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Biological Monitoring of Exposure to Organic Solvent Vapors II. Simulation Studies using a Physiological Pharmacokinetic Model for m-Xylene

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Abstract: The relationship between external and internal doses of m-xylene and the effects of body weight, body fat content, sex, and physical activity on the pharmacokinetics of m-xylene were studied using a physiological simulation model.

1. At low exposure concentrations, equal time-weighted average (TWA) concentrations gave almost the same internal dose of m-xylene.
2. The m-xylene concentration in the blood increased continuously with increasing m-xylene concentration in inhaled air. By contrast, the excretion rate of m-methyl hippuric acid (m-MHA) in the urine approached a plateau with increasing m-xylene exposure concentration.
3. The larger the body size, the larger the amount of m-xylene absorbed. However, no significant change was found in m-xylene concentration in the blood with increase in body size. By contrast, the amounts of m-MHA excreted in the urine varied with body size: the larger the body size, the greater was the rate of urinary m-MHA excretion.
4. Both m-xylene concentration in the blood and the rate of urinary m-MHA excretion were higher in a slim than in an obese man during exposure, but this relationship was reversed in due course of time after exposure.
5. The physical activity (50 W) during exposure greatly increased the blood concentration of m-xylene as well as the rate of urinary m-MHA excretion.
6. The concentration of m-xylene in the blood during exposure was lower in women than in men, while the opposite was true starting about 10 hours after the end of exposure. The rate of m-MHA excretion in the urine was lower in women than in men both during and after exposure.

Key words: Physiologically based pharmacokinetic model, m-Xylene, m-Methyl hippuric acid, External and internal doses, Biological exposure monitoring

INTRODUCTION

The term "dose-effect relationship" is often used in the field of toxicology. The toxic potential of a chemical is expressed on the basis of this dose-effect relationship. In animal experiments, the "dose" is generally expressed as the amount of the chemical administered per unit body weight or, when the chemical is inhaled, as the concentration of the inhalant multiplied by the duration of inhalation. Aside from local toxicity observed at the site of entry of the chemical, toxicity of the chemical develops as it is absorbed, distributed, metabolized, and excreted. The concentration of the chemical (or its metabolites) in the target tissue determines the degree of toxicity[1].

Toxicity after inhalation of a fixed concentration of solvent vapor is not equal among individual organisms even in the simplest scheme of an animal experiment. This individual variation of toxicity is accounted for in part by differences in the sensitivity of the

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target tissue, but it is mostly derived from differences in the concentration of the chemical in the target tissue. In inhalation exposure, the absorption of an inhalant changes greatly with alveolar ventilation even when the concentration of the inhalant is fixed. Therefore, to accurately define the dose-effect relationship, the "dose" must be the concentration in the target tissue (target tissue dose) or, at least, the amount effectively absorbed by the body (internal dose) instead of the inhalant concentration (external dose).

When the toxicity is caused by the chemical itself, the internal dose may be represented by the area under the concentration-time curve (AUC) of the chemical. However, the situation is more complex when metabolites are responsible for the toxicity, because the toxicity in this case is proportional to the amount of adducts generated, and this is determined by the relative rates of metabolic activation and detoxification.

The objective of biological exposure monitoring is to estimate the internal dose on the basis of measurements of the concentration of the chemical or its metabolites in biological samples[2]. Ideally, the health effect should be assessed from the internal dose and a known dose-effect relationship. However, to date little is known of the internal dose-effect relationship of organic solvents. Only maximum allowable concentrations for external exposure have been established from external dose-effect relationships based on data obtained from longstanding field work or laboratory investigations. This maximum allowable concentration is generally expressed as the exposure concentration at which the solvent is considered to pose no health problems in an average worker who inhales it for 8 hours a day, 5 days a week, for a prolonged period[3]. However, the concentration in the work environment greatly varies during the work shift. Therefore, the maximum allowable concentration is expressed as the time-weighted average (TWA) concentration during the 8-hour period.

Recently, close correlations between the exposure concentration (external dose) and the concentration of the solvents or their metabolites in biological samples (internal dose) have been found for some solvents[4]. The biological exposure index (BEI) recommended in 1984–1985 by the American Conference of Governmental Industrial Hygienists (ACGIH)[3] is expressed as the concentration of a chemical or its metabolite in a biological sample which corresponds to the maximum allowable TWA. The BEI was intended to indicate possible excessive exposure. When the concentration in a biological sample exceeds the BEI, it may be necessary to reassess the work environment.

