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Distribution of m-xylene to subcutaneous adipose tissue in short-term experimental human exposure

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ENGSTRÖM, J. and RIIHIMÄKI, V. Distribution of m-xylene to subcutaneous adipose tissue in short-term experimental human exposure. *Scand. j. work environ. & health* 5 (1979) 126—134. When volunteers were exposed in three different patterns of exposure to approximately 3.7—8.2 $\mu\text{mol/l}$ (90—200 ppm, constant or time-weighted average concentration) of m-xylene for five consecutive days plus one day after the weekend, approximately 3.7—8.0 % of the total body uptake was estimated to be distributed to the adipose tissue on the basis of m-xylene determinations made from subcutaneous fat. Distribution seemed to be affected by the exposure pattern; a proportionately greater distribution to subcutaneous fat occurred when the volunteers performed physical exercise part of the time, particularly when the peak xylene concentrations in the air coincided with the exercise. The median elimination half-time of m-xylene from subcutaneous fat was 58 h (range 25—128 h). A positive correlation was found between the individual elimination half-times of m-xylene in subcutaneous fat and the relative fat mass of the individuals in two exposure groups, but not in one.

Key words: human exposure, m-xylene, subcutaneous adipose tissue.

Adipose tissue has become the object of increasing interest as an indicator of exposure to fat-soluble environmental contaminants. Of special importance from the point of view of environmental safety is the storage and cumulation in fat of highly lipid-soluble compounds that are resistant to biodegradation, such com-

pounds as DDT and halogenated biphenyls (6).

Industrial solvents possess differing characteristics of lipid solubility and biodegradation. Recent investigations have shown that occupational exposure to styrene is accompanied by a rather modest styrene load in subcutaneous fat (9, 21). Styrene is quite lipid-soluble with a fat/air distribution coefficient on the order of 4,000 (16), but it is effectively and rapidly biotransformed (3). This phenomenon counteracts its storage and cumulation. In volunteers exposed to styrene during work at different intensities for short 2-h periods, approximately 8 % of the styrene uptake was estimated to have been distributed to the fatty tissue, with a half-time in the subcutaneous fat of 48—96 h (11).

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Similar studies with mixed xylenes indicated an approximately 5 % distribution to body fat (10).

Xylene is almost as equally soluble in lipids as styrene; it has a fat/air distribution coefficient of 3,600 (19). In inhalation exposures to m-xylene at moderate concentrations (4.1–8.2 $\mu\text{mol/l}$, 100–200 ppm), uptake is nearly constant (60 %) at different degrees of physical exercise over the full length of a normal workday (1, 18, unpublished results of Riihimäki et al). In the postexposure period the m-xylene concentration in the blood declines rapidly to barely detectable levels by the next morning (1). Urinary excretion of the only major metabolite, methylhippuric acid, is also rapid, and after an 8-h exposure about 90 % of the absorbed amount is eliminated in the urine within 32 h (20). Thus the biotransformation of m-xylene is efficient and roughly corresponds to that of styrene.

In our present study we wanted to in-

vestigate the kinetics of m-xylene in the subcutaneous fat of volunteers after several daily repetitive exposures. In addition, it was of interest to determine how different exposure patterns constituting stable and periodically varying m-xylene concentrations in inhaled air and different levels of physical exercise affected the distribution of the compound in subcutaneous fat.

MATERIAL AND METHODS

Subjects

The subjects were 18 healthy male volunteers, 18–35 years of age. Their anthropometric characteristics are shown in table 1. Routine clinical examinations of the

Table 1. Some individual characteristics and study findings of the subjects.

