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Exposure to xylene and ethylbenzene

II. Concentration in subcutaneous adipose tissue

by JÖRGEN ENGSTRÖM, M.D., and RASMUS BJURSTRÖM, B.Sc.¹

ENGSTRÖM, J. and BJURSTRÖM, R. Exposure to xylene and ethylbenzene: II. Concentration in subcutaneous adipose tissue. *Scand. j. work. environ. & health* 4 (1978) 195—203. The amount of body fat in 12 male subjects was determined by means of underwater weighing and anthropometric calculation of skeletal weight. Six subjects (group I) were exposed to 200 ppm of industrial xylene during 30 min of rest and 90 min of exercise at a work load of 50 W. Six subjects (group II) were exposed to 100 ppm for 30 min at rest and during three 30-min periods of exercise at work loads of 50, 100 and 150 W, respectively. The amount of solvent taken up in the organism was highly correlated to the amount of body fat. When the groups were analyzed together, a correlation was found between the uptake per kilogram of body weight and the alveolar concentrations 4 and 19 h after exposure, even though the groups were exposed under different conditions. However, no correlation was found between total uptake and the alveolar air concentrations after exposure. Needle biopsies of subcutaneous adipose tissue were taken 0.5, 2, 4 and about 22 h after the end of exposure. Industrial xylene is a mixture of ethylbenzene and o-, m- and p-xylene. The concentrations of ethylbenzene and m- and p-xylene were determined with gas chromatography after evaporation into nitrogen at 150° C. Ortho-xylene, which constituted 8.8 % of the inspired gas mixture, could not be separated with the column used. Elimination of ethylbenzene-xylene from adipose tissue was slow. The mean concentrations in both groups of subjects were on about the same level after 22 h as during the first 4 h after exposure. In both groups, there was a negative correlation between the concentrations in adipose tissue and the degree of obesity, i.e., obese persons had lower concentrations.

Key words: adipose tissue concentration, alveolar air, body fat, ethylbenzene, exercise, exposure, rest, uptake, xylene.

Solvents taken up in the lungs from inspired air are transported by the blood to the tissues. Adipose tissue is of special interest in this context because of the often large volume and the high capacity of solvent uptake per gram of tissue. As this tissue has a low blood perfusion,

solvents often accumulate for a long time before equilibrium is reached between adipose tissue and the rest of the body. A long time is often required for the elimination of organic solvents from adipose tissue after exposure.

Before the accumulated amount of an organic solvent in adipose tissue can be estimated, it is necessary to measure the concentration in this tissue and the total amount of the tissue. Measurement of the rates of uptake and elimination and of the amounts accumulated in adipose tissue may be of importance in a risk evaluation.

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In conjunction with experimental studies of methylene chloride a head space method was developed for the gas chromatographic analysis of the solvent in adipose tissue (9, 10). The discussion of the results was primarily devoted to the significance of the magnitude of fat depots to the uptake and distribution of the solvent in the human organism. In the present study the method was further refined, and the concentrations in adipose tissue were followed during a prolonged period of time after exposure. Also in this study the significance of the magnitude of body weight and fat depots to the uptake in the body and to alveolar concentration has been considered. Other results have been reported in part I (3).

Industrial xylene contains varying amounts of ethylbenzene. The mixture in the present study contained an unusually large amount of this substance. It constituted 40.4 % by weight of the solvents in the gas mixture used for the exposure. Most of the xylene itself consisted of m-xylene (49.4 %); o-xylene and p-xylene were present in small quantities (8.8 % and 1.4 %, respectively).

There are only slight differences between the xylene isomers in regard to the percentage uptake in the body via the airways. Nor do there appear to be any differences of importance in metabolic respects (15). Xylene is eliminated mainly via the urine following biotransformation into methylhippuric acid. Only about 5 % of the amount taken up is exhaled (3, 15). Ethylbenzene is taken up in the lungs to the same extent as xylene. For both chemicals an uptake of about 60 % of the inspired amount has been reported (5, 15). Ethylbenzene is metabolized mainly into mandelic acid, which is eliminated in the urine (5).

