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Exposure to toluene

Uptake, distribution and elimination in man

by Anders Carlsson, MD¹

CARLSSON A. Exposure to toluene: Uptake, distribution and elimination in man. *Scand j work environ health* 8 (1982) 43—55. Twelve male subjects were exposed to a toluene concentration of about 300 mg/m³ in the inspiratory air during rest and/or physical exercise on a bicycle ergometer. Each subject was exposed during four consecutive 30-min periods. The uptake of toluene was about 50 % of the inspired amount at rest, with a decrease to about 30 % at a work load of 150 W during the fourth period. The total uptake of toluene during 2 h of work at 50 W was about 2.4 times higher than at rest. There was a close linear correlation between the alveolar and arterial concentrations of toluene, both during and after exposure. The means of the exhaled amounts of unchanged toluene during the first 20 h after exposure ranged between 7 and 14 % of the amount taken up. The urinary excretion of hippuric acid indicated an influence of food, especially at low uptake levels.

Key terms: alveolar air, arterial blood, exercise, hippuric acid, human, rest, venous blood.

The solubility of a gaseous solvent in blood and other tissues is of great importance for the total uptake via the lungs in the body. The solubility of toluene in blood and adipose tissue (18) should imply a solvent with a fairly high uptake. The uptake of toluene during the exposure of humans at rest is reported to be about 50 % of the inspired amount (13, 19, 21). In a photogravure printing plant, the uptake of toluene amounted to about 50 % of the quantity supplied, irrespective of the time for sampling or the degree of exposure on all the days during a week (16).

In humans, solvents are mainly eliminated unchanged via the lungs or excreted as metabolites in the urine. Other elimination takes place via the biliary system and the skin.

The exhaled quantities of toluene depend on the difference between the con-

centrations in mixed venous blood and alveolar air, the distribution coefficient blood/air, and the pulmonary ventilation. The minute volume of the heart is comparatively insignificant in the case of toluene, which has a relatively high blood/air distribution coefficient (2, 11). Previous studies reported a total respiratory elimination of unchanged toluene that ranged between 4 % (21) and 18 % (14, 19) of the uptake.

The conventional test for monitoring the uptake of toluene is based on the excretion of hippuric acid in the urine. Earlier studies (15, 22) reported that about 70 % of the quantity of toluene absorbed in humans is excreted in the urine as hippuric acid. Hippuric acid is a conjugation product of benzoic acid, which is a common food constituent (20).

In the present study, the toluene concentrations in alveolar air and arterial and venous blood were followed both during and after exposure. Furthermore, the total and relative uptake of toluene was determined.

The elimination of toluene from the body was also studied. Both the exhaled

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amounts of unchanged toluene and the excretion of hippuric acid were measured.

Subjects

A group of 12 men, 22–43 a of age, were used as subjects. They were given a careful clinical examination (2) and were classified as healthy. None had suffered from any disease having a detrimental effect on respiratory or circulatory organs. Except for two overweight subjects, the results from the anthropometric measurements, the pulmonary function tests, and submaximal and maximal exercise tests were all normal (1, 9, 12).

Experimental design

The experiments were performed in basically the same way as in earlier studies of solvents (2, 3, 4, 5, 6, 7). After catheters were introduced into a brachial artery and vein, the subjects were exposed to 306 ± 13 (SD) mg/m^3 (about 80 ppm) of toluene in the inspiratory air with the aid of a valve and a mouthpiece. The exposure periods lasted for 30 min, and each subject was exposed during four consecutive periods at each session, ie, for a total of 2 h. Subjects were exposed according to the following four alternatives (fig 1): series I: four subjects were exposed during 2 h at rest; series II: three subjects were exposed during 2 h of exercise on a bicycle ergometer at a work load of about

Fig 1. Twelve subjects [five subjects were used in two of three series (I, III, IV)] were exposed to toluene in inspiratory air for four consecutive 30-min periods at rest and during exercise according to four alternatives, series I, II, III, and IV. Exposure concentration of toluene: about $300 \text{ mg}/\text{m}^3$ in inspiratory air.

50 W; series III: six subjects were exposed during rest (30 min) and during exercise (30 + 30 + 30 min) at work loads of about 50, 100, and 150 W; series IV: four subjects were exposed during exercise (30 + 30 + 30 min) at work loads of about 150, 100, and 50 W and during rest (30 min). Five subjects participated in two of three series (I, III, IV) with at least a three-month interval. In order to reduce the possible influence of food on the amount of hippuric acid in the urine, the subjects in series IV were not allowed to eat, only to drink water from the evening before exposure until 4 h after the end of exposure. All the subjects were told to avoid benzoic acid-containing food.

During exposure, the uptake of toluene was continuously measured and the concentrations of toluene in alveolar air and arterial and venous blood were followed (series I–III). The exact times of the sampling can be found in fig 4. The heart rate was recorded every second minute, and the electrocardiogram every fifth minute, during exposure.

