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Percutaneous absorption of m-xylene from a mixture of m-xylene and isobutyl alcohol in man

by VESA RIIHIMÄKI, M.D., M.Sc.¹

RIIHIMÄKI, V. Percutaneous absorption of m-xylene from a mixture of m-xylene and isobutyl alcohol in man. *Scand. j. work environ. & health* 5 (1979) 143—150. Xylene is a common solvent and thinner in paints and varnishes, and it is frequently accompanied by other types of solvents, for instance, isobutyl alcohol. Percutaneous absorption of xylene was studied under conditions in which both hands were immersed once for 15 min in pure m-xylene, in a mixture of equal parts of m-xylene and isobutanol, and in a 1:1 mixture of m-xylene and isobutanol saturated with water. Estimates for absorption were derived from the postexposure urinary and pulmonary excretion of xylene. Immersion of the hands in a mixture of equal parts of xylene and isobutanol saturated with water showed a nearly identical percutaneous absorption of xylene when compared to corresponding exposure to pure xylene. The rate of absorption was on the order of 20 nmol per square centimeter per minute. In a similar exposure to equal parts of xylene and isobutanol without water the total absorption of xylene was 50 % smaller than during the other types of exposure and the absorption seemed to be delayed. This phenomenon was probably associated with the conspicuous dehydration of the skin elicited by isobutanol. In work involving exposure to xylene and isobutanol, the latter is likely to dehydrate the skin and decrease the percutaneous absorption of both components initially, but after repeated exposures skin irritation may be enhanced and the permeability characteristics of the stratum corneum may be altered and possibly result in greater absorption.

Key words: human exposure, isobutyl alcohol, m-xylene, percutaneous absorption.

The possibility that exposing chemicals may be absorbed into the body through the skin has been the object of increasing interest in recent years. Industrial accidents have occurred in which percutaneously absorbed phenolic substances and aromatic amine and nitro compounds (2,

4), as well as a great many pesticides (1, 12, 13), caused systemic poisonings. Even if percutaneous absorption is of smaller magnitude, or the compound absorbed of less acute toxicity, percutaneous exposure may be of great practical significance. Illustrative examples are skin-penetrating, potent, aromatic amine carcinogens for which, due to their low vapor pressure, the percutaneous route may be the predominant portal of entry into the body in the occupational environment (15). Similarly, a risk to health was thought to arise from the percutaneous absorption

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of the flame retardant tris(2,3-dibromopropyl)-phosphate, a mutagen, from children's sleepwear (3).

Previously, penetration of an aromatic industrial solvent, m-xylene, both in the form of a concentrated liquid and a vapor, through the human skin has been investigated in this laboratory (10, 17). It was shown that pure m-xylene penetrated the skin of the hand at a rate of approximately 19 nmol per square centimeter per minute ($2 \mu\text{g}/\text{cm}^2$ per min) (10), and a later study verified this finding (14). A comparative study suggested that other common aromatic solvents, i.e., toluene and styrene, as well as a representative of chlorinated aliphatic hydrocarbons, tetrachloroethylene, penetrated the human skin in corresponding vapor concentrations at relatively similar rates as m-xylene (17). These rates of absorption are not likely to allow for hazardous quantities to be absorbed through the normal skin, but penetration may be greatly increased in cases of skin disease and skin injury (16, 17). Some solvents are known to penetrate the skin more readily. Examples are skin damaging compounds such as methanol, acetone, ether, hexane, and mixed solvents like chloroform-methanol and ether-ethanol (18). Also dichloromethane (methylenechloride) (22) and methyl n-butyl ketone (6), which leave the skin penetration barrier fairly intact, appear to be absorbed efficiently.

Xylene is a common component of paints and varnishes, but it seldom occurs alone. It is frequently accompanied with alcohols, ketones, and esters. A combination of xylene and isobutyl alcohol is one of the more common paint thinners in this country. Because painters handle these mixtures, it was of interest to investigate the percutaneous absorption of m-xylene from a 1:1 mixture (v/v) with isobutanol.

SUBJECTS

The study was performed with 12 healthy male volunteers, aged 20–36 years. Each subject gave his informed consent and

was clinically examined prior to the study. Special emphasis was placed on a thorough examination of the skin of the exposed hands, which had to be free of any signs of physical injury or dermatitis. None of the subjects had a history of recurring skin disease. Most (10 of the 12) of the study persons had also participated in a previously reported investigation (10), and the geometrically measured exposed area of their hands varied from 807 to 1,028 cm^2 . The corresponding measures for the two additional persons fell within this range. Although the subjects were different sizes, they were all lean and roughly of the same bodily constitution.