The literature contains only sparse information on the blood/air and fat/air partition coefficients for xylene. Sato et al. reported a blood/air partition coefficient of 29 for m-xylene at 37° C (14). This substance has a much greater affinity for blood than methylene chloride, the partition coefficient of which has been reported to be about 8 under the same conditions (12). Sherwood reported an olive oil/air partition coefficient of 4,050 for xylene at 37° C (16). This level is of the same mag-

nitude as the coefficient of 4,100 for styrene at the same temperature (13). There is no information on the human adipose tissue/air partition coefficient for xylene.

EXPERIMENTAL DESIGN

Twelve male subjects, 19 to 35 years of age (mean age 27), were exposed to industrial xylene for 2 h under experimental conditions. The subjects were divided into two groups of six subjects. Group I was exposed to approximately 870 mg/m³ (200 ppm) in inspired air for 30 min at rest and for three 30-min periods during exercise on a bicycle ergometer at a work load of 50 W. Group II was exposed to about 435 mg/m³ (100 ppm) for 30 min at rest and for three 30-min periods of physical exercise at work loads of 50, 100 and 150 W. In both groups, exposure was interrupted for 20 min prior to the physical exercise. The method was basically the same as in previous solvent experiments, in which the solvent was given in the inspired air (4). Thus determinations were made of the concentrations in inspired, expired and alveolar air, of continuous uptake in the organism, and of the concentrations in arterial and venous blood. For the first 4 h after exposure food intake and physical activity were standardized. The subjects had lunch an hour after exposure and performed physical exercise on a treadmill at a work load corresponding to about 50 W for 5 min of each 15-min period.

Prior to exposure underwater weighing and skeletal measurements of the subjects were performed. The amount of body fat of each subject was calculated according to the method of von Döbeln (7, 8). The solvent analysis technique was tested on biopsy specimens from two subjects. The solvent concentrations in adipose tissue described in the following comprise the remaining 10 subjects. In other respects, the tabulation comprises all 12 subjects.

The adipose tissue biopsies were performed in the upper lateral gluteal quadrant following intracutaneous anaesthesia with a 1 % lidocaine solution (Xylocaine®, Astra). The needle was lance-shaped, and

the dimensions were 2.0×80 mm (KN 1480W, Medioplast AB). It was connected via a Luer-Lok to a 50-cc syringe with a glass barrel and plunger (B-D Yale, Becton, Dickinson & Co.). The small operation elicited no pain response if a fold of skin and subcutaneous fat was first pinched and the needle then inserted longitudinally into the fold parallel to the skin and muscle fascia. Before sufficient specimen material could be obtained, a powerful vacuum and, as a rule, several rapid thrusts with the needle were necessary.

Adipose tissue specimens were taken prior to exposure so that substances interfering with the solvent analyses might be revealed. Moreover, biopsies were performed 0.5, 2, 4 and 20–24 h after the conclusion of exposure. A double biopsy was performed on nine subjects on one occasion, i.e., after 2 or 4 h and from one subject at both times. When the second sample was taken, the needle was inserted into the same skin puncture, but the needle direction was changed 180° . From each subject three to four biopsies were taken from each gluteal region. The puncture channels were kept as far apart as possible so that samples from tissue with circulation disturbed by a previous puncture would be avoided. The biopsy needle containing the specimen was replaced in the plastic container in which the needle was supplied, and the container was sealed. In most instances, the specimen was assayed in immediate conjunction with the sampling. In some cases, the specimen was frozen until the following morning.

In addition to the aforementioned double biopsies taken from human subjects, white adipose tissue from rat was also studied so that the error of the method in the solvent analysis could be estimated. The rats were exposed to ^{14}C -labeled p-xylene in connection with another, as yet unpublished, experimental study by Carlsson. The results of liquid scintillation counting were compared to the results obtained with the gas chromatographic method used in the present study. Four specimens of white adipose tissue, from four rats exposed to ^{14}C -labeled p-xylene under different conditions, were used. Each specimen was divided into 7–12

samples that were analyzed by the gas chromatographic method. In addition seven samples from each of the original specimens were analyzed by liquid scintillation counting.