Organic solvents may be absorbed percutaneously because they are more or less absorbable through the skin, and they may enter the mouth via contaminated hands. If the results of biological monitoring have exceeded the BEI and the exposure concentration has been within the allowable range, investigations are warranted to determine whether or not the solvent entered the body by routes other than the airway, whether or not there has been non-occupational contact with the solvent, and whether or not there are other factors that may explain the abnormal values.

However, the concentrations of the chemical and its metabolites in the body also change with time. Therefore, questions arise as to when samples should be collected for the most accurate estimate of the internal dose. Also, physiological and environmental factors affecting the pharmacokinetics of chemicals influence the estimate. This variation poses the greatest difficulty in biological exposure monitoring.

The present study was intended to clarify the relationship between external and internal doses and to assess the effects of physiological factors on the relationship using our newly developed physiological pharmacokinetic model for m-xylene[5].

Methods

1. Simulation model

Our physiological model of m-xylene pharmacokinetics in humans[5] was used in this study.

2. Simulation parameters and exposure conditions

1) Relationship between external and internal doses

a) Continuous exposure and intermittent exposure

Continuous exposure of a 70 kg male to 50 ppm m-xylene for 8 hours was simulated using the parameters in Table 1. Intermittent exposure of the same man to 100 ppm m-xylene for 1 hour 4 times at 1-hour intervals was also simulated.

b) Internal dose by random exposure

Effects of fluctuations in the exposure concentration with time on the internal dose were evaluated. Sixteen 30-min exposures of a 70 kg male (Table 1) to m-xylene at various concentrations (0 ppm × 2, 5 ppm, 10 ppm, 20 ppm, 40 ppm × 2, 50 ppm × 4, 75 ppm × 3, 110 ppm, and 150 ppm) were simulated. We used four exposure patterns: random (exposure concentrations arranged in a random order), incremental (exposure concentrations arranged in order from lowest to highest), decremental (exposure concentrations ar-

Table 1. Simulation parameters for m-xylene pharmacokinetics in man and woman.

Compartment	Volume[a], *l*		Blood flow[a], *l*/min		Partition coefficient[b] (tissue/blood)
	Man	Woman	Man	Woman	
Lung (LC)	V_L[c]	V_L[c]	Qc	Qc	4.09
Vessel-rich (VRC)	0.030BW[d]	0.030BW[d]	0.379Qc	0.379Qc	4.42
Vessel-poor (VPC)	0.085BW	0.085BW	0.063Qc	0.063Qc	2.01
Muscle (MC)	0.415BW	0.315BW	0.114Qc	0.087Qc	3.01
Fat (FC)	0.211BW	0.365BW	0.053Qc	0.092Qc	77.8
Gastrointestinal (GC)	0.019BW	0.019BW	0.171Qc	0.171Qc	4.67
Hepatic (HC)	0.023BW	0.023BW	0.069Qc	0.069Qc	3.02
Shunt	—	—	0.151Qc	0.139Qc	—
Blood/air partition coefficient (λ)[e]			26.4		
Cardiac output (Qc)[a], *l*/min	Man			Woman	
	$0.296(BW)^{0.7}$			$0.267(BW)^{0.7}$	
Vmax[b][f], mmol/min	$Vmax_1$			$Vmax_2$	
	$1.394\times10^{-3}(BW)^{0.7}$			$1.115\times10^{-2}(BW)^{0.7}$	
Km[b], mmol/*l*	Km_1			Km_2	
	0.033			0.330	
Kex[b], min^{-1}	0.012				
Q_L	Qc				

a) Reference 7.
b) Experimentally determined.
c) V_L = Functional residual capacity + 1/3 of tidal volume + volume of arterial blood × λ + volume of lung tissue × lung/air partition coefficient (Reference 8).
d) Body weight in kg.
e) Reference 9.
f) Extrapolated from rat data as follows: (Vmax of rats) × (BW of humans/BW of rats)$^{0.7}$.

ranged in order from highest to lowest), and increase-decrease (peak concentration occurred in the middle of the exposure period) pattern. With all exposure patterns, the TWA concentration during the 8-hour period was 50 ppm. The blood concentration was expressed as the concentration in the blood flowing out of the vessel-rich tissue compartment (VRC).

c) Exposure concentration and pharmacokinetics

An 8-hour continuous exposure of a 70 kg male (Table 1) to m-xylene at various concentrations (from 0 ppm to 4,000 ppm) was simulated.