EXPOSURE

The volunteers kept both their hands immersed up to the wrists in the solvents for 15 min at room temperature. The solvents were in a vat placed in a fume cupboard, and the subjects sat in front of the cupboard wearing a face mask equipped with an activated charcoal filter to prevent inhalation of the compounds. For practical reasons the same volunteers took part in several experiments within a minimum time interval of one week. Ten different subjects exposed their hands to pure m-xylene (laboratory grade, Merck, Darmstadt, Federal Republic of Germany) (exposure to X), five subjects, one of them three times and another two times, exposed their hands to a 1:1 (v/v) mixture of m-xylene and isobutanol (both laboratory grade, Merck, Darmstadt, Federal Republic of Germany) (exposure to XI), and the same five subjects, one four times and two others two times, exposed their hands to a 1:1 (v/v) mixture of m-xylene and isobutanol saturated with water (60 ml of water was added to 400 ml of isobutanol and thoroughly mixed on the day before exposure) (exposure to XIW). Altogether, 10 experiments in exposure to X, 8 experiments in exposure to XI, and 10 experiments in exposure to XIW were carried out. Two of the subjects participating in exposures to XI and XIW took

part in exposure to X also. Exposure to X has been earlier reported in full (10).

After exposure to X the hands were rinsed with ethanol and thereafter washed thoroughly with soap and water. After exposures to XI and XIW the hands were first let to dry in the fume cupboard and then thoroughly washed with soap and water.

If the few subjects overrepresented in exposures to XI and XIW had been significantly different in skin penetration from the other group members, these series of experiments would have been difficult to compare with those of exposure to X, which was carried out on 10 different individuals. It was found, however, that this was not the case. The overrepresented individuals exhibited absorption which fell rather evenly within the overall range of variation.

METHODS

Collection of samples

Exhaled air (end-expired air) samples were collected in 250-ml polyester-lined polyethylene bags at specified time intervals over 5–6 postexposure hours (fig. 1) and analyzed immediately. The sample taking has been described in detail elsewhere (10).

Urine was voided at specified time intervals (fig. 2) and collected in full over a 22-h postexposure period. The samples were kept a few hours at +5°C and then at –20°C until analyzed.

Analysis of samples

The content of m-xylene in the exhaled air was analyzed with gas chromatography as described previously (17). Urine samples were analyzed for methylhippuric acid (total toluic acid after alkaline hydrolysis) according to the method of Engström et al. (9).

Statistical treatment

The 22-h cumulative urinary excretion of methylhippuric acid and the concentration of m-xylene in end-expired air in the three exposure types were tested for differences with the Wilcoxon test for independent series.

RESULTS

The appearance and sensations of the skin, inspected by the investigator and assessed subjectively by the volunteers during and after the exposures, varied for the three different exposure types (table 1). The most noticeable differences occurred between exposure to xylene-isobutanol (XI) and the other two exposures — xylene (X) and xylene-isobutanol-water (XIW). Exposure to XI clearly dehydrated the skin and the skin became grossly wrinkled. The XIW mixture also seemed to dry the skin somewhat more than pure m-xylene, but the difference in skin appearance between these two exposures was small. Immersion of the hands in X and XIW resulted in erythema (red skin color due to vasodilatation) after a few minutes and a burning sensation which at times was quite intense. In contrast, immersion of the hands in XI caused only a mild and sometimes barely distinguishable erythema or a burning feeling.

The cumulative 22-h urinary excretion of methylhippuric acid was about the same after exposure to X (median 212.3 μmol) and XIW (median 229.7 μmol) but significantly less after exposure to XI (median 92.5 μmol) (table 2). Similar differences were also found in the excretion rates of methylhippuric acid in urine after the respective exposures (fig. 1). A graphic presentation of the cumulative urinary excretion of methylhippuric acid illustrates the similarities between exposure to X and XIW and points out the delayed excretion of methylhippuric acid after exposure to XI (fig. 2).

The concentration of m-xylene in end-expired air in the postexposure period also indicates the overall similarities between

Table 1. Appearance and sensations of the skin during and after exposure.

Exposure	Erythema and burning sensation	Dehydration (wrinkled skin)	Other observations
Xylene	Erythema and a burning feeling of fluctuating intensity appeared after a few minutes of exposure; symptoms lasted up to 30–60 min after exposure	No wrinkles or feeling of "tightness" but skin felt dry	Scaling of exposed skin on the day after exposure
Xylene-isobutanol 1:1 (v/v)	Only mild burning after 5–10 min of exposure and erythema hardly noticeable; few symptoms immediately after exposure	Strong wrinkling and skin felt tight and very dry	Fluctuating itching of skin, increased by washing of hands, for several hours after exposure; reticular or punctate reddening at the dorsum of the hands (it subsided overnight); scaling of skin more intense than in other types of exposure
Xylene-isobutanol + water 1:1 (v/v) (60 ml of water in 400 ml of isobutanol)	As for xylene (above); a short period of increased burning occurred when the hands were washed immediately after exposure	Mild wrinkling noticeable at times; skin felt dry and oily	Scaling of exposed skin on the day after exposure

Table 2. Urinary excretion of methylhippuric acid over 22 postexposure hours. Median values and ranges (in parentheses) are given.