After the conclusion of exposure, a 4-h monitored period of elimination followed. The elimination phase was standardized with regard to rest and physical exercise. Physical exercise consisted of treadmill walking (5 min every half hour). The treadmill velocity and inclination were selected so that the load on the respiratory and circulatory organs was equivalent to a work load of about 50 W on the bicycle ergometer. Except for the subjects in series IV, lunch was taken 1 h after the conclusion of exposure.

After exposure, the concentrations of toluene in the alveolar air and arterial and venous blood were followed (series I–III). The exact times for sampling can be found in fig 6. In series IV, only the concentration of toluene in alveolar air was followed up to 4 h after the exposure was concluded.

Urine was collected from the subjects in series I–III at various hours after the conclusion of exposure and up to the following morning. The urinary excretion from the subjects in series IV was followed hourly from the end of exposure up to 4 h thereafter.

Adipose tissue biopsies were performed up to 12 d after the exposure was con-

cluded, and the concentration of toluene in the subcutaneous adipose tissue was determined. The results from these measurements have been published in another report (10).

Methods

The toluene/air mixtures were prepared in the same manner as in a previous study (2). The concentration of toluene in inspiratory air was continuously monitored with a hydrocarbon analyzer (Scott model 116). The toluene concentration in the air was prepared with accuracy sufficient to produce 294 to 332 mg/m³, when the objective was 300 mg/m³. Throughout the entire exposure expiratory air was continuously collected in bags made of polyester laminated aluminium foil. The air volume in the bags was measured with a well-balanced spirometer and the pulmonary ventilation ($\dot{V}_E$) was calculated for each period of exposure. Alveolar ventilation ($\dot{V}_A$) was calculated according to the formula: $\dot{V}_A = \dot{V}_E - \text{deadspace} \times \text{respiratory rate}$. Deadspace was set at 150 cm³, and the respiratory rate was continuously followed with a thermistor, located in the inspiratory valve and connected to an oscilloscope.

The concentrations of toluene in expiratory air were measured with a gas chromatograph (Antek model 464-LP) equipped with a stainless steel column (length 0.5 m, inner diameter 2.2 mm) packed with 8 % Carbowax 1540 on Chromosorb W (80–100 mesh). The column temperature was 50°C, and the flow rate of the carrier gas nitrogen was 25 ml/min. The error of the method for a single determination was calculated on the basis of 35 double determinations, ranging from 108 to 242 mg of toluene/m³ of expiratory air, and amounted to ± 1.8 % of the mean value.

The uptake of toluene in the organism was calculated as the difference between the total amounts in inspiratory and expiratory air.

The oxygen and carbon dioxide concentrations in expiratory air were analyzed (Beckman OM-11 and LB-2, respectively) in the last bag during each 30-min period, and oxygen uptake was calculated.

At the end of a normal expiration, so-called alveolar air samples were taken either from the breathing valve with the use of a glass syringe during exposure or in glass tubes after the conclusion of exposure. The alveolar air samples were analyzed with a gas chromatograph (Perkin-Elmer model F11) equipped with a stainless steel column (length 1.0 m, inner diameter 2.2 mm) packed with 8 % Carbowax 1540 on Chromosorb W (80–100 mesh). The column temperature was 80°C, and the flow rate of the carrier gas nitrogen was 24 ml/min.

The error of the method for a single determination during and after exposure amounted to ± 8.9 and 5.9 %, respectively, of the mean value. In both cases the calculations were based on 15 double determinations, ranging from 65 to 220 mg of toluene/m³ of alveolar air during exposure and from 3 to 60 after exposure.

Arterial and venous blood samples (approximately 0.5 g) were taken from the catheters and collected in gas-tight glass bottles (approximately 10 ml). Earlier studies on solvents provide the details of these techniques (2, 5). The blood samples were analyzed with a gas chromatograph (Perkin-Elmer model F33), equipped with a stainless steel column (length 2.0 m, inner diameter 2.2 mm) packed with 2 % Carbowax 400 on Chromosorb G (60–80 mesh), using a headspace technique (5). The column temperature was 90°C, and the flow rate of the carrier gas nitrogen was 30 ml/min. The concentration of toluene in the blood was calculated from the headspace concentration on the basis of equilibrated individual blood samples and standard air samples with known toluene concentrations. The error of the method was calculated from 15 double assays of blood, ranging from 0.12 mg (1.3 μ mol) to 3.13 mg (34.4 μ mol) of toluene/kg of blood, and amounted to ± 7 % of the mean value.

The concentrations of toluene in alveolar air and arterial and venous blood were calculated for each subject, and each period, on the basis of the final three determinations.