2) Physiological factors affecting the pharmacokinetics of m-xylene

a) Body size

i) Body weight

The effects of body weight on the pharmacokinetics of m-xylene were simulated for three males of standard (70 kg), large (100 kg), and small (40 kg) body build. Body size was scaled up or down without changing the body framework.

ii) Body fat content

Since organic solvents are generally highly soluble in lipids, body fat content is likely to have a major effect on their pharmacokinetics. The effects of body fat content on the pharmacokinetics of m-xylene were simulated for three males of standard (body weight 70 kg, fat tissue volume 14.8 *l*), obese (body weight 85 kg, fat tissue volume 29.5 *l*), and slim (body weight 62 kg, fat tissue volume 7.4 *l*) body build. Blood flow through the fat tissue was changed in proportion to the tissue volume. All parameters other than the volume and blood flow of fat tissue were assumed to be the same.

b) Exercise

The pharmacokinetics of m-xylene was simulated for a standard man (70 kg, 14.8 *l* fat tissue) who inhaled the solvent at 50 ppm for 8 hours while working at 50 W and rested after the inhalation period. The work was assumed not to alter Vmax or Km. Simulation parameters were set according to Johanson[6] as shown in Table 2.

c) Sex differences

Sex differences in the pharmacokinetics of m-xylene were studied by using male and female models with a standard body build. The male was assumed to weigh 70 kg, and the female 55 kg (Table 1). In short, the volume of the muscle compartment was assumed to equal 0.315 BW (BW is body weight in kg) and the volume of fat tissue was assumed to equal 0.365 BW in the female as opposed to 0.415 BW and 0.211 BW in the male, respectively.

Table 2. Physiological parameters used for assessing the effects of physical activity on pharmacokinetics of m-xylene.

	Rest	50 W
Alveolar ventilation (Q_L), *l*/min	5.8	21.3
Cardiac output (Q_C), *l*/min	5.8	10.4
Blood flow, *l*/min		
Vessel-rich (Q_R)	0.379Qc	0.271Qc
Vessel-poor (Q_P)	0.063Qc	0.036Qc
Muscle (Q_M)	0.114Qc	0.318Qc
Fat (Q_F)	0.053Qc	0.077Qc
Gastrointestinal (Q_G)	0.171Qc	0.095Qc
Hepatic (Q_H)	0.069Qc	0.038Qc
Arteriovenous shunt	0.151Qc	0.164Qc

Values were taken from Reference 6 with several modifications.

The blood perfusion through muscle or fat tissue was changed in proportion to the change in volume of each tissue. The cardiac output and alveolar ventilation in female were assumed to be 90% of those in the male.

Results

1. Relationship between external and internal doses

1) Continuous exposure and intermittent exposure

The results of a simulated 8-hour inhalation exposure of a 70 kg male to 50 ppm m-xylene are shown in Fig. 1, including the time-associated changes in the concentrations of m-xylene in VRC (vessel-rich tissue compartment), MC (muscle compartment), and FC (fat compartment) and the rate of urinary m-methyl hippuric acid (m-MHA) excretion. The solvent concentration in VRC rapidly increased immediately after the beginning of inhalation, but the increases in MC and FC were slower than in VRC. At the end of inhalation, the ratios of m-xylene concentration in the three compartments were VRC: MC: FC = 1:0.6:1.9. The concentrations of m-xylene in VRC and MC approached a steady state at the end of the 8-hour exposure, but FC still had a considerable capacity for m-xylene uptake.

After the end of inhalation, the solvent concentrations in VRC and MC began to decrease in a manner similar to the pattern of increase during inhalation. The decrease was rapid in VRC but slightly slower in MC. However, the decrease in the concentration in FC was very slow. The concentration ratios at 16 hours after the end of inhalation were VRC: MC: FC = 1:0.8:81. At this time, the rate of m-xylene disappearance was nearly equal among these compartments, which suggests that the release rate from adipose tissue is the rate-regulating factor in the pharmacokinetics of m-xylene.