METHOD FOR ANALYZING SOLVENT IN ADIPOSE TISSUE

Xylene proved to have a considerably higher adipose tissue/air partition coefficient than methylene chloride. Therefore, simple head space determinations of xylene only yielded relatively low concentrations. In the present study, xylene and ethylbenzene in adipose tissue were analyzed by means of evaporation at 150°C into nitrogen that was passed over the specimen. The collected gas was then analyzed.

The operation of the evaporation unit is illustrated in fig. 1. The adipose specimen was placed in a brass evaporation chamber with a volume of 0.6 ml. After being closed with a teflon stopper, the chamber and specimen were weighed. The chamber was then screwed onto the end of a metal cylinder with two capillary tubes, one for the admission and one for the removal of nitrogen. The metal cylinder and the chamber were then placed in a thermoblock with a temperature of 150°C . Nitrogen of atmospheric pressure was then drawn at a velocity of 1 ml/min through the chamber into a motor-driven, gas-tight

Fig. 1. Diagram of the evaporation unit.

Table 1. Body height, body weight, and estimated amount of body fat. Mean values $\pm$ standard errors of the means are given.

Group	Body height (cm)	Body weight (kg)	Estimated body fat (kg)	Estimated body fat (% of body weight)
I (200 ppm—50 W)				
Subject 1	187	71.3	3.1	4.3
Subject 2	164	58.0	5.1	8.8
Subject 3	169	57.9	5.2	9.0
Subject 4	176	76.1	12.6	16.6
Subject 5	175	84.0	14.5	17.3
Subject 6	195	135.5	49.9	36.8
Subjects 1—6	178 $\pm$ 4.7	80.5 $\pm$ 11.8	15.1 $\pm$ 7.2	15.5 $\pm$ 4.7
II (100 ppm—50, 100, 150 W)				
Subject 1	192	77.2	0.7	0.9
Subject 2	184	71.9	1.4	1.9
Subject 3	182	73.8	3.5	4.7
Subject 4	181	69.5	6.3	9.1
Subject 5	177	73.9	9.2	12.4
Subject 6	177	86.6	12.8	14.8
Subjects 1—6	182 $\pm$ 2.3	75.5 $\pm$ 2.5	5.7 $\pm$ 1.9	7.3 $\pm$ 2.3

glass syringe with a temperature of 45—50° C. The capillary tubes above the thermoblock were surrounded by air with a temperature of 50—60° C in order to counteract condensation. The glass syringe was replaced with an empty syringe after 30 min and transferred to a heated cabinet which maintained a temperature of 45—50° C. The evaporation lasted 60 min in the analyzes of rat tissue and 30 min in the assay of human specimens. The analysis was made on 0.5 ml of the gas in the syringes by injection into a Perkin-Elmer F 30 gas chromatograph. The analysis details were as follows: (a) stainless steel capillary column (Perkin-Elmer, 50 m long with an internal diameter of 0.5 mm; (b) stationary phase of polypropylene glycol LB-550-X; (c) carrier gas of nitrogen with a flow rate of 5 ml/min; and (d) temperature of column 90° and of injection block and detector 150° C. The xylene and ethylbenzene concentrations were calculated on the basis of the chromatogram with the aid of air samples containing known solvent concentrations.

The method did not permit determination of o-xylene. The retention time for this isomer coincided with that of a substance in adipose tissue. The aggregate

concentrations of xylene and ethylbenzene were not compensated in the calculations for o-xylene, the concentration of which in inspiratory air constituted 8.8 % by weight. Thus the method entails some underestimation of the xylene-ethylbenzene concentrations in adipose tissue.

Liquid scintillation counting of ¹⁴C-labeled p-xylene in rat adipose tissue was performed according to the method described earlier by Carlsson and Lindqvist (6).