Exposure	Excretion of methylhippuric acid (μ mol)	
Xylene (10 experiments)	(a)	212.3 (144.7–341.4)
Xylene-isobutanol 1:1 (v/v) (8 experiments)	(b)	92.5 (28.1–216.0)
Xylene-isobutanol + water 1:1 (v/v) (10 experiments)	(c)	229.7 (89.2–353.0)

Tests for difference

a vs. b: $p < 0.05$ (Wilcoxon, 2-tailed).
c vs. b: $p < 0.005$ (Wilcoxon, 2-tailed).
a vs. c: not significant ($p > 0.05$) (Wilcoxon, 2-tailed).

exposures to X and XIW, while exposure to XI seems to result in a different pattern of excretion in exhaled air (fig. 3). Immediately after the termination of the exposures the m-xylene concentration in

end-expired air was significantly different for the three different exposure types; later in the course of excretion the differences did not reach statistical significance. After the completion of exposure to X, the concentration of m-xylene in the expiratory air was highest and had already reached the peak value. There seemed to be a slight delay in m-xylene excretion in connection with exposure to XIW, but after 20 min the excretion conformed to that of exposure to X, and there was a steady decline in the xylene concentration of exhaled air with time. The excretion of m-xylene in exhaled air after exposure to XI was at first clearly less than after the other exposures, but the excretion continued at approximately the same level up to 4 h after the exposure and only then started to decline. Therefore the areas under the end-expired air xylene concentration time curves of the three exposure types are roughly the same. If it is assumed that the mean pulmonary ventilation over the whole 22-h postexposure period was 10 l/min, that the xylene concentration in end-expired air declines at the same mo-

Fig. 1. Excretion rate (mean + SD) of methylhippuric acid in urine after percutaneous exposure to pure m-xylene (●.....●, 10 experiments), to a mixture of equal parts of m-xylene and isobutanol (◆-----◆, 8 experiments) and to a mixture of equal parts of m-xylene and isobutanol saturated with water (▲——▲, 10 experiments).

Fig. 2. Cumulative urinary excretion of methylhippuric acid after percutaneous exposure to pure m-xylene (●.....●), to a mixture of equal parts of m-xylene and isobutanol (◆-----◆) and to a mixture of equal parts of m-xylene and isobutanol saturated with water (▲——▲).

Fig. 3. Concentration (mean + SD) of m-xylene in end-expiratory air after percutaneous exposure to pure m-xylene (●.....●, 10 experiments), to a mixture of equal parts of m-xylene and isobutanol (◆-----◆, 8 experiments) and to a mixture of equal parts of m-xylene and isobutanol saturated with water (▲——▲, 10 experiments). Numbers in parentheses denote the actual number of observations if the collection of samples was incomplete.

noexponential rate as between the first 4 and 5 h following exposure, and that the relationship between the xylene concentration in tidal air and end-expiratory air sampled with this method is 0.7–1.0 (V. Riihimäki, unpublished results), the excretion of xylene in exhaled air can be approximated to be 5–15 % of that excreted (as methylhippuric acid) into the urine.

DISCUSSION

Percutaneous penetration of chemicals takes place via passive diffusion, mainly through the stratum corneum (18). The rate of steady-state absorption is often directly proportional to the concentration of the applied compound; thus Fick's law is obeyed (19). This phenomenon is particularly true of dilute solutions, while the same principle cannot be applied directly to concentrated and pure liquid systems (19). Therefore, it cannot be stated with confidence that a significantly (twofold) greater rate of xylene absorption can be expected from pure liquid xylene as compared to a 50 % xylene solution. The present results show that there is no difference in the total xylene absorption from a 50 % solution with isobutanol saturated with water than from pure liquid xylene. On the other hand, it was shown that the absorption of xylene from a 1:1 mixture of xylene and isobutanol without water was only about half of that from pure xylene. In this case, however, the kinetics of xylene absorption, as seen from the time course of the urinary methylhippuric acid excretion (fig. 2) and xylene expiration (fig. 3), point to impaired and delayed penetration. A plausible explanation for this phenomenon is skin dehydration by isobutanol. Pure higher alcohols are known to be absorbed less efficiently due to the dehydration and compaction of the stratum corneum elicited by them (18).