Figure 2 shows concentration-time curves of m-xylene in VRC, MC, and FC and a urinary excretion-time curve of m-MHA when 100 ppm m-xylene was inhaled for 1 hour 4 times at 1-hour intervals. The solvent concentration in VRC responded quickly to the marked changes in inhalation concentration from 100 ppm to 0 ppm and back to 100 ppm. The responses were also relatively fast in MC, but those in FC were slow. The rate of urinary m-MHA excretion was not markedly affected by the fact that the exposure was intermittent.

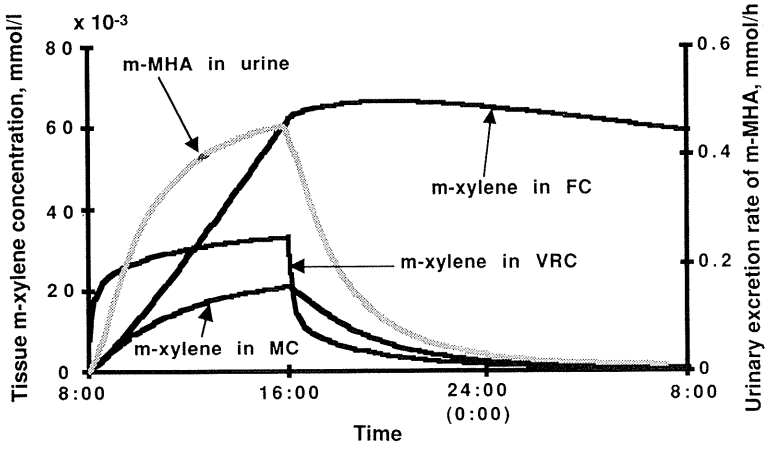

Fig. 1. Tissue m-xylene concentration and rate of urinary m-MHA excretion during and after a 50-ppm × 8-hour continuous m-xylene exposure. VRC, vessel-rich compartment; MC, muscle compartment; FC, fat compartment.

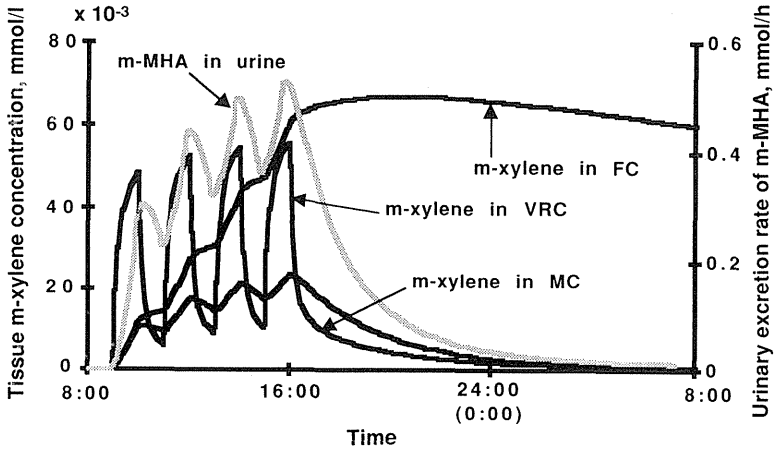

Fig. 2. Tissue m-xylene concentration and rate of urinary m-MHA excretion during and after four 100-ppm × 1-hour intermittent m-xylene exposures. VRC, vessel-rich compartment; MC, muscle compartment; FC, fat compartment.

Table 3. Comparison between continuous and intermittent exposures. m-Xylene concentration in VRC, MC and FC and rate of urinary m-MHA excretion 24 hours after the start of exposure.

Exposure	VRC, mmol/l	MC, mmol/l	FC, mmol/l	m-MHA, mmol/h
Continuous	7.3×10^{-4}	6.1×10^{-4}	5.9×10^{-2}	1.15×10^{-2}
Intermittent	7.5×10^{-4}	6.4×10^{-4}	6.0×10^{-2}	1.20×10^{-2}

After the end of inhalation, both the solvent concentration in each compartment and the rate of urinary m-MHA excretion exponentially decreased in almost the same manner as after continuous inhalation.