RESULTS

Body height, body weight, and the estimated amount of body fat (in kilograms and as percentage of body weight) are listed in table 1 for groups I and II. On the average, the subjects in group II were 5 kg lighter than the subjects in group I. Values for both the calculated amount of body fat and the relative degree of obesity were lower in group II. The calculated amount of body fat averaged 15.5 % of body weight in group I and 7.3 % in group II. An average value of 10.6 % was reported by von Döbeln for young, healthy, well-trained men (7).

A linear regression analysis was made of the relation between total uptake in the organism and body weight. The correlation coefficient was found to be 0.95 in group I. In group II, for which inter-subject differences in weight were slight, the correlation coefficient was 0.58. The correlation coefficient for the relation between uptake in the organism and the amount of body fat was 0.94 for group I and 0.98 for group II (fig. 2). The uptakes at rest and at different work loads have been listed in part I (3).

No particular correlation was found between total uptake and the alveolar air concentrations 4 and 19 h after the end of exposure when the groups were analyzed together ($r = 0.25$ and 0.06 , respectively). However, the correlation was high between the amount taken up per kilogram of body weight and the alveolar air concentrations at the aforementioned times ($r = 0.80$ and 0.79 , respectively; figs. 3 and 4). It should be noted that the physical activity of the subjects was standardized during the first 4 h after the end of exposure. Thus, even though there was no standardization thereafter, the same high correlation was found between uptake and alveolar air concentration the following morning, when body weight was taken into account. The mean values for the concentration in alveolar air during and after exposure have been listed in part I (3).

The mean weight of the 36 specimens of rat adipose tissue analyzed by gas chromatography was of the same magnitude as that of the human specimens. The mean weight was 42.2 mg (range 13.6–84.9 mg). The concentrations of p-xylene in adipose tissue, analyzed by gas chromatography and liquid scintillation counting, are reported in table 2. No systematic difference was noted between the results of the two methods. The standard deviations, expressed as percentage of the mean values, were smaller in the gas chromatographic assay than in the liquid scintillation counting, on an average 10.9 as compared to 20.3 in liquid scintillation counting. In the analyses of the rat adipose tissue specimens evaporation for 60 min was used. During that time two 30-ml syringes were used; $94.0 \pm 2.7\%$ (mean $\pm$ SD) of the totally obtained amount was recovered in

Fig. 2. Uptake of xylene and ethylbenzene in the body in relation to estimated amount of body fat. Regression line, group I: $y = 11.2x + 1,210$; group II: $y = 20.6x + 875$. (● = group I; ○ = group II)

Fig. 3. Alveolar air concentration of xylene and ethylbenzene 4 h after exposure in relation to uptake per kilogram of body weight. Regression line: $y = 0.51x - 2.62$. (● = group I; ○ = group II)

Fig. 4. Alveolar air concentration of xylene and ethylbenzene 19 h after exposure in relation to uptake per kilogram of body weight. Regression line: $y = 0.12x - 0.83$. (● = group I; ○ = group II)

Table 2. Concentration of p-xylene in white adipose tissue of rats. Comparison between results of liquid scintillation and gas chromatography.

Rat	Concentration of p-xylene in adipose tissue (mg/kg)				Two-tailed p-values from Student's t-test
	Gas chromatography		Liquid scintillation		
	Mean $\pm$ SD	N	Mean $\pm$ SD	N	
1	3.1 $\pm$ 0.40	8	3.5 $\pm$ 0.58	7	0.14
2	10.4 $\pm$ 1.58	9	12.9 $\pm$ 2.39	7	0.03
3	14.2 $\pm$ 0.98	7	12.2 $\pm$ 3.84	7	0.15
4	30.0 $\pm$ 2.54	12	29.3 $\pm$ 4.25	7	0.68

the first 30-ml syringe. Therefore, during the rest of the study, evaporation during 30 min was applied.