During the elimination period, the expired amounts of toluene were calculated as the product of alveolar ventilation and alveolar concentration up to 20 h after the

Table 1. Amounts of toluene given and taken up per each 30-min period of exposure to about 300 mg/m³. Series I: four periods at rest (4 subjects); series II: four periods at 50 W (3 subjects); series III: rest, 50 W, 100 W, and 150 W (6 subjects). Mean values and standard errors of the means are given. (1 mg of toluene = 11 μ mol)

Period	Given amount (mg)	Uptake (mg)	Uptake in % of given amount
<i>Series I</i>			
1	86 $\pm$ 4	48 $\pm$ 4	55 $\pm$ 3
2	87 $\pm$ 3	44 $\pm$ 4	50 $\pm$ 4
3	85 $\pm$ 5	42 $\pm$ 5	50 $\pm$ 4
4	85 $\pm$ 6	43 $\pm$ 6	51 $\pm$ 4
1—4	343 $\pm$ 18	176 $\pm$ 18	51 $\pm$ 4
<i>Series II</i>			
1	222 $\pm$ 11	116 $\pm$ 3	52 $\pm$ 2
2	231 $\pm$ 14	107 $\pm$ 6	47 $\pm$ 2
3	251 $\pm$ 16	105 $\pm$ 7	42 $\pm$ 1
4	243 $\pm$ 11	98 $\pm$ 2	40 $\pm$ 1
1—4	948 $\pm$ 38	426 $\pm$ 15	45 $\pm$ 1
<i>Series III</i>			
1	93 $\pm$ 6	48 $\pm$ 3	52 $\pm$ 1
2	219 $\pm$ 3	107 $\pm$ 3	49 $\pm$ 1
3	351 $\pm$ 20	142 $\pm$ 10	40 $\pm$ 1
4	517 $\pm$ 36	152 $\pm$ 14	29 $\pm$ 2
1—4	1,179 $\pm$ 63	449 $\pm$ 29	38 $\pm$ 1

Fig 2. The amounts of toluene given and taken up (mean values) in exposure to about 300 mg/m³ in the inspiratory air at rest and during exercise. Mean values for four subjects (series I), three subjects (series II), and six subjects (series III) are given. (1 mg of toluene = 11 μ mol)

Fig 3. The total uptake of solvents in the lungs as the percentage of the amount supplied in relation to the quotient between the concentrations (conc) of alveolar (alv) and inspired (insp) air. The total uptake was continuously measured for 30-min periods, and the corresponding concentrations in alveolar air were based on three measurements during the last 10 min of the same period. Each symbol represents a mean value of three to eight subjects. The equation of the regression line was calculated on the basis of 70 such mean values. The number of exposed subjects was 14 for methylene chloride, 15 for trichloroethylene, 4 for aliphatic (aliphatic) and aromatic (aromat) white spirit, 7 for styrene, 12 for xylene, 19 for toluene (12 from the present study), and 16 for acetone (altogether about 90 subjects). Regression line: $y = -0.72 X + 74.6$; $r = -0.93$; $SD = \pm 4.4$.

conclusion of exposure. During the first 4 h after exposure, pulmonary ventilation was measured with a Wright respirometer (dead-space was set at 150 cm³ and respiratory rate was counted) and alveolar ventilation was calculated every 30 min from the earlier-mentioned formula. For the next 16 h, alveolar ventilation was set at 8 l/min for the first 5 h and 5 l/min for the following 11 h. The expired quantities of toluene, in milligrams per minute, were plotted versus time. A fitted curve was drawn for each individual, and the area under the curve was measured with a planimeter.

The analysis of urinary hippuric acid was performed by an isotachophoretic method, which is to be published elsewhere.

Results

In exposure at rest for 2 h (series I), the total uptake of toluene was 48 mg (528 μ mol) during period 1, corresponding to about 55 % of the amount supplied (table 1, fig 2). During continued exposure at rest (periods 2–4), the uptake dropped to about 43 mg (473 μ mol)/period and corresponded to about 50 % of the amount supplied.

In exposure at 50 W for 2 h (series II), the uptake declined successively. It amounted to 116 mg (1,276 μ mol) during period 1, dropping to 98 mg (1,078 μ mol) in period 4, and constituted 52 and 40 %, respectively, of the amount supplied. The total uptake of toluene during 2 h of work at 50 W was about 2.4 times higher than at rest.

In work with increasing work loads (series III) during four consecutive 30-min periods, the uptake was 48 mg (528 μ mol) at rest, 107 mg (1,177 μ mol) at 50 W, 142 mg (1,562 μ mol) at 100 W, and 152 mg (1,672 μ mol) at 150 W and constituted 52, 49, 40, and 29 %, respectively, of the amount supplied.

The ratio between the relative uptake of toluene (total uptake as percentage of inspired amount) and alveolar concentrations (as percentage of the concentration in the inspiratory air) correlated well with the ratio found for previously studied solvents (fig 3).

After 30 min of exposure at rest to about 300 mg/m³ of toluene in inspiratory air (series III), the concentration in alveolar air amounted to about 85 mg/m³ or about 28 % of the concentration in the inspiratory air (table 2 & fig 4). The corresponding arterial blood concentration was about 0.7 mg (7.7 μ mol)/kg. During continued exposure at rest for 2 h (series I), both alveolar air and arterial blood concentrations remained relatively constant throughout the entire exposure (fig 4). In series I, the alveolar air concentrations of the overweight subject were consistently lower than those of the normal-weight subjects.

