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by Åstrand I, Engstrom J, Övrum P

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Exposure to xylene and ethylbenzene

I. Uptake, distribution and elimination in man

by IRMA ÅSTRAND, M.D., JÖRGEN ENGSTRÖM, M.D.,
and PER ÖVRUM, M.Sc.¹

ÅSTRAND, I., ENGSTRÖM, J. and ÖVRUM, P. Exposure to xylene and ethylbenzene: I. Uptake, distribution and elimination in man. *Scand. j. work environ. & health* 4 (1978) 185—194. Industrial xylene is a mixture of xylene and ethylbenzene. Twelve male subjects were exposed to industrial xylene in inspired air, six subjects in series I to 870 mg/m³ at rest (30 min) and light exercise on a bicycle ergometer (90 min) and six subjects in series II to 435 mg/m³ at rest (30 min) and during exercise of increasing work loads (90 min). The measurements of xylene uptake were performed continuously with the Douglas bag technique. In both series, about 60 % of the amount of xylene supplied to the lungs was taken up. In both series, the concentration in alveolar air was relatively low throughout the entire exposure. The relative concentration in alveolar air displayed a linear correlation to the percentage uptake in the lungs. The ratio between the concentration in arterial blood (mg/kg) and alveolar air (mg/l) amounted to 30—40 at the different work loads. The total amount of xylene expired after the exposure was estimated from the alveolar concentration and alveolar ventilation. In series I, with a total uptake of 1.4 g, the subjects expired about 70 mg, i.e., about 5 %. The corresponding value in series II was 40 mg of a total uptake of 1.0 g, i.e., about 4 %.

Key words: alveolar air, arterial blood, exercise, exposure, metabolism, rest, uptake, xylene.

Xylene is one of the most commonly used aromatic solvents in industry. It is often combined with other aromatic and aliphatic hydrocarbons (e.g., in paints, lacquers, thinner, and white spirit). Even when industrial xylene is used as a solvent on its own, it still consists of a mixture of the three xylene isomers, o-xylene, m-xylene and p-xylene, and ethylbenzene. Many studies with human and animal subjects have been devoted to the metabolism

and elimination of xylene. A summary of conclusions from such studies can be found in a report recently published by the National Institute for Occupational Safety and Health in the United States (11). However, there have been few studies dealing with xylene uptake and distribution in man.

As one phase of work on biological limit values for a number of solvents (2), the study described in this report was performed to investigate the total uptake of xylene in the body. The concentration of xylene in adipose tissue is dealt with in part II (8), while the effects on the nervous system at different uptakes were recorded in a parallel series of studies reported in part III (9).

¹ Department of Occupational Health, National Board of Occupational Safety and Health, Stockholm, Sweden.

Reprint requests to: Prof. Irma Åstrand, National Board of Occupational Safety and Health, S-100 26 Stockholm, Sweden.

SUBJECTS

The subjects consisted of a group of men, 19 to 35 years of age, who were exposed to xylene in laboratory experiments. All were healthy and none had ever suffered from any disorder regarded as significant to the results. In tables 1 and 2 data on the subjects are presented, including results of pulmonary function tests and exercise stress tests on a bicycle ergometer. All the values were normal, and all the subjects displayed a normal physical work capacity. No abnormal ECG changes were found. A detailed description of the method has been given elsewhere (3, 4).

EXPERIMENTAL DESIGN AND METHODS

The experiments were performed in basically the same way as in earlier studies of solvents (4). The subjects were exposed to the xylene mixture through a breathing valve. The exposure started at about 1000 in the morning. Each period of exposure lasted 30 min, and each subject was ex-

posed for four periods at each session, i.e., for a total of 2 h.

The xylene used in the preparation of the air mixture had the following composition in gas form: ethylbenzene 40.4 %, p-xylene 1.4 %, m-xylene 49.4 %, and o-xylene 8.8 %. The gas mixtures were obtained in the same way as before (4). Henceforth, the concept of xylene will include both the xylene isomers and the ethylbenzene.