The TWA concentrations during the 8-hour period for both continuous and intermittent exposures had been set to 50 ppm. No significant differences were observed between the continuous and intermittent exposures either in the solvent concentration or in the rate of urinary m-MHA excretion 24 hours after the start of inhalation (Table 3). There were also no significant differences either in the area under the concentration-time curve of m-xylene in VRC for 120 hours after the beginning of exposure (AUC of blood m-xylene concentration) or in the area under the rate-time curve of urinary m-MHA excretion during the same period of time between the two exposure patterns (Table 4). These results indicate that the internal dose resulting from intermittent exposure is equal to that resulting from continuous exposure as long as the TWA concentration is the same.

Table 4. Comparison between continuous and intermittent exposures. AUC of m-xylene concentration in blood and cumulative amounts of urinary m-MHA.

Exposure	AUC, mmol/l × h	m-MHA, mmol
Continuous	7.17×10^{-2}	4.49
Intermittent	7.22×10^{-2}	4.50

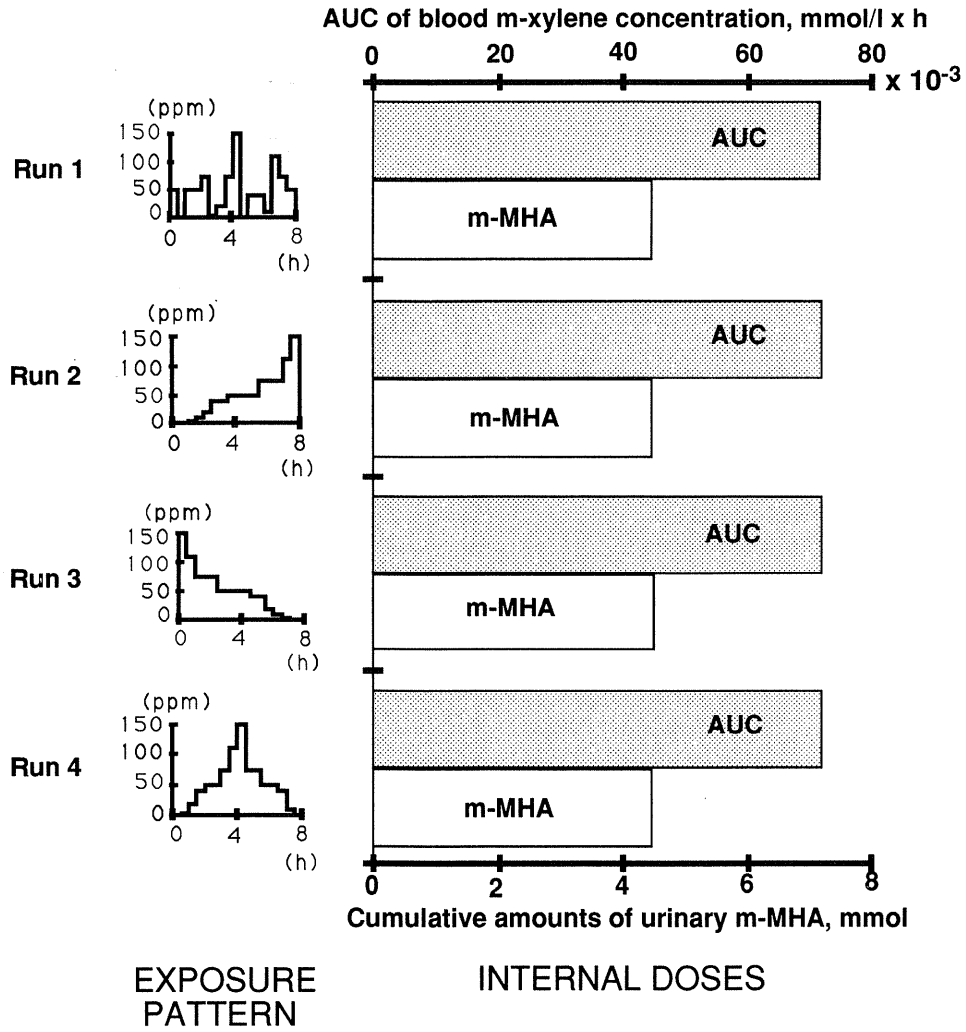

Fig. 3. Internal doses of m-xylene (AUC of blood m-xylene concentration and cumulative amounts of urinary m-MHA) in m-xylene exposures of various patterns. Run 1, random exposure; Run 2, ascending pattern; Run 3, descending pattern; Run 4, ascending and descending pattern. The 8-hour time-weighted average concentration of each exposure is 50 ppm.