At 50 W (series III), with a more than doubled pulmonary ventilation than at rest, the alveolar air concentration increased to 120 mg/m³ and corresponded to 39 % of the concentration in inspiratory air. The corresponding arterial blood concentration at 50 W was 1.7 mg (18.7 μ mol)/kg. In work at 50 W for 2 h (series II), the alveolar air concentration rose from 115 mg/m³ in period 1 to 142 mg/m³ in period 4. The corresponding arterial blood concentrations rose from 1.6 mg (17.6 μ mol)/kg to 2.1 mg (23.1 μ mol)/kg.

During work at work loads of 100 and 150 W (series III), the pulmonary ventilation increased about four and six times, respectively, in comparison to the resting level. The alveolar concentrations rose to 169 and 220 mg/m³, respectively, corresponding to 53 and 69 % of the concentration in inspiratory air. The corresponding arterial blood concentrations rose to 2.4 mg (26.4 μ mol)/kg and 3.3 mg (36.3 μ mol)/kg, respectively.

In exposure at rest and at 50 W for 2 h, the concentrations of alveolar air and arterial and venous blood achieved a plateau value after about 30 and 60 min, respectively, while there was no such tendency during work with increasing work loads throughout the entire exposure (fig 4).

Table 3 lists the concentrations of toluene in alveolar air and arterial blood as the percentage of the concentration in the inspiratory air and the calculated quotients between these concentrations. The concentrations are based upon the final three determinations in every period. The quotients between the arterial blood

and alveolar air concentrations changed from about 9 at rest to about 15 during exercise at 150 W. The arterial blood concentration was 4.25 times higher at 150 W

than at rest, while the corresponding value for the alveolar concentration was 2.5.

In fig 5 the relationship is shown be-

Table 2. Physiological variables and experimental data at the end of each 30-min period during exposure to a toluene concentration of about 300 mg/m³ at rest and during exercise. Series I: four periods at rest (4 subjects); series II: four periods at 50 W (3 subjects); series III: rest, 50 W, 100 W, and 150 W (6 subjects). Every period (1—4) comprised 30 min, every series 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) (1 mg of toluene = 11 μ mol)

Period	Heart rate (beats/min)	$\dot{V}_{O_2}$ STPD ^a (l/min)	$\dot{V}_E$ BTPS ^b (l/min)	Toluene concentration		
				Alveolar air (mg/m ³)	Arterial blood (mg/kg)	Venous blood (mg/kg)
<i>Series I</i>						
1	68 ± 5	0.37 ± 0.04	9.7 ± 0.9	71 ± 7	0.6 ± 0.1	0.4 ± 0.1
2	68 ± 4	0.35 ± 0.02	9.5 ± 0.7	73 ± 5	0.6 ± 0.0	0.4 ± 0.1
3	65 ± 6	0.35 ± 0.03	9.4 ± 0.9	74 ± 3	0.6 ± 0.0	0.4 ± 0.0
4	67 ± 5	0.36 ± 0.02	9.4 ± 1.0	75 ± 5	0.6 ± 0.0	0.5 ± 0.1
<i>Series II</i>						
1	92 ± 9	1.07 ± 0.05	25.5 ± 1.3	115 ± 22	1.6 ± 0.1	0.8 ± 0.1
2	93 ± 9	1.05 ± 0.11	27.0 ± 1.6	119 ± 11	1.8 ± 0.0	1.2 ± 0.2
3	97 ± 12	1.09 ± 0.03	28.7 ± 1.4	141 ± 2	2.1 ± 0.2	1.2 ± 0.1
4	98 ± 12	1.04 ± 0.03	28.0 ± 1.2	142 ± 3	2.1 ± 0.1	1.1 ± 0.2
<i>Series III</i>						
1	67 ± 4	0.37 ± 0.01	10.6 ± 0.8	84 ± 3	0.7 ± 0.1	0.4 ± 0.1
2	93 ± 4	1.08 ± 0.03	24.7 ± 0.6	120 ± 1	1.7 ± 0.1	1.1 ± 0.1
3	120 ± 5	1.69 ± 0.06	38.6 ± 2.2	169 ± 7	2.4 ± 0.1	1.8 ± 0.2
4	152 ± 7	2.39 ± 0.07	56.4 ± 3.9	220 ± 8	3.3 ± 0.2	2.7 ± 0.2

^a STPD = 0°C, 760 mm Hg, dry (standard conditions).

^b BTPS = temperature of 37°C, ambient pressure, saturated with water.

Fig 4. The toluene concentrations (conc) in alveolar (alv) air and arterial (art) and venous (ven) blood during exposure. Mean values for four subjects (series I), three subjects (series II), and six subjects (series III) are given. [$\dot{V}_A$ = alveolar ventilation (l/min); 1 mg of toluene = 11 μ mol]

tween arterial blood and alveolar air concentrations at the end of each exposure period for all subjects. The relationship was linear, and the arterial blood concentration was closely correlated to the alveolar air concentration.