Subject	Age (years)	Skin surface area (m^2)	W Weight (kg)	F Fat mass (kg)	$\frac{F}{W} \times 100$	Ventilation at basal conditions (table values) (l/min)	Ventilation at 100-W exercise (in the laboratory) (l/min)	m-Xylene concentration in fat at termination of exposure ($\mu\text{mol/kg}$)	Half-time of m-xylene in fat (h)
<i>Exposure I</i>									
H.R.	26	1.99	78	11.9	15.3	7.2	38	149	64
P.K.	23	2.09	80	5.9	7.4	7.5	40	87	28
E.M.	26	1.91	75	12.0	16.0	6.9	38	185	50
H.L.	23	2.10	82	8.2	10.0	7.6	38	196	45
<i>Exposure II</i>									
M.N. ^a	18	1.81	71	14.3	20.1	6.5	38	231	48
J.P.	22	1.67	56	1.9	3.3	6.0	42	220	40
V.R. ^a	35	1.90	70	9.8	14.0	6.8	35	185	83
K.S.	27	2.00	79	17.6	22.3	7.2	34	150	72
H.R.	26	1.99	78	11.9	15.3	7.2	38	185	72
A.L.	20	1.77	63	4.4	7.0	6.4	37	203	98
V-M.A.	21	1.90	70	3.2	4.6	6.8	42	167	88
P.L.	22	1.92	75	14.1	18.8	6.9	38	208	128
<i>Exposure III</i>									
E.I.	21	1.82	68	9.3	13.7	6.6	32	73 ^b	66
P.S.	24	1.78	65	10.5	16.2	6.4	37	50 ^b	54
H.M.	28	1.79	67	7.1	10.6	6.4	36	92 ^c	25
E.Ö.	22	1.95	68	3.5	5.1	7.0	30	110 ^b	44
K.L.	23	2.00	77	15.6	20.3	7.2	37	101 ^c	88
D.K.	22	1.94	74	10.2	13.8	7.0	32	51 ^c	45

^a Model person for the determination of mean ventilation.

^b Six days of exposure.

^c Eight days of exposure.

Fig. 1. Exposure type I: Stable concentration of m-xylene in the air of the chamber; subjects exercised on a bicycle ergometer at 100 W for 10 min four times a day.

volunteers disclosed no abnormal findings, nor did the subjects' energy balance vary greatly from normal during or after the experiment. The subjects were rather similar in bodily constitution. A few persons were rather lean and none were obese. The median estimated body fat was 14 % of the body weight.

Exposure

The exposures were carried out in a dynamic controlled-environment exposure chamber, the technical features of which have been described elsewhere (17). Three different exposure patterns were chosen which encompassed either stable or periodically varying m-xylene concentrations in the air, with or without periodic physical exercise. The xylene concentration in the air was adjusted to approximate the Finnish threshold limit value, either constant or time-weighted average (TWA),

for xylene ($4.1 \mu\text{mol/l}$, 100 ppm v/v) with a temporary elevation to a two times higher level on Friday afternoon. Fig. 1 and 2 illustrate the characteristics of exposure types I and II, respectively. Exposure type III was a mixture of type I and II, but the subjects were sedentary throughout the experiment. In type III conditions were as in exposure type I from Monday to Friday and as in exposure type II on the following Monday. This exposure was continued for two additional days with conditions identical to Tuesday and Friday, respectively, of exposure type II (fig. 3). The actual measured concentrations of m-xylene in the chamber air in the different types of exposure are presented in table 2.

Collection of samples

Needle biopsies of subcutaneous adipose tissue were taken from the gluteal region

Fig. 2. Exposure type II: Varying concentration of m-xylene in the air of the chamber, duration of peak concentration 10 min, rise and fall 5 min each; subjects exercised on a bicycle ergometer at 100 W for 10 min four times a day.

Fig. 3. Exposure type III: Subjects were sedentary throughout the experiment.

Table 2. The m-xylene concentration in the chamber air during the different types of exposure. Mean values and ranges (in parentheses) are given.

Exposure	Number of days	Xylene concentration (ppm v/v)	
		Constant concentration	TWA of varying concentration ^a
Type I			
Monday — Thursday & Monday	10	90 (87—93)	
Friday			
Morning	2	89	
Afternoon	2	191 (188—193)	
Type II			
Monday — Thursday & Monday	10		93 (87—99)
Friday			
Morning	2		89 (87—91)
Afternoon	2		187 (175—199)
Type III			
Monday — Thursday	4	94 (87—100)	
Friday			
Morning	1	91	
Afternoon	1	200	
Monday	1		103

^a TWA = Time-weighted average.

as described elsewhere (9). Samples were collected prior to the exposures, after the exposures on the second Monday (the last exposure day of exposure types I & II) and also on the second Wednesday in the case of exposure type III. During the postexposure period samples were taken as indicated in fig. 3. The mean weight of the 78 specimens analyzed was 31.3 mg (range 7.6–108.1 mg). Immediately after the sample taking, the specimens were weighed and stored at -70°C until analyzed, within one to two weeks.