Six subjects were exposed to xylene at a concentration of about 870 mg/m³ of air (200 ppm) for 30 min at rest and for 90 min during exercise on a bicycle ergometer at a work load of about 50 W (series I). This work load demanded about 30 % of the subject's maximal oxygen uptake and can be regarded as physically light for all six subjects. The other six subjects were exposed to xylene at a concentration of about 435 mg/m³ of air (100 ppm) for 30 min at rest and for 90 min during exercise on the bicycle ergometer at work loads of about 50, 100 and 150 W (series II) (fig. 1). The work load of 150 W demanded about 55 % of the subject's maximal oxygen uptake and can be regarded as moderately heavy physical work for all six subjects.

Table 1. Data from the health survey of 12 subjects 19 to 35 years of age. Mean values and standard errors of the means are given. (FEV % = forced expiratory volume for 1 s as the percentage of vital capacity, MVVf = maximal voluntary ventilation at free rate)

Body height (cm)	Body weight (kg)	Body fat (kg)	Vital capacity (l)	Residual volume (l)	FEV (%)	MVVf (l/min)
180 ± 2.6	78.0 ± 5.8	10.4 ± 3.0	6.1 ± 0.2	1.6 ± 0.1	85 ± 2	205 ± 7

Table 2. Results of the exercise tests performed by the 12 subjects on a bicycle ergometer without exposure to xylene. Mean values and standard errors of the means are given. ($\dot{V}_E$ = pulmonary ventilation, $\dot{V}_{O_2}$ = oxygen uptake per unit of time)

Work load (W)	Heart rate (beats/min)	$\dot{V}_E$ BTPS (l/min)	$\dot{V}_{O_2}$ STPD (l/min)	Blood lactic acid (mmol/l)
50	98 ± 2	24.1 ± 1.0	1.00 ± 0.02	1.6 ± 0.2
100	115 ± 3	35.7 ± 1.9	1.51 ± 0.03	2.5 ± 0.3
150	138 ± 4	51.2 ± 2.8	2.09 ± 0.04	5.0 ± 0.6
Maximal work	190 ± 3	149.3 ± 5.0	3.67 ± 0.15	15.9 ± 0.5

The Swedish threshold limit value for xylene in air is 100 ppm or about 435 mg/m³ at a temperature of 25° C and a barometric pressure of 760 mm Hg. All air concentrations will henceforth be stated in milligrams per cubic meter at 25° C and at the prevailing barometric pressure unless otherwise noted.

The concentration of xylene in inspired air was continuously monitored with the aid of a hydrocarbon analyzer. The concentration varied from experiment to experiment in the course of the investigation, i.e., from 835 to 980 mg/m³ of air in series I and from 424 to 490 mg/m³ of air in series II, but it was maintained constant in each individual experiment.

Throughout the entire exposure, the volume of expired air was measured continuously with the Douglas bag technique, and the xylene concentration in the air was measured with gas chromatography. The volume of inspired air was estimated to be the same as the volume of expired air. The amount of xylene taken up in the lungs was calculated as the difference between the total amount in inspired and expired air. The mean value for pulmonary ventilation was calculated for each 30-min period and each subject. The mean value for the six subjects in each series was then calculated. Oxygen uptake was determined according to the method described elsewhere (4).

Alveolar air samples were taken during exposure, and the xylene concentration was assayed with gas chromatography. In addition the concentration was monitored for about 19 h after the conclusion of exposure. Arterial and venous blood samples (about 0.5 g) were taken from two catheters introduced into a cubital vein and the brachial artery, respectively. An arterialized capillary blood sample was taken from a prewarmed fingertip in the morning of the day after exposure. The xylene concentration in blood was assayed with the head space technique. The assays were performed with a gas chromatograph in a manner reported elsewhere (3, 4). The times at which the samples were taken in the two series of experiments are shown in the respective figures.

The concentrations of xylene in air and blood samples were calculated with the aid of chromatograms made with known

Fig. 1. Experimental design of the exposure to xylene. In series I six subjects were exposed to a xylene concentration of about 870 mg/m³, and in series II six subjects were exposed to a xylene concentration of about 435 mg/m³ in air. In series I the subjects were exposed at rest and during exercise on a bicycle ergometer with a work load of 50 W; in series II the subjects were exposed at rest and during exercise with work loads of 50, 100 and 150 W.

concentrations in air and in individual blood samples. In the calculations, it was assumed that the xylene composition was always the same as in inspired air, and measurements were made of two of the components of xylene, i.e., ethylbenzene and m-xylene. Random samples were taken to ensure that this xylene composition was constantly maintained even in the blood, both during and after exposure.