In the continuous exposure of the subjects during four 30-min periods at rest, 50 W, 100 W, and 150 W (series III), the arterial and peripheral venous concentrations were measured. The mixed venous toluene concentration (C_v) was calculated at the end of each 30-min period according to the Fick equation [$U_L = (C_a - C_v)$

$\times \dot{Q}$] and the assumed cardiac outputs ($\dot{Q}$) (3, 4, 5). The measured uptakes (U_L) and arterial concentrations (C_a) from the present study were put into the formula. The peripheral venous concentration averaged about 82 % (range 57–125 %) of the calculated mixed venous concentration at rest. The corresponding values at 50, 100 and 150 W were 94 % (range 68–114 %), 88 % (range 58–101 %), and 90 % (range 65–103 %), respectively. The calculated mixed venous concentration averaged about 60 % (range 50–67 %) of the arterial concentration at rest. The

Table 3. Arterial and alveolar concentrations of toluene at the end of each 30-min period, as the percentage of the concentrations in inspiratory air, and the quotients between these concentrations. Exposure was performed with a toluene concentration of about 300 mg/m³ during rest and exercise. Series I: four periods at rest (4 subjects); series II: four periods at 50 W (3 subjects); series III: rest, 50 W, 100 W, and 150 W (6 subjects). Mean values and standard errors of the means are given.

Period	Alveolar concentration (%)	Arterial concentration (%)	Quotient (arterial/alveolar concentration)
<i>Series I</i>			
1	23 ± 2	195 ± 40	8.6 ± 0.8
2	24 ± 2	198 ± 16	8.5 ± 0.1
3	24 ± 1	189 ± 5	7.9 ± 0.1
4	25 ± 1	209 ± 1	8.9 ± 0.5
<i>Series II</i>			
1	39 ± 7	528 ± 30	14.4 ± 1.8
2	40 ± 4	622 ± 9	15.9 ± 1.8
3	46 ± 1	688 ± 40	14.9 ± 1.0
4	47 ± 1	687 ± 16	14.6 ± 0.2
<i>Series III</i>			
1	28 ± 1	246 ± 20	8.9 ± 0.8
2	39 ± 1	534 ± 33	13.8 ± 0.8
3	53 ± 1	764 ± 39	14.5 ± 0.8
4	69 ± 1	1,046 ± 52	15.2 ± 0.9

Fig 5. The relationship between the concentration (conc) of toluene in arterial blood and alveolar air after 30 min of exposure to a toluene concentration of about 300 mg/m³ at rest and during exercise. Each symbol stands for one exposure period, ie, a subject is represented by more than one symbol. Symbols: ○ rest; □ 50 W; ▲ 100 W; ◆ 150 W. Regression line: $y = 0.018x - 0.55$; $N = 52$; $r = 0.95$. (1 mg of toluene = 1 μmol)

corresponding values at 50, 100, and 150 W were 77 % (range 70–81 %), 86 % (range 84–89 %), and 92 % (range 88–94 %), respectively.

After the conclusion of exposure, the concentrations of toluene in alveolar air and arterial and venous blood dropped very rapidly (fig 6). The decrease was the most pronounced within the first few min-

utes, whereas the further decline occurred much more gradually. After 30 min the arterial mean concentration for series I–III amounted to about 22 % of the concentration at the end of exposure (table 4), with a drop to about 9 % 60 min later. The corresponding values for peripheral venous blood were 49 and 23 %, respectively, and for alveolar air 14 and 6 %, respectively.

Fig 6. The toluene concentrations (conc) in alveolar (alv) air and arterial (art) and venous (ven) blood after the end of exposure. Exposure was performed with a toluene concentration of about 300 mg/m³ in the inspiratory air during four consecutive 30-min periods. Mean values are given. Series I: four periods at rest (4 subjects); series II: four periods at 50 W (3 subjects); series III: rest, 50 W, 100 W, and 150 W (6 subjects). (1 mg of toluene = 11 µmol)

Table 4. Arterial, venous and alveolar concentrations of toluene 30 and 90 min after the end of exposure, as the percentage of the concentration at the end of exposure. Exposure was performed with a toluene concentration of about 300 mg/m³ in the inspiratory air during four consecutive 30-min periods. Series I: four periods at rest (4 subjects); series II: four periods at 50 W (3 subjects); series III: rest, 50 W, 100 W, and 150 W (6 subjects). Mean values and standard errors of the means are given.

