,1-trichloroethane was detected in postexposure expiration, as well as the comparatively slow percutaneous absorption of 1,1,1-trichloroethane, suggests that this compound is an inferior penetrant in comparison to aromatic solvents and even tetrachloroethylene. This assumption is to some extent supported by Fukabori's studies with liquid 1,1,1-trichloroethane (10). He observed that the immersion of both hands of volunteers into the liquid 11 times for 10 min at a time over the workday resulted in an absorption that corresponded roughly to 2 h of inhalation at 10–20 ppm. Stewart and Dodd, on the other hand, have previously estimated

that the immersion of both hands in 1,1,1-trichloroethane would correspond to an equally long inhalation exposure of 100 to 500 ppm (23). In close agreement with our observation on the quantity of percutaneously absorbed 1,1,1-trichloroethane vapor is a recent report on the percutaneous absorption of vinyl chloride vapor in rhesus monkeys (14).

The barrier for percutaneous penetration is formed by the stratum corneum, which is physicochemically composed of a lipid network and polar regions. Therefore, hydrated stratum corneum has an affinity to both lipid-soluble and polar compounds. Lipid solubility and solubility in the stratum corneum are considered crucial determinants in percutaneous absorption if the penetrant is not in a solute-solvent system (18). Our suggestive findings of intercompound differences in percutaneous absorption would conform to this principle. The aromatic solvents styrene, xylene and toluene (in that order) are remarkably lipid soluble (17, 21, 25), and they also exhibit polar characteristics. Tetrachloroethylene is supposedly quite lipid soluble because, although its solubility in water is poor, it is soluble in blood (25) and its elimination half-time is exceptionally long. On the other hand, 1,1,1-trichloroethane displays poor blood and water solubility (25), and hence, although exact information is lacking, it supposedly has only modest lipid solubility. Vinyl chloride is poorly lipid soluble (21).

It was previously observed that initially symptomfree atopic skin allowed a three times greater penetration of xylene when compared to normal skin during and after a 15-min immersion of both hands in the liquid (7). Very little is known about changes in the permeability characteristics of disease-affected skin. It would be understandable that acutely inflamed or injured skin may, in the relative absence of stratum corneum, provide little resistance against penetration, but also chronic inflammation, as in psoriasis and eczema, is likely to produce inferior stratum corneum that manifests in increased transepidermal water loss (12). We had an opportunity to expose a volunteer who was suffering from atopic dermatitis to 600 ppm of xylene. During the exposure he displayed approximately two times higher blood concentra-

tions than the other three exposed subjects and his postexposure urinary concentrations of methylhippuric acid were similarly increased (fig. 6). His incomplete 14-h urinary excretion of methylhippuric acid was more than three times larger than the corresponding average excretion of the other subjects.

Percutaneous absorption of solvents may prove hazardous in the work environment if toxic compounds, like carbon tetrachloride, in the form of concentrated liquids come into contact with more extensive skin areas for long periods of time. Although a large skin surface, the area depending on the protective clothing used, is more often exposed to small or moderate vapor concentrations of solvents in the ambient air, this type of exposure is not likely to result in any significant absorption.

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