A solvent may greatly influence the percutaneous penetration of the solute by means of favoring the distribution of the

solute to the skin (and not to the solvent medium). In fact, an efficient penetration of a lipid-soluble compound is guaranteed only when the vehicle is polar (18). A solvent could also damage the skin penetration barrier and by this mechanism enhance the absorption of the solute. The present results preclude the possibility that isobutanol, even in a saturated water solution, would greatly enhance the percutaneous penetration of high concentrations of xylene. At the most a two times greater absorption from a xylene-isobutanol-water mixture could be suggested if Fick's law is applied to these concentrated liquids. Even this level is unlikely because the 50 % smaller xylene absorption from a xylene-isobutanol mixture without water displayed an abnormally slow penetration of the compound.

Single immersion of the hands in xylene or xylene-isobutanol mixtures caused little apparent damage to the skin, and this result agrees with previous reports indicating that most hydrocarbon solvents, including higher alcohols, do not injure the skin penetration barrier (18, 19). The exposed skin was soon reddened and felt a burning sensation, but the symptoms generally subsided within an hour after exposure. On the next day scaling of the top layers of the stratum corneum indicated that the permeability barrier had been slightly affected, probably due to the extraction of lipids. Xylene causes vasodilatation and increases capillary permeability in experimental animals due to the release of histamine and 5-hydroxytryptamine (5), an effect common to many other solvents, too, but not representative of higher alcohols such as isopropanol (21).

The biological responses to the three different exposures employed in the present study were consistent with the kinetic differences. Erythema and a burning sensation were the most pronounced and were nearly identical during the exposures to X and XIW, which were accompanied with greater and more rapid percutaneous absorption. In exposure to XI the immediate histamine-like symptoms were slight, but for several hours into the post-exposure period washing of the hands or rubbing of the dorsum of a hand caused increased itching, and localized red maculae developed which did not disappear

until the next day. These symptoms could have resulted from the gradual and protracted absorption of xylene through the stratum corneum that was illustrated by the course of events in xylene expiration. It might be thought that xylene-induced vasodilatation could enhance the transport of the compound into systemic circulation once it has passed the skin permeability barrier, the stratum corneum, and via maintenance of a greater concentration gradient this phenomenon could increase the rate of percutaneous absorption. Studies with experimental animals have shown, however, that the clearance of intradermally injected ^{24}Na is not increased in xylene-induced erythema (5).

In exposure to a mixture of m-xylene and isobutanol, isobutanol is likely to be absorbed at a somewhat smaller rate than m-xylene. This concept is based on the finding that a close analogue, n-butanol, is absorbed from pure liquid at a rate of about 11 nmol/cm^2 per minute (18). It is of interest then to consider whether the present estimations of xylene absorption, derived from urinary and pulmonary excretion, could have been influenced by kinetic interactions between the two solvents. Such an interaction could be possible because xylene is biotransformed after initial microsomal oxidation via alcohol and aldehyde dehydrogenases in the cytoplasm (11). Although little information is available, isobutanol was thought to be metabolized primarily via similar enzyme systems (23). These results, however, point to essentially identical kinetics for m-xylene after percutaneous absorption from a pure liquid and from a mixture also containing isobutanol and water. Kinetic differences were notable only in the case of exposure to xylene-isobutanol without water. It can be postulated that even if kinetic interactions between m-xylene and isobutanol were possible, the likelihood that they would play a significant role in this investigation is reduced by the small and presumably rather similar doses of the two compounds absorbed. There is no information available on the capacity of the skin to metabolize m-xylene. There have been reports that the overall metabolism of ethylbenzene and styrene are different in percutaneous as compared to pulmonary

absorption (7, 8). This investigation and previous ones (10, 17) do not suggest that the metabolic fate of percutaneously absorbed xylene, on the basis of, e.g., pulmonary and urinary excretion ratios, is materially different from that of xylene absorbed via the lungs (20).

In conclusion, single immersion of the hands in a 1:1 mixture of xylene and isobutanol saturated with water resulted in almost identical percutaneous absorption of xylene as corresponding immersion in pure xylene; furthermore the gross appearance and sensations of the skin during and after the two types of exposure were similar. In contrast, exposure to equal parts of xylene and isobutanol without water caused a conspicuous dehydration of the skin and, probably by this mechanism, impaired the percutaneous absorption of xylene. In this instance the immediate symptoms were fewer but more severe signs, such as scaling of the keratinous layer, appeared a day later. During the handling of paints and varnishes containing mixtures of xylene and isobutanol, isobutanol is likely to dehydrate the skin and to decrease the absorption of both components initially. After repeated exposure, however, cutaneous dehydration and removal of fat may cause greater irritation and enhance skin fatigue. In such an instance the permeability characteristics of the stratum corneum may be significantly altered and greater absorption may occur.

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