Minutes after exposure	Arterial concentration (%)	Venous concentration (%)	Alveolar concentration (%)
<i>Series I</i>			
30	20.6 ± 4.2	41.2 ± 2.0	10.1 ± 1.3
90	9.0 ± 1.0	18.1 ± 2.1	4.8 ± 0.9
<i>Series II</i>			
30	22.8 ± 0.9	69.6 ± 14.3	16.7 ± 3.3
90	10.0 ± 0.8	30.8 ± 10.0	8.1 ± 0.8
<i>Series III</i>			
30	23.0 ± 1.5	37.0 ± 7.0	15.3 ± 1.0
90	9.3 ± 0.7	18.5 ± 3.6	6.3 ± 0.4

In fig 7 the relationship is shown between alveolar air and arterial blood concentrations, during 15 to 90 min after the end of exposure, for all subjects in series I—III. The relationship was linear, and the alveolar air concentration correlated closely with the arterial blood concentration.

The amounts of unchanged toluene exhaled via the respiratory tract were about 2.5 times higher during exercise at 50 W than at rest (fig 8). During the first 20 h after the conclusion of exposure at rest (series I), the respiratory elimination of unchanged toluene was about 7 % of the uptake (table 5). The corresponding mean value after exposure at work with increasing work loads (series III) was about 14 %, the difference being significant (Mann-Whitney test, $p < 0.05$).

The respiratory elimination of unchanged toluene, as the percentage of the total uptake, was 2.6 times higher for series III than for series IV during the first 30 min after the end of exposure. The difference was significant (Mann-Whitney test, $p < 0.05$). Series III and IV were performed with a stepwise increase and decrease in work loads, respectively.

During the first 4 h, the urinary mean excretion of hippuric acid for series I, II, III, and IV was 102, 94, 94, and 77 %, respectively, of the uptake (table 6). There was no significant difference between the subjects with and without food intake (Mann-Whitney test, $p > 0.05$). Within 20 h after exposure the urinary excretion of hippuric acid averaged 410 % (series I), 222 % (series II), and 211 % (series III) of

Fig 7. The relationship between the concentration of toluene in alveolar air and arterial blood during 15 to 90 min after the end of exposure for all the subjects in series I—III. Exposure was performed with a toluene concentration of about 300 mg/m³ in the inspiratory air during four consecutive 30-min periods. Every subject is represented by six symbols. Symbols: ▲ series I; ○ series II; ◆ series III. Regression line: $y = 47.6 X + 1.8$; $r = 0.94$. (1 mg of toluene = 11 μ mol)

Fig 8. The calculated amounts of expired toluene in milligrams per minute up to 2 h after the end of exposure in series III. The calculations were made both at rest and during exercise equivalent to a work load of about 50 W on the bicycle ergometer. Exposure was performed with a toluene concentration of about 300 mg/m³ in the inspiratory air during four consecutive 30-min periods. Mean values are given. Series III: rest, 50 W, 100 W, and 150 W (6 subjects). (1 mg of toluene = 11 μ mol)

the total toluene uptake for subjects with food intake.

After four months, one subject from each of series II and III was exposed on a second occasion. The same concentration of toluene in the inspiratory air and the same work loads as in the first occasion were chosen. The results from the two occasions showed a good reproducibility of the laboratory experiments. The relative uptakes during 2 h of exposure for the subject from series II were 42.3 and 43.4 %, respectively, on the two occasions. The corresponding values for the subject from series III were 37.4 and 36.3 %, respectively.

Discussion

In the present study, the relative uptake of toluene was about 50 % during 2 h of con-

tinued exposure at rest, which is in close agreement with the uptakes found in the literature (13, 19, 21). During exposure for 2 h at 50 W the relative uptake dropped from 52 % in period 1 to 40 % in period 4. In work with increasing work loads, the relative uptake dropped from 52 % at rest to 29 % at 150 W.

Veulemans & Masschelein (21) exposed subjects to 50 ppm of toluene in the inspiratory air at rest and during periods of 10–15 min at 25, 50, 75, 100, and 125 W. Between the different periods of work, there was an exposure period of about 20 min at rest. They found a close correlation between the total uptake of toluene per minute and the pulmonary ventilation. This result indicates that the relative uptake is constant during exposure at rest and during short periods at work.

Table 5. Accumulated respiratory elimination of unchanged toluene, as the percentage of toluene uptake, at different times after exposure. The uptakes of toluene during 2 h of exposure are also stated. Exposure was performed with a toluene concentration of about 300 mg/m³ in the inspiratory air during four consecutive 30-min periods. Series I: four periods at rest (4 subjects); series II: four periods at 50 W (3 subjects); series III: rest, 50 W, 100 W, and 150 W (6 subjects); series IV: 150 W, 100 W, 50 W, and rest (4 subjects). Mean values and standard errors of the means are given. (1 mg of toluene = 11 μ mol)