Mean values for the concentration in alveolar air, arterial blood, and venous blood, based on the last three determinations, were calculated for each subject and for each 30-min period of exposure. The values stated after the end of exposure constitute the mean values for six subjects at every sampling session.

The error of the method for a single determination of xylene in blood was calculated on the basis of 10 double determinations with a xylene concentration ranging from 0.87 to 1.64 mg/kg. The error of the method was $\pm 6\%$ of the mean value.

The ECG was continuously recorded during all exposures. No changes of importance were noted. Heart rate was determined every other minute. The mean value of the final three determinations for each subject in each period was used in the calculation of the final mean value for each period and series.

The physical activity was standardized for 4 h after exposure. For 5 min of every 15-min period each subject walked on a treadmill. The treadmill velocity and incline were selected so that the oxygen uptake was equivalent to the 50-W load on the bicycle ergometer.

Table 3. Milligrams of xylene in the inspired air and the amount taken up per 30-min period and after 2 h of exposure to approximately 870 and 435 mg/m³ of xylene in inspired air during rest and exercise. Mean values and standard errors of the means are given. Each series lasted 2 h and included six subjects; each period (1–4) lasted 30 min.

Exposure period	Given amount (mg)	Amount taken up (mg)	Uptake in % of given amount
Series I			
1	242 ± 16	166 ± 9	70 ± 4
2	618 ± 22	407 ± 23	66 ± 3
3	655 ± 18	400 ± 28	61 ± 3
4	688 ± 15	405 ± 31	59 ± 4
1–4	2,204 ± 62	1,379 ± 86	63 ± 3
Series II			
1	126 ± 4	79 ± 1	63 ± 1
2	343 ± 11	219 ± 6	64 ± 1
3	516 ± 19	301 ± 11	58 ± 1
4	762 ± 52	392 ± 25	51 ± 1
1–4	1,747 ± 80	991 ± 40	57 ± 1

During the first 4 h after exposure the amount of xylene exhaled was individually measured. During the first 20 min the amount was measured by the Douglas bag technique. Thereafter, the pulmonary ventilation was measured during 5-min periods with a Wright respirometer (Medishield Harlow, Essex CM195AB, England). The corresponding respiratory frequency was estimated. Such measurements were made in ten 5-min periods evenly distributed to cover 4 h after the exposure to xylene. The measurements were made both at rest and during walking on the treadmill. The amount of expired xylene was calculated as the product for alveolar ventilation and alveolar concentration of each period. Alveolar ventilation ($\dot{V}_A$) was estimated according to the equation: $\dot{V}_A = \dot{V}_E - \text{dead space} \times \text{respiratory frequency}$ ($\dot{V}_E$ = pulmonary ventilation and dead space = 150 cm³). Mean values of the pulmonary ventilation ($\dot{V}_E$) and respiratory frequency of each subject were used for both the rest and work periods. The estimation of the alveolar concentration of xylene at intervals of 5 min was interpolated from individual curves based on concentrations determined at various times after the actual exposure (fig. 5 and 6).

In the calculation of a mean value for the amount of xylene expired by the subjects until the following morning (from 4 to 19 h after the conclusion of exposure), the alveolar ventilation was set at 8 l/min for 4 h and 5 l/min for 11 h. The mean values for the alveolar concentration measured during the corresponding time were plotted in a diagram, and a linear decline with time was assumed between measurement occasions. The expired amount was then calculated in the aforementioned manner. For the following day, alveolar ventilation was set at 8 l/min for 9 h. The alveolar concentration was assumed to display a linear decline with time at the same rate as the preceding night. The alveolar concentration declined to zero by about 1700 the day after exposure in both series when this procedure was employed.

RESULTS

In exposure at rest and during light exercise corresponding to a pulmonary ventilation of about 25 l/min (series I), about 65 % of the inspired amount of xylene was taken up (table 3). About 1.4 g was taken up during the 2-h exposure to about 870 mg/m³ (fig. 2).

During exposure with increasing work loads (series II), the amount of xylene inspired naturally increased in step with the increased ventilation. The uptake raised from about 80 mg during the resting period to about 390 mg during the last period of heavy exercise. However, the percentage uptake dropped from the aforementioned 65 % at a ventilation of about 25 l/min to 50 % at about 55 l/min (table 3). The quantity taken up in the 2-h exposure to about 435 mg/m³ amounted to about 1.0 g (fig. 3).