Analysis of samples

The content of m-xylene in the samples was analyzed with gas chromatography after evaporation of the compound to a constant flow of nitrogen at 150°C for 30 min. The method has been described in detail elsewhere (10). The detection limit of m-xylene was $5\text{ }\mu\text{mol/kg}$ (adipose tissue) for the mean specimen size. Six large specimens were divided into two parts and analyzed separately. The methodological error of duplicate assays ($s = \sqrt{\sum d^2/2n}$; d = difference between paired samples; n = number of pairs) was estimated to be $19\text{ }\mu\text{mol/kg}$, which is 28 % of the mean value ($67\text{ }\mu\text{mol/kg}$) of the observations. In fact, this estimate also includes biological variation within the divided sample. In the collection of the specimens the needle was thrust three to four times in slightly different directions into the subcutaneous fat. It is plausible that the m-xylene concentration of the fat varied somewhat in different locations because of local perfusion and other physiological factors.

Estimation of individual elimination half-times of xylene in fat

For each individual the measured concentrations were plotted against time on semi-log paper. The best linear fit was drawn graphically, and the half-time was read on the graph.

Estimation of body fat

We chose to estimate the fat-free body weight by means of anthropologic measurements, a method which, according to von Döbeln (7), has shown a good correlation with respective estimations based on body density when applied to male and female physical education students. The body fat mass was taken as the difference between the actual body weight and the estimated fat-free body weight. Adipose tissue contains lipids (mainly triglycerides), cellular material, and water. We assumed that the fat content of adipose tissue was 80 % (13) and, for calculations of total m-xylene stores in the body fat, that the compound was evenly distributed in all adipose tissue, of which subcutaneous fat makes up at least one-half (15).

Estimation of m-xylene uptake

For each exposure pattern an estimate was made of the cumulative whole-body uptake of m-xylene over the 6 d of exposure. For practical reasons it was impossible to measure the actual pulmonary ventilation and retention. Therefore, it was assumed that on the average 60 % of the inhaled amount of m-xylene was retained (1, 18), that the mean ventilation was 9.0 l/min at rest, and 22.5 l/min over a 20-min period encompassing 100-W exercise for 10 min. (During this period xylene concentration peaked in the chamber air, too.) These ventilation values were the means of two subjects representing all the volunteers, and they were derived from measurements of actual ventilation performed on both persons several times a day. For interindividual comparison pulmonary ventilation values during basal conditions (calculated from standard tables, $\dot{V}_E = 3.6 \times \text{surface area}$) (5) and during bicycle ergometer exercise of 100 W, performed in the laboratory by all the subjects, are given in table 1.

Statistical treatment

The Wilcoxon test for independent series was used when the results were tested for differences.

RESULTS

From the mean pulmonary ventilation values at rest and during exercise and the mean pulmonary xylene retention, it can be estimated that the three different exposure patterns result in different quantities of uptake, i.e., uptake is smallest when the subjects are sedentary, about 27 % larger when they exercise 40 min (out of 360 min) at 100 W, and about 50 % larger when the exercise coincides with 8.2—16.4 $\mu\text{mol/l}$ (200—400 ppm) peak air con-

centrations (table 3). The differences are due to the effect of exercise-increased pulmonary ventilation on uptake. The group medians of the m-xylene concentrations in subcutaneous fat at the termination of an exposure period varied in a similar fashion (table 4) although there was an overlapping of the individual values in different groups (fig. 4). The mean amount of m-xylene in the total body fat of the exposure groups (the product of the group mean concentration and group mean fat mass $\times 1.25$) at the termination of exposure was calculated

Table 3. Estimated uptake of m-xylene in the body and in the fatty tissue during three different types of 6-d exposure.

Exposure	a Estimated mean cumu- lative uptake in the body (mmol)	Mean amount in fat at termi- nation of exposure (mmol)	Half-time in fat ^a (h)	b Estimated mean cumu- lative uptake in fat (mmol)	$\frac{b}{a}$ %
Type I (N = 4)	62.7	1.9	approx. 58	4.7	7.5
Type II (N = 8)	73.9	2.3	approx. 58	5.9	8.0
Type III (N = 3)	49.3	0.7	approx. 58	1.8	3.7

^a Mean of group medians.

Table 4. Relative amount of fat and the concentration and half-time of m-xylene in the fat of volunteers during three different types of exposure. Median values and ranges (in parentheses) are given.