Series	Uptake (mg)	Accumulated respiratory elimination of unchanged toluene, as % of uptake, at different times after exposure				
		0.5 h	1 h	2 h	4 h	20 h
I	177 $\pm$ 18	1.4 $\pm$ 0.1	2.2 $\pm$ 0.2	3.5 $\pm$ 0.2	5.2 $\pm$ 0.3	7.4 $\pm$ 0.4
II	426 $\pm$ 15	2.6 $\pm$ 0.1	3.5 $\pm$ 0.2	5.0 $\pm$ 0.3	7.0 $\pm$ 0.6	9.8 $\pm$ 1.0
III	449 $\pm$ 29	4.4 $\pm$ 0.2	5.6 $\pm$ 0.3	7.6 $\pm$ 0.4	10.2 $\pm$ 0.6	14.3 $\pm$ 1.1
IV	395 $\pm$ 24	1.7 $\pm$ 0.2	2.9 $\pm$ 0.2	5.0 $\pm$ 0.3	7.8 $\pm$ 0.5	—

Table 6. Accumulated urinary excretion of hippuric acid, as the percentage of toluene uptake, at different times after exposure. The uptakes of toluene during 2 h of exposure are also stated. Exposure was performed with a toluene concentration of about 300 mg/m³ in the inspiratory air during four consecutive 30-min periods. Series I: four periods at rest (4 subjects); series II: four periods at 50 W (3 subjects); series III: rest, 50 W, 100 W, and 150 W (6 subjects); series IV: 150 W, 100 W, 50 W, and rest (4 subjects). Mean values and standard errors of the means are given. (1 mg of toluene = 11 μ mol)

Series	Uptake (mg)	Accumulated urinary excretion of hippuric acid, as % of uptake, at different times after exposure	
		4 h	20 h
I	177 $\pm$ 18	102 $\pm$ 36	410 $\pm$ 122
II	426 $\pm$ 15	94 $\pm$ 33	222 $\pm$ 37
III	449 $\pm$ 29	94 $\pm$ 8	211 $\pm$ 13
IV	395 $\pm$ 24	77 $\pm$ 14	—

One explanation of the successive decline in the relative uptake during exercise is the increasing tissue toluene concentrations which reduce the rate of uptake in the tissues. More toluene appears in venous blood, the alveolar-mixed venous partial pressure difference is reduced, and toluene uptake is similarly reduced. During short periods of work, as used by Veulemans & Masschelein, such a decline will not take place.

The quotient between toluene concentrations in arterial blood and alveolar air should be constant during both rest and exercise if the equilibration of alveolar to arterial partial pressure is completed instantaneously, no disparities in ventilation:perfusion ratios are present, and the blood solubility remains constant. The calculated quotients in the present study remained relatively stable around 15 during exposure at work. The value agrees closely with the one calculated from *in vitro* experiments with blood/air (18). The lower quotients at rest may be explained by ventilation/perfusion disparities, when resting in the sitting position (23).

The peripheral venous toluene concentration varied to a great extent in relation to the calculated mixed venous concentration between the subjects, both at rest and during exercise. The differences may be explained by different body composition, especially with regard to the amount of body fat.

The main reason for the decreasing differences between the arterial and mixed venous concentrations is the increasing tissue equilibration. One possible explanation for the differences between rest and exercise may be a different distribution of blood in the two situations (8). Another explanation is the influence of metabolism. About 25 % of the cardiac output at rest flows through the liver (17), which is the organ with the largest metabolic capacity. It will lower the mixed venous toluene concentration. This occurrence is naturally of great importance for the respiratory uptake, as solvent uptake increases in proportion to the magnitude of the solvent partial pressure difference between alveoli and mixed venous blood. During exercise the ratio between the blood flow through the liver and car-

diac output is reduced (17) and results in a decreased influence of liver metabolism on the concentration of toluene in mixed venous blood.

After the conclusion of exposure, the concentration of toluene in alveolar air reflects the amount of toluene in mixed venous blood. A previous study (2) reported a poor correlation between alveolar air and peripheral venous blood during the elimination. However, there was a high correlation between the concentrations of toluene in alveolar air and arterialized capillary blood in workers after exposure to toluene (16). This result agrees with the findings in the present study. It means that arterial blood concentrations can be estimated from alveolar air samples or arterialized capillary blood samples, but not from peripheral venous blood, during the elimination phase.

During the first 30 min after exposure, the accumulated respiratory elimination of toluene, as percentage of uptake, was much lower for series I and IV than for series II and III. The difference may be partly explained by the fact that the subjects in series II and III finished the exposure at work, and therefore a higher alveolar ventilation occurred after exposure than after exposure in series I and IV. The exhalation rate of toluene via the lungs is increased by increasing alveolar ventilation (11), which is illustrated in fig 8.

The exhaled amounts of unchanged toluene during the first 20 h after the conclusion of exposure ranged between about 7 % (series I) and 14 % (series III) of the uptake (table 5). The higher value was mainly explained by a significantly increased ratio between the alveolar concentration and total uptake after exposure during rest and exercise compared to during rest (Mann-Whitney test, $p < 0.05$). The reason for the increased ratio is probably a different distribution of the solvent during exercise as compared to that during rest. In previous studies (14, 19, 21) a total elimination of about 4–18 % was reported. The reason for the differences in the respiratory elimination of unchanged toluene in the mentioned studies may be varying physical activity during the elimination period.