The alveolar concentration was relatively low in both series, i.e., it was about 15, 20 and 30 % of the concentration in inspired air at rest, during light exercise and during the heaviest exercise, respectively (table 4). These relative alveolar concentrations displayed a linear correlation to the corresponding percentage uptakes (fig. 4).

Fig. 2. Inspired and taken up amount of xylene in exposure to 870 mg/m³. The exposure was provided at rest and during exercise with a work load of 50 W on a bicycle ergometer. Mean values for six subjects are given. The total amount supplied was 2.2 g, and the total amount taken up was 1.4 g. (Same experiments as in fig. 5)

Fig. 3. Inspired and taken up amount of xylene in exposure to 435 mg/m³. The exposure was provided at rest and during exercise with work loads of 50, 100 and 150 W on a bicycle ergometer. The given amount was 1.7 g, and the amount taken up was 1.0 g. (Same experiments as in fig. 6)

In both series the arterial blood concentration rose continuously during exercise (figs. 5 and 6). However, there was some flattening of the slope of the curve towards the end of the constant exercise at 50 W (fig. 5). In both series, the venous blood concentrations paralleled the arterial concentrations.

At the end of each period the ratio between the concentrations in arterial blood (mg/kg) and alveolar air (mg/l) was about

15 at rest and 30—40 at the different work loads in both experimental series (table 4).

Table 5 lists the concentrations in alveolar air and blood after the end of exposure. The concentrations declined rapidly, but there was still some xylene left in both alveolar air and blood 19 h after the end of exposure.

In series I (rest + 50 W), the subjects expired 51 ± 10 mg in the first 4 h after exposure. In series II (rest, 50, 100 and

Table 4. Results during rest and exercise with exposure to xylene. Series I: exposure to a xylene concentration of about 870 mg/m³ for six subjects at rest and during exercise with a work load of 50 W; series II: exposure to a xylene concentration of about 435 mg/m³ for six subjects at rest and during exercise with work loads of 50, 100 and 150 W. Each period (1—4) lasted 30 min (see fig. 1), and each series lasted 2 h. Mean values and standard errors of the means are given. ($\dot{V}_E$ = pulmonary ventilation, $\dot{V}_{O_2}$ = oxygen uptake per unit of time)

Exposure period	Heart rate (beats/min)	$\dot{V}_{O_2}$ STPD (l/min)	$\dot{V}_E$ BTPS (l/min)	Xylene concentration		
				Alveolar air (mg/m ³)	Arterial blood (mg/kg)	Venous blood (mg/kg)
Series I						
1	71 ± 1	0.32 ± 0.01	9.5 ± 0.8	125 ± 21	1.6 ± 0.2	1.1 ± 0.2
2	101 ± 3	0.96 ± 0.04	23.3 ± 1.2	173 ± 10	5.2 ± 0.7	3.6 ± 0.7
3	106 ± 4	1.01 ± 0.04	24.7 ± 1.0	197 ± 19	6.8 ± 1.0	5.6 ± 0.8
4	109 ± 4	1.05 ± 0.04	26.0 ± 0.9	208 ± 14	7.3 ± 1.3	6.1 ± 1.0
Series II						
1	68 ± 2	0.31 ± 0.02	9.2 ± 0.2	70 ± 5	0.9 ± 0.1	0.6 ± 0.3
2	99 ± 5	1.02 ± 0.02	24.7 ± 0.6	84 ± 5	2.8 ± 0.2	1.5 ± 0.2
3	125 ± 7	1.54 ± 0.04	37.8 ± 1.1	120 ± 8	4.5 ± 0.4	3.2 ± 0.4
4	154 ± 7	2.26 ± 0.03	55.7 ± 3.1	157 ± 10	6.8 ± 0.2	5.2 ± 0.5

Fig. 4. Uptake of solvents in the lungs as the percentage of the amount supplied in relation to the quotient between the concentrations of alveolar and inspired air. The uptake was measured during a 30-min period, and the corresponding alveolar concentration was based on three measurements during the last 10 min of the same period. In most cases each symbol represents a mean value of four to six subjects. The equation of the regression line was calculated on the basis of 46 such mean values. The number of subjects was: for methylene chloride 14, for trichloroethylene 15, for white spirit 4, for styrene 7, for xylene 12 and for toluene 7 (altogether about 60 subjects). The deviation from the line (SD) = $\pm 5 \cdot r = -0.949$.