2) Internal dose by random exposure

AUC of the blood m-xylene concentration and the cumulative urinary excretion of m-MHA for 120 hours from the beginning of exposure were nearly equal in all exposure patterns (Fig. 3). Therefore, the same external dose (the same TWA concentration) will give the same internal dose despite marked changes in the exposure pattern as long as the TWA concentration is around 50 ppm.

3) Exposure concentration and pharmacokinetics

Figure 4 shows the blood concentration of m-xylene and the rate of urinary m-MHA excretion at the end of an 8-hour continuous exposure of a 70 kg male to m-xylene at various concentrations.

The blood concentration did not increase linearly with the exposure concentration but showed biphasic changes above and below

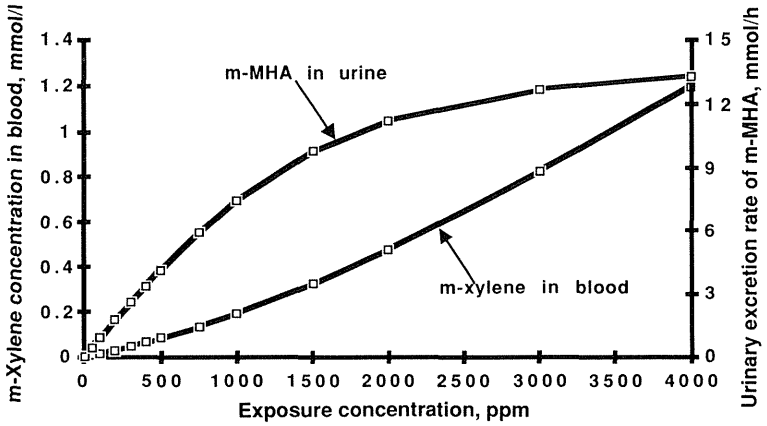

Fig. 4. m-Xylene concentration in blood and rate of urinary m-MHA excretion at the end of 8-hour m-xylene exposure at various concentrations.

about 500 ppm. On the other hand, the rate of metabolite excretion increased almost linearly with the exposure concentration up to 500 ppm, but it reached a plateau at 2,000 ppm. The apparent Km was about 500 ppm.

2. Physiological factors affecting the pharmacokinetics of m-xylene

1) Body size

a) Body weight

The blood concentration during exposure showed no significant difference among the three individuals despite the differences in body weight (Fig. 5A). On the other hand, the rate of urinary metabolite excretion was always higher in the heavier man (Fig. 5B).

b) Body fat content

m-Xylene concentration in the blood during exposure was highest in the slim and lowest in the obese man (Fig. 6A). Similarly, the amount of urinary m-MHA excreted by the obese man was smaller than that excreted by the standard or slim man (Fig. 6B). On the other hand, 16 hours after the end of exposure the blood concentration was higher in the man with a larger body fat content (Fig. 6A). This is because the disappearance of the solvent at this time is regulated by the volume of fat tissue and the blood flow through the tissue.

2) Exercise

The pharmacokinetics of m-xylene was greatly influenced by exercise. At the end of the 8-hour exposure with exercise, the blood concentration was about 2.5 times higher than without exercise (Fig. 7A). A similar increase was observed in the urinary metabolite excretion (Fig. 7B). Even 16 hours after the end of exposure the blood concentration and urinary metabolite excretion were still higher when the inhalation occurred with exercise than without exercise. This indicates that the effects of work load during exposure last until the beginning of the next day's work.

3) Sex differences

The blood m-xylene concentration was higher in the male during exposure, but after the exposure it decreased faster than in the female and this eventually resulted in a slightly lower blood concentration in the male (Fig. 8A). This is because the disappearance rate of m-xylene long after the end of the exposure is regulated by its release rate from the fat tissue. Urinary excretion of the metabolite was higher in the male than in the female both during and after exposure (Fig. 8B).