The urinary excretion of hippuric acid was measured up to 20 h after the conclusion of exposure. The high values indicated an influence of the diet on the excretion of hippuric acid, even if this influence was not established by the comparison of the urinary excretion of the subjects with and without food intake.

In summary, the presented data demonstrate (i) a relative uptake of toluene at about 50 % at rest, with a decrease to about 30 % at a work load of 150 W, (ii) a total uptake of toluene about 2.5 times higher during 2 h of work at 50 W than at rest, (iii) a close linear correlation between alveolar air and arterial blood concentrations both during and after exposure, (iv) a respiratory elimination of unchanged toluene ranging in mean between 7 and 14 % of the uptake, (v) an indication of influence from food on the excretion of hippuric acid, especially at low uptake levels of toluene.

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References

1. Åstrand I. Aerobic work capacity in men and women with special reference to age. *Acta physiol scand* 49 (1960): suppl 169, p 83.
2. Åstrand I, Ehrner-Samuel H, Kilbom Å, Övrum P. Toluene exposure: I Concentration in alveolar air and blood at rest and during exercise. *Work environ health* 9 (1972) 119—130.
3. Åstrand I, Kilbom Å, Övrum P. Exposure to white spirit: I Concentration in alveolar air and blood during rest and exercise. *Scand j work environ health* 1 (1975) 15—30.
4. Åstrand I, Kilbom Å, Övrum P, Wahlberg I, Vesterberg O. Exposure to styrene: I Concentration in alveolar air and blood at rest and during exercise and metabolism. *Work environ health* 11 (1974) 69—85.
5. Åstrand I, Kilbom Å, Wahlberg I, Övrum P. Methylchloroform exposure: I Concentration in alveolar air and blood at rest and during exercise. *Work environ health* 10 (1973) 69—81.
6. Åstrand I, Övrum P. Exposure to trichloroethylene: I Uptake and distribution in man. *Scand j work environ health* 4 (1976) 199—211.
7. Åstrand I, Övrum P, Carlsson A. Exposure to methylene chloride: I Its concentration in alveolar air and blood during rest and exercise and its metabolism. *Scand j work environ health* 1 (1975) 78—94.
8. Åstrand P-O, Rodahl K. Textbook of work physiology. Second edition. McGraw-Hill Book Co, New York, NY 1977, pp 154—155.
9. Berglund E, Birath G, Bjure J, Grimby G, Kjellmer I, Sandqvist L, Söderholm B. Forced expirograms in subjects between 7 and 70 years of age. *Acta med scand* 173 (1963) 185—192.
10. Carlsson A, Ljungquist E. Exposure to toluene: Concentration in subcutaneous adipose tissue. *Scand j work environ health* 8 (1982) 56—62.
11. Goldstein A, Aronow L, Kalman SM. Principles of drug action: The basis of pharmacology. Second edition. Wiley International Edition. John Wiley & Sons, Inc, New York, NY 1974, p 347.
12. Grimby G, Söderholm B. Static lung volumes and maximum voluntary ventilation in adults with a note on physical fitness. *Acta med scand* 173 (1963) 199—206.
13. Nomiya K, Nomiya H. Respiratory retention, uptake and excretion of organic solvents in man: Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. *Int Arch Arbeitsmed* 32 (1974) 75—83.
14. Nomiya K, Nomiya H. Respiratory elimination of organic solvents in man: Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. *Int Arch Arbeitsmed* 32 (1974) 85—91.
15. Ogata M, Tomokuni K, Takatsuka Y. Urinary excretion of hippuric acid and m- or p-methylhippuric acid in the urine of persons exposed to vapours of toluene and m- or p-xylene as a test of exposure. *Br j ind med* 27 (1970) 43—50.
16. Övrum P, Hultengren M, Lindqvist T. Exposure to toluene in a photogravure printing plant: Concentration in ambient air and uptake in the body. *Scand j work environ health* 4 (1976) 199—211.
17. Rowell LB. Human cardiovascular adjustments to exercise and thermal stress. *Physiol rev* 54 (1974) 75—159.
18. Sato A, Nakajima T. Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. *Br ind med* 36 (1979) 231—234.
19. Srbova J, Teisinger J. Absorption and elimination of toluene in man. *Prac lek* 4 (1952) 41—47.
20. Szadkowski D, Borkamp A, Lehnert G. Hippursäureausscheidung in harn in abhängigkeit von tagesrythmik und alimentären einflüssen. *Int arch occup environ health* 45 (1980) 141—152.
21. Veulemans H, Masschelein R. Experimental human exposure to toluene: Factors influencing the individual respiratory uptake

- and elimination. Int arch occup environ health 42 (1978) 91—103.
22. Veulemans H, Masschelein R. Experimental human exposure to toluene: III Urinary hippuric acid excretion as a measure of individual solvent uptake. Int arch occup environ health 43 (1979) 53—62.
23. West JB. Regional differences in gas exchange in the lung of erect man. J appl physiol 17 (1962) 893—898.

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