Fig. 5. Concentration of xylene in alveolar air and arterial and venous blood during and after exposure to 870 mg/m³ of xylene. Mean values for six subjects are given. The exposure was provided at rest and during exercise on a bicycle ergometer with a work load of 50 W. ($\dot{V}_E$ = pulmonary ventilation l/min) (Same experiments as in fig. 2)

Fig. 6. Concentration of xylene in alveolar air and arterial and venous blood during and after exposure to 435 mg/m³ of xylene. Mean values for six subjects are given. The exposure was provided at rest and during exercise on a bicycle ergometer with work loads of 50, 100 and 150 W. ($\dot{V}_E$ = pulmonary ventilation l/min) (Same experiments as in fig. 3)

150 W), the corresponding quantity was 29 ± 2 mg. Between the 4th and 19th hour after exposure, the subjects in series I expired an additional 16 mg and the subjects in series II another 10 mg. The corresponding quantities the following day were 3 and 2 mg, respectively. Thus the subjects in series I expired a total of about 70 mg, and the subjects in series II about 40 mg. These figures constitute 5 and 4 %, respectively, of the total amount taken up.

DISCUSSION

According to Sato et al. (12), the blood/air partition coefficient for m-xylene is about 29 in in vitro experiments. The ratio between the concentrations in arterial blood and alveolar air in the present study with a mixture of different components was about 30–40 after about 1 h of exposure. This value was obtained both during exercise with a constant, low work load and a

Table 5. Concentration of xylene in the alveolar air and blood of 12 subjects after exposure. Mean values and standard errors of the means are given. Series I: rest and 50 W, exposure to 870 mg/m³, series II: rest, 50, 100 and 150 W, exposure to 435 mg/m³ of xylene.

Series	Number of subjects	Xylene concentrations		
		Alveolar air (mg/m ³)	Arterial blood (mg/kg)	Venous blood (mg/kg)
I				
End of exposure	6	208 ± 14	7.3 ± 1.3	6.1 ± 1.0
After 5 min	6	67 ± 9	3.8 ± 0.9	4.0 ± 0.7
After 15 min	6	48 ± 8	2.9 ± 0.7	3.0 ± 0.6
After 30 min	6	40 ± 8	2.1 ± 0.5	2.1 ± 0.4
After 45 min	6	27 ± 4	1.5 ± 0.3	2.0 ± 0.4
After 1 h	6	23 ± 4	1.2 ± 0.2	1.6 ± 0.3
After 1 h 30 min	6	16 ± 3	0.8 ± 0.1	1.1 ± 0.2
After 2 h	6	12 ± 2		0.9 ± 0.2
After 2 h 30 min	6	10 ± 2		0.7 ± 0.1
After 3 h	6	8 ± 1		0.6 ± 0.1
After 3 h 30 min	6	7 ± 1		0.4 ± 0.1
After 4 h	6	6 ± 1		0.3 ± 0.05
After 8 h	6	3 ± 0.5		
After 19 h	6	1 ± 0.3		0.06 ± 0.01
II				
End of exposure	6	157 ± 10	6.8 ± 0.2	5.2 ± 0.5
After 5 min	6	51 ± 2	3.4 ± 0.1	2.8 ± 0.5
After 15 min	6	34 ± 3	1.9 ± 0.1	1.7 ± 0.2
After 30 min	6	29 ± 3	1.6 ± 0.1	1.7 ± 0.3
After 45 min	6	21 ± 1	1.3 ± 0.3	1.4 ± 0.2
After 1 h	6	14 ± 1	0.9 ± 0.2	1.2 ± 0.2
After 1 h 30 min	6	11 ± 1	0.5 ± 0.1	1.0 ± 0.2
After 2 h	6	8 ± 1		0.6 ± 0.08
After 2 h 30 min	6	6 ± 0.4		0.4 ± 0.03
After 3 h	6	5 ± 0.2		0.4 ± 0.02
After 3 h 30 min	6	4 ± 0.3		0.3 ± 0.02
After 4 h	6	4 ± 0.2		0.3 ± 0.02
After 8 h	6	2 ± 0.3		
After 19 h	6	0.8 ± 0.1		0.05 ± 0.01