Exposure	Relative amount of fat (% of body weight)	m-Xylene concen- tration in fat at termination of ex- posure ($\mu\text{mol/kg}$ fat)	Half-time of m-xylene in fat (h)
Type I (N = 4)	12.7 (7.4—16.0)	(a) 167 (87—196)	(e) 47.5 (28—64)
Type II (N = 8)	14.7 (3.3—22.3)	(b) 194 (150—231)	(f) 77.5 (40—128)
Type III (N = 6)	13.8 (5.1—20.3)	(c) 73 (50—110) ^a (d) 92 (51—101) ^b	(g) 49.5 (25—88)

Tests for difference

- a vs. c + d combined; $p \sim 0.025$ (Wilcoxon, 1-tailed).
- b vs. c + d combined; $p \sim 0.0025$ (Wilcoxon, 1-tailed).
- b vs. a; not significant ($p > 0.05$) (Wilcoxon, 1-tailed).
- e vs. f; not significant ($p < 0.10$) (Wilcoxon, 2-tailed).
- e vs. g; not significant ($p > 0.05$) (Wilcoxon, 2-tailed).
- f vs. g; not significant ($p > 0.05$) (Wilcoxon, 2-tailed).

^a Six days of exposure (N = 3).

^b Eight days of exposure (N = 3).

Fig. 4. Concentration (median and range) of m-xylene in subcutaneous fat after exposure in three groups of volunteers differently exposed. $\diamond$ — $\diamond$: exposure type I ($N = 4$); $\bullet$ — $\bullet$: exposure type II ($N = 8$) (note that for two subjects the last sample was taken on the 9th postexposure day and for four subjects on the 11th such day); $\blacktriangle$ — $\blacktriangle$: exposure type III. Numbers in parentheses denote the actual number of observations if the collection of samples was incomplete.

to be 1.9 mmol (exposure type I), 2.3 mmol (exposure type II), and 0.7 mmol (exposure type III, three subjects). In the last group the respective figure after two additional days of exposure (three different subjects) was 1.1 mmol. If the mean elimination half-time of m-xylene in fat is assumed to be 58 h, the mean cumulative uptake in fat can be calculated from the previous figures according to the following equation:

$$y(t) = \sum_i c E_{t_{1i} - t_{0i}} (1 - e^{-(t_{1i} - t_{0i}) \times k}) \times e^{-(t_{0i} - t) \times k}, \quad (a)$$

where $y(t)$ = the amount of m-xylene in fat at (point in) time t , i = each individual day of exposure, t = time of sampling (= zero time), c = exposure specific coefficient of absorption, $E_{t_{1i} - t_{0i}}$ = daily exposure, t_{1i} = time at beginning of day's exposure (in relation to time t) t_{0i} = time at end of day's exposure (in relation to time t), k = rate constant of elimination ($\ln 2/T^{1/2}$), and $T^{1/2}$ = elimination half-

time of m-xylene in fat. Because $y(t)$ is known, c can be solved for. When elimination is not taken into account, equation a will be simplified to:

$$y = \sum_i c E_{t_{1i} - t_{0i}}, \quad (b)$$

where y is the cumulative uptake of m-xylene in fat.

The values for cumulative uptake thus obtained were 4.7 mmol (exposure type I), 5.9 mmol (exposure type II), and 1.8 mmol (exposure type III). Furthermore, the estimated mean cumulative uptake of m-xylene in fat relative to that in the whole body was 7.5 % in exposure type I, 8.0 % in type II, and 3.7 % in type III (table 3).

With reservation for the fact that there were only three point estimations, the elimination of m-xylene from subcutaneous fat seemed to follow a monoexponential course (fig. 4). In tables 1 and 4 specific elimination half-times are given for the individuals and exposure groups. The median elimination half-time for the whole group of 18 subjects was 58 h (range 25–128 h). Longer individual half-times tended to occur in exposure type II than in types I and III, but the intergroup differences were not statistically significant. A positive correlation was found between the individual elimination half-times of m-xylene in fat and the relative fat mass of individuals in exposure groups I and III ($r = 0.83$ and 0.73 , respectively), but no corresponding significant correlation appeared for exposure group II. The relative fat mass and m-xylene concentrations in the subcutaneous fat of individuals at the termination of exposure were not correlated in any logical fashion in the different exposure groups.