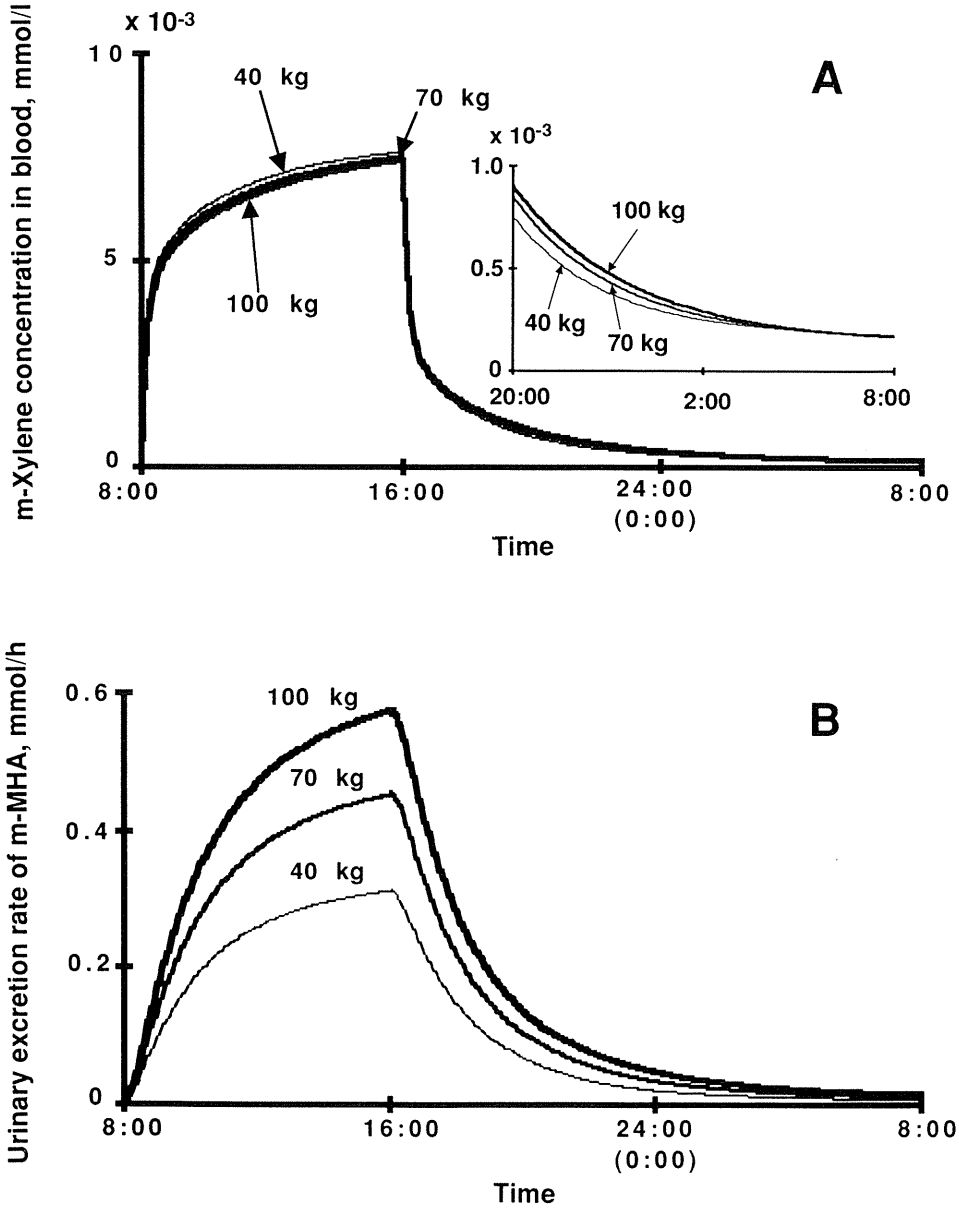

Fig. 5. Pharmacokinetics of m-xylene in relation to body size. These simulations assumed that men of various body weights (40, 70 and 100 kg) were exposed to 50 ppm m-xylene for 8 hours. A, m-xylene concentration in blood. B, m-MHA excretion rate in urine.

Discussion

The most important aspects of biological monitoring of exposure to organic solvents elucidated by the present study can be summarized as follows.