high level of exposure and during exercise with stepwise increases in work load and half the level of exposure. However, after 30 min of exposure at rest, the ratio was only about half as large. A longer period of exposure would probably be required if an in vivo quotient is to be obtained which coincides with a coefficient determined in vitro. It should be emphasized, however, that there was no attainment of equilibrium between the two mediums, not even after 2 h of exposure. However, apart from the resting value, the value presented by Sato et al. was in close agreement with the value obtained by us in vivo. The conclusion can be drawn that compared to other common solvents, xylene is highly soluble in blood (1, 14).

The high solubility in blood resulted in a large uptake during 2 h of exposure.

With 2.2 and 1.7 g administered, approximately 1.4 and 1.0 g, respectively, were taken up, i.e., about 60 %. Sedivec and Flek (13) found a resting uptake of 62 % for o-xylene, 64 % for m-xylene and 64 % for p-xylene. Bardodej and Bardodejova (7) reported the value of 64 % for ethylbenzene. The values are in close agreement with the results reported here for the entire mixture. According to the results presented in fig. 4, xylene was found to conform to the same rules for uptake in the lungs as toluene, styrene, methylene chloride, trichloroethylene, etc. However, this was not the case for butyl alcohol (6).

As the rate of work increases, pulmonary ventilation and blood circulation through the lungs increase. Consequently a larger amount of the solvent is inhaled,

and it is possible to transport more of the solvent via the blood to various tissues. For a solvent highly soluble in blood, an increase in pulmonary ventilation is more important than a raised blood flow with regards to a rapid equilibrium between blood and air. For solvents which are less soluble in blood, the reverse is true (10).

For most solvents the solubility in tissues is greater than in blood (10). Therefore the blood can continue to transport the solvent to the tissues despite a maintained equilibrium between blood and air. Also a biotransformation of the solvent will contribute to this course of events. After 2 h of exposure the blood only contained about 35 mg of xylene (about 7 mg/kg of blood and about 5 kg of blood). (The value is overestimated as the whole blood volume does not consist of arterial blood.) This calculated amount of xylene in blood is about 2 to 3 % of the total uptake during 2 h. Accordingly, the greatest part of the uptake had been transported to the different organs and tissues of the body. In series I the equilibrium between blood and air was approaching at the end of exposure, but the uptake per unit of time remained high. The conclusion is that the solubility in tissues and/or the degree of biotransformation for xylene is high.

In series II of the present study, the xylene uptake increased per unit of time from one stage to the other, i.e., from rest to 50, 100 and 150 W. However, there was probably a potential for a still higher uptake. The percentage uptake never dropped below 50. A corresponding series of experiments has previously been performed with other solvents. In exposure to methylene chloride (5) the highest uptake per unit of time was achieved already at a work load of 50 W. The percentage uptake declined, whereas the uptake per unit of time remained unchanged. In exposure to trichloroethylene, total uptake per unit of time declined through the course of the experiments. Thus, in one subject the uptake decreased from 320 mg during the second 30-min period at 50 W to about 90 mg in the fourth 30-min period at 150 W (4). When the uptake of a solvent declines to zero, an equilibrium must soon appear between the concentration in blood and air and between tissues and blood.

Accordingly, the solubility in tissues for trichloroethylene must be comparatively low. The higher the solubility and/or the greater the metabolism, the greater the amount that can still be taken up at the end of an exposure period of 2 h. At that time the total uptake was great for xylene, whereas it was low for methylene chloride. The conclusion is that xylene has a greater solubility in tissues and/or a greater metabolism than methylene chloride.

According to our calculations approximately 5 % of the amount of xylene taken up in the body was exhaled. Sedivec and Flek (13) found a corresponding degree of elimination in expired air. In addition, these authors based their calculations on the measurement of the excretion of metabolites in the urine. They found that 95 % of the amount taken up was metabolized. Thus, the present results agree very well with those of Sedivec and Flek.

A great deal of the xylene taken up is apparently quickly metabolized. Due to the high solubility in fat tissue, however, there must be an evident risk for accumulation in this tissue during prolonged exposure. The consequence would be a prolonged exposure of body tissues to xylene in obese individuals.

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