DISCUSSION

The distribution of lipid-soluble volatiles, e.g., anesthetic agents and solvents in tissue compartments, is determined by tissue perfusion and the capacity of tissue to hold the compound. This capacity equals the product of the solubility of the compound in tissue (tissue/blood partition coefficient) and tissue volume (8). Many industrial

solvents are quite lipid-soluble and hence have an affinity for the fat compartment of the body. Fat mass in a normal individual is considerable, constituting at least some 10 % of the body weight, frequently even much more. On the other hand, blood perfusion of fat as opposed to that of parenchymal organs and muscles is small (8). Therefore, although the adipose tissue of the human body has a large capacity for the more lipid-soluble industrial solvents, uptake in this compartment and elimination therefrom are relatively slow processes.

Moreover, the distribution of a compound to adipose tissue must also be greatly affected by the efficiency of biotransformation. Biotransformation in the parenchymal organs (liver, kidneys) clears the blood of the compound, and less will be transported to the fat. Thus it is not surprising that, for the efficiently metabolized aromatics m-xylene and styrene, only 4–8 % of the total body uptake has been distributed to the adipose tissue at the termination of exposure. This small distribution to fat is in contrast to the distribution of another lipid-soluble, poorly metabolized solvent, tetrachloroethylene, for which one-half of the daily whole-body uptake will be distributed to the fatty tissue, according to a mathematical model (14).

In this study the estimated cumulative uptake of m-xylene in the fatty tissue relative to that in the whole body varied from 3.7 to 8.0 % for the three different exposure patterns (table 2). These figures are based on the assumptions that (a) the mean ventilation and retention were the same in all the groups at rest and during 100-W exercise and (b) the elimination half-time of m-xylene from the fatty tissue was uniformly 58 h. Accepting these uncertainties, which make m-xylene estimations in the adipose tissue only rough approximations, one may note that they follow a logical pattern. The distribution of m-xylene to the adipose tissue was the least (3.7 % of total uptake) during the exposure in which the subjects were sedentary and the greatest (8.0 %) during the exposure which involved exercise during the peak concentrations. The corresponding figure of distribution (7.5 %) for the exposure encompassing exercise at a stable concentra-

tion falls to an intermediate position. It is plausible that exercise and varying uptake rates of m-xylene under the described conditions could influence the distribution of the compound in the subcutaneous fat. One hundred-watt exercise for 10 min, which causes frank sweating, is likely to increase the relative skin and adipose tissue perfusion (4) (proportion of cardiac output), while the relative perfusion of metabolically active parenchymal organs, such as the liver and the kidney, may actually decrease (2). In this way, at great uptake rates, a larger share of uptake may escape metabolism and be transported to the fat stores and vice versa.

The observed half-times of m-xylene in subcutaneous fat agree well with the findings of previous studies on styrene (11). Mathematical model simulations for benzene (12) and tetrachloroethylene (14) also predict very similar half-times in fat. A correlation which we noted for two groups only, between the relative amount of fat and m-xylene half-time in subcutaneous fat, could be explained on the basis of perfusion differences between the fatty tissues of lean and obese persons. The bodily constitution of our subjects was relatively uniform, however, and we cannot be certain that the anthropologic method of total body fat estimation accurately predicted the true differences between our volunteers.

It is also of some interest to note the tendency for longer elimination half-times for m-xylene in subcutaneous fat in the context of exposure type II. This exposure resulted in the greatest cumulative uptake of m-xylene in fat and also distinctly greater uptake rates when ergometer exercise coincided with peak air concentrations of xylene. Although no conclusions can be made on the basis of this material, it can be suggested that the elimination kinetics of xylene from subcutaneous fat may be dependent on the characteristics of exposure, e.g., on the rate of xylene absorption.

Due to the relatively long elimination half-time of m-xylene in body fat, some cumulation of the compound in the body will be inevitable during normal work schedules over a few weeks until a steady state is achieved. The cumulated amounts are relatively small, however, and only

small m-xylene concentrations in the blood will result from the slow elimination of the compound from fat stores. These blood xylene concentrations are per se unlikely to cause harmful effects in the perfused tissues. It is our understanding that the storage of m-xylene in body fat is not so marked as to necessitate its accurate monitoring in occupational health practice. With regard to other industrial solvents which are lipid-soluble and poorly metabolized, such as tetrachloroethylene, a different conclusion could be reached.

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