Two of the 61 human adipose tissue specimens were rejected for technical reasons. The remaining 59 specimens had a mean weight of 40 mg (range 5.3–112.4 mg). The aggregate concentrations of m- and p-xylene and ethylbenzene varied from 0.5 to 19.8 mg/kg of adipose tissue in the double-biopsy specimens. The mean value for the double determinations was 6.8 mg/kg. The error of the method(s) was 2.8 mg/kg [$s = \sqrt{(\sum d^2)/2n}$]. The error probably included considerable biological variations since the calculation was performed from measurements on samples taken a short time after the exposure from tissue with sparse and probably irregular blood circulation.

The mean values at different times for the aggregate concentrations of m- and p-xylene and ethylbenzene in the adipose tissue for the two experimental groups are given in fig. 5. The subjects in group II had been exposed to lower concentrations

in inspired air and had taken up less in the organism. During the first 4 h after exposure they had a lower concentration in their adipose tissue than the subjects in group I. However, after 22 h the mean value was higher in group II than in group I. But the difference was not significant according to Student's t-test ($p > 0.10$). Four hours after the end of exposure the mean value in both groups was lower than after 2 and 22 h, respectively. However, the mean values after 4 h were only based on the results from four subjects in each group, whereas the values at other times represented five subjects in each group. Therefore the 4-h value should be viewed with caution. According to the t-test there was no significant difference between the concentrations in the adipose tissue of the groups 2 and 22 h after the end of exposure ($p > 0.10$). Thus the elimination of xylene and ethylbenzene from adipose tissue appeared to be slow.

In a linear regression analysis a negative correlation was found between the concentrations in adipose tissue and the degree of

Fig. 5. Concentrations of m- and p-xylene and ethylbenzene in the subcutaneous fat tissue after exposure. (● = mean of group I; ○ = mean of group II; vertical bars = standard errors)

relative obesity in both groups. Thus the correlation coefficient between the values 30 min after exposure and relative obesity was -0.92 for group I and -0.95 for group II (fig. 6).

For the two groups together a linear regression analysis was made between the concentrations in the alveolar air and in the adipose tissue. Four hours after exposure there was a positive correlation ($r = 0.82$, fig. 7). No such correlation was found after about 22 h ($r = 0.03$).

The subjects had an indwelling catheter in the brachial artery up to 1.5 h after exposure. The correlation between the concentration in arterial blood and adipose tissue 30 min after exposure was relatively high ($r = 0.68$). The coefficient was lower for the correlation between samples taken later on. No correlation whatever could be found between the concentration after 22 h in arterialized, capillary blood and adipose tissue ($r = -0.07$). The correlation between the concentration in peripheral venous blood and adipose tissue was poor. The correlation coefficients were 0.38, 0.34 and 0.42 after 1.5, 2 and 4 h, respectively.

In order to gain knowledge on the differences in the turnover rates of ethylbenzene and m- and p-xylene, we compared the concentration ratio ethylbenzene/m- and p-xylene in inspired air during exposure to the ratio in alveolar air and adipose tissue at different times. According to the t-test there was no difference between the ratio in inspired air and in the alveolar air samples taken 4–12 h after exposure ($p > 0.10$). The mean value

Fig. 6. Concentration of m- and p-xylene and ethylbenzene in subcutaneous fat tissue 30 min after exposure. The concentration is related to estimated amount of body fat expressed as the percentage of body weight. Regression line, group I: $y = -0.39x + 14.48$; group II: $y = -0.29x + 5.79$. (● = group I; ○ = group II)

for the ratio in inspired air was 0.80 during exposure. In the adipose tissue specimens taken 30 min after the end of exposure, the ratio was 0.72 ($SD = \pm 0.26$). About 22 h after the end of exposure, the ratio in adipose tissue was 0.73 ± 0.12 (mean $\pm$ SD). There was no significant difference between the two ratios in adipose tissue ($p > 0.10$). Thus there were no signs of any important differences in the turnover rates of ethylbenzene and m- and p-xylene. The comparison of the ratios in adipose tissue was based on results from

Fig. 7. Relationship between the concentrations in alveolar air and in subcutaneous fat tissue 4 h after exposure. In the air concentration all the xylene isomers and ethylbenzene were included, whereas o-xylene was not included in the fat tissue concentration. Regression line: $y = -0.29x + 3.72$. (● = group I; ○ = group II)

nine subjects, since the 22-h sample of one subject contained only traces of ethylbenzene.

DISCUSSION

In this study, as in previous experimental studies of toluene and methylene chloride (6, 10), a correlation was found between the magnitude of uptake in the organism and the amount of body fat. Alveolar air concentrations within 22 h after exposure were related to the amount taken up per kilogram of body weight, whereas no correlation was found between alveolar air concentrations and total uptake.

It is now well known that a given concentration of a solvent in inspired air can result in widely varying uptakes in the organism at different work loads with attendant differences in pulmonary ventilation and blood circulation (1, 2). However, the magnitude of uptake in the body also varies according to differences in somatic constitution.

In the light of these findings, the risks of exposure to solvents must be related to the amount taken up in the organism. However, the distribution volume of the respective substance must also be taken into account. By dividing the amount taken up during 2 h of exposure by body weight, we obtained a measure of the mean concentration of the solvent and any of its metabolites in the body at the end of exposure. Even if body weight is not really a measure of the distribution volume, uptake per kilogram of body weight is probably a better measure than total uptake in the organism when biological risks from exposure to solvents are being assessed.

In part I of this study it was shown that xylene is very soluble in blood and tissues (3). An olive oil/air partition coefficient of about 4,000 for xylene and styrene at 37° C is the highest value reported for solvents (12, 14). The slow decline in the concentration of xylene in adipose tissue in the present study concurred with the findings of previous *in vitro* studies, even if these studies were not performed on human adipose tissue. In a methylene chloride study

comprising 12 subjects (9, 10), adipose tissue specimens were taken from two subjects about 24 h after the end of exposure. Relatively rapid elimination from adipose tissue was noted. If these two subjects were representative of the subjects exposed to methylene chloride, then xylene and ethylbenzene are eliminated from adipose tissue much more slowly than methylene chloride. There is probably a certain risk of xylene accumulation in adipose tissue during exposure of long duration. This question is currently being studied in collaboration with the Institute of Occupational Health in Helsinki, Finland, in conjunction with experimental exposure to xylene corresponding to a work week.

In the present study with brief exposure the amount of solvent retained in the adipose tissue was probably not large, despite the fact that the partition coefficient of adipose tissue/air is high. The total amount of adipose tissue can be estimated from body fat weight on the assumption that the average fat content of adipose tissue is 80 % (11). If the concentration of solvent in the subcutaneous fat tissue is supposed to be representative of the fat depots, then the total amount of solvent in these depots can be calculated. Such an estimate gave the result of a mean retention of about 5 % of the total uptake of xylene and ethylbenzene 22 h after exposure. On the other hand, however, the distribution of solvent in human adipose tissue is probably not uniform. After 8 h of exposure to *p*-xylene the concentrations in abdominal and subcutaneous white fat tissue of rats were on the same level (unpublished results of Carlsson). Since the metabolism is rapid (15), it is reasonable that about 24 h after a short exposure the concentration of xylene in human fat tissue is low. However, there is still a possibility of accumulation in fat tissue during prolonged exposure.

It should be emphasized that in this study the concentrations of solvents in adipose tissue were somewhat underestimated. As a matter of fact the values should be about 15 % higher. The 8.8 % of *o*-xylene in inspiratory air was not accounted for. In addition about 6 % of the amount evaporated from the samples and was excluded.

The experimental design described in the present study with two levels of exposure during differing degrees of activity may be said to reflect conditions in a work environment where both these factors often vary. Therefore, it was interesting to note that the alveolar air concentrations up to 19 h after exposure correlated with the amount taken up per kilogram of body weight. Future studies may provide the answer to the question of whether or not alveolar air concentrations can be employed in field studies as an indirect measure of the uptake per kilogram of body weight. Moreover, epidemiologic studies are required for the evaluation of the determinations of adipose tissue concentration, total uptake, and uptake per kilogram of body weight when the risks presented by exposure to a solvent are being assessed.

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