1. Organic solvents generally have a very short biological half-life, which, moreover, changes with time. When the blood concentra-

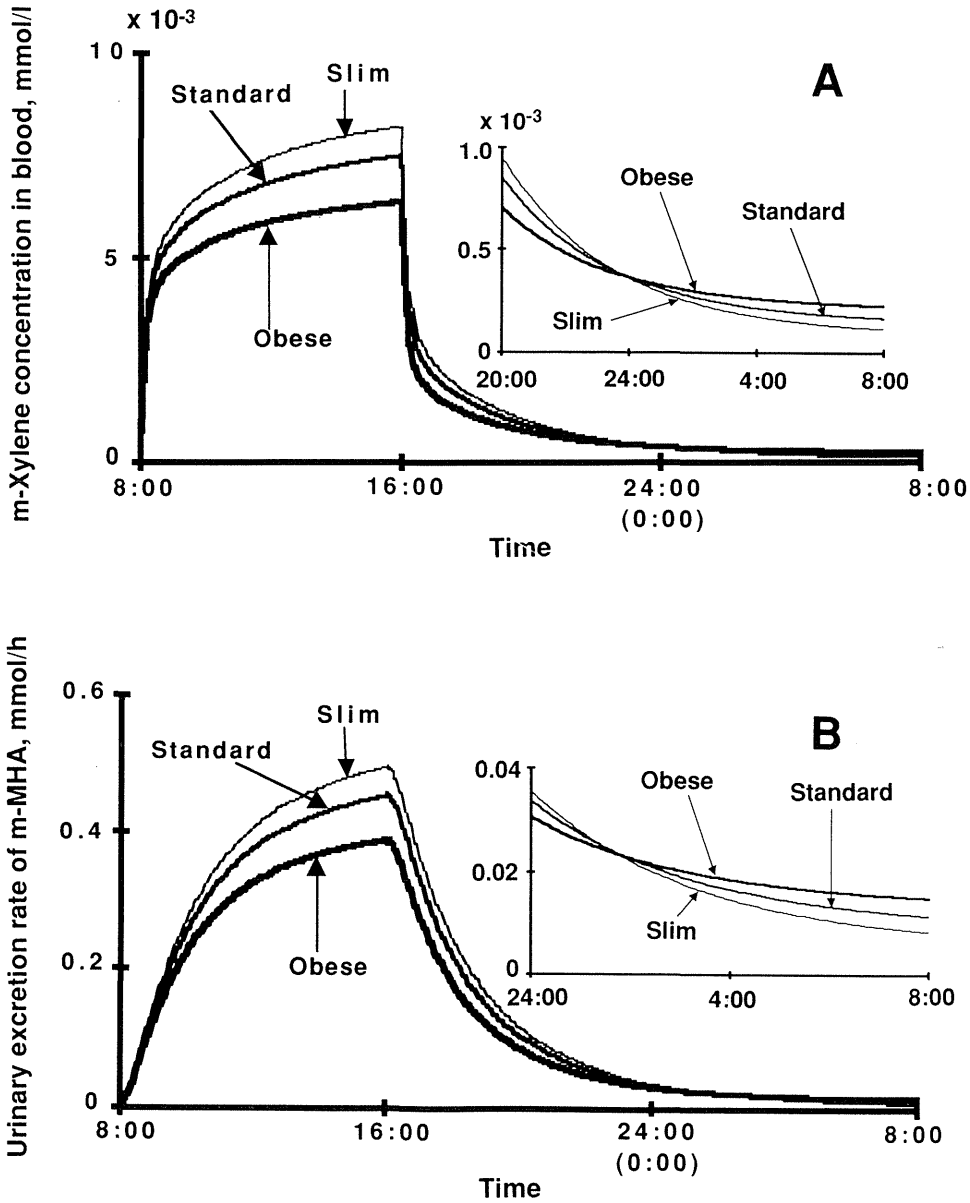

Fig. 6. Effects of body fat content on pharmacokinetics of m-xylene. These simulations assumed that three men with different body fat contents inhaled 50 ppm m-xylene for 8 hours. Standard, a 70 kg man (body fat 14.8 *l*); Slim, a 62 kg man (7.4 *l*); Obese, an 85 kg man (29.5 *l*). A, m-xylene concentration in blood. B, m-MHA excretion rate in urine.

tion of the solvent is used as an index of internal dose, the timing of sample collection greatly affects the results of biological exposure monitoring. For example, when the sample is taken shortly after the end of the work shift, a few minutes difference in sampling time can result in a large difference in blood concentration of the solvent, so the timing must be precise. When the blood is collected before the next day's work (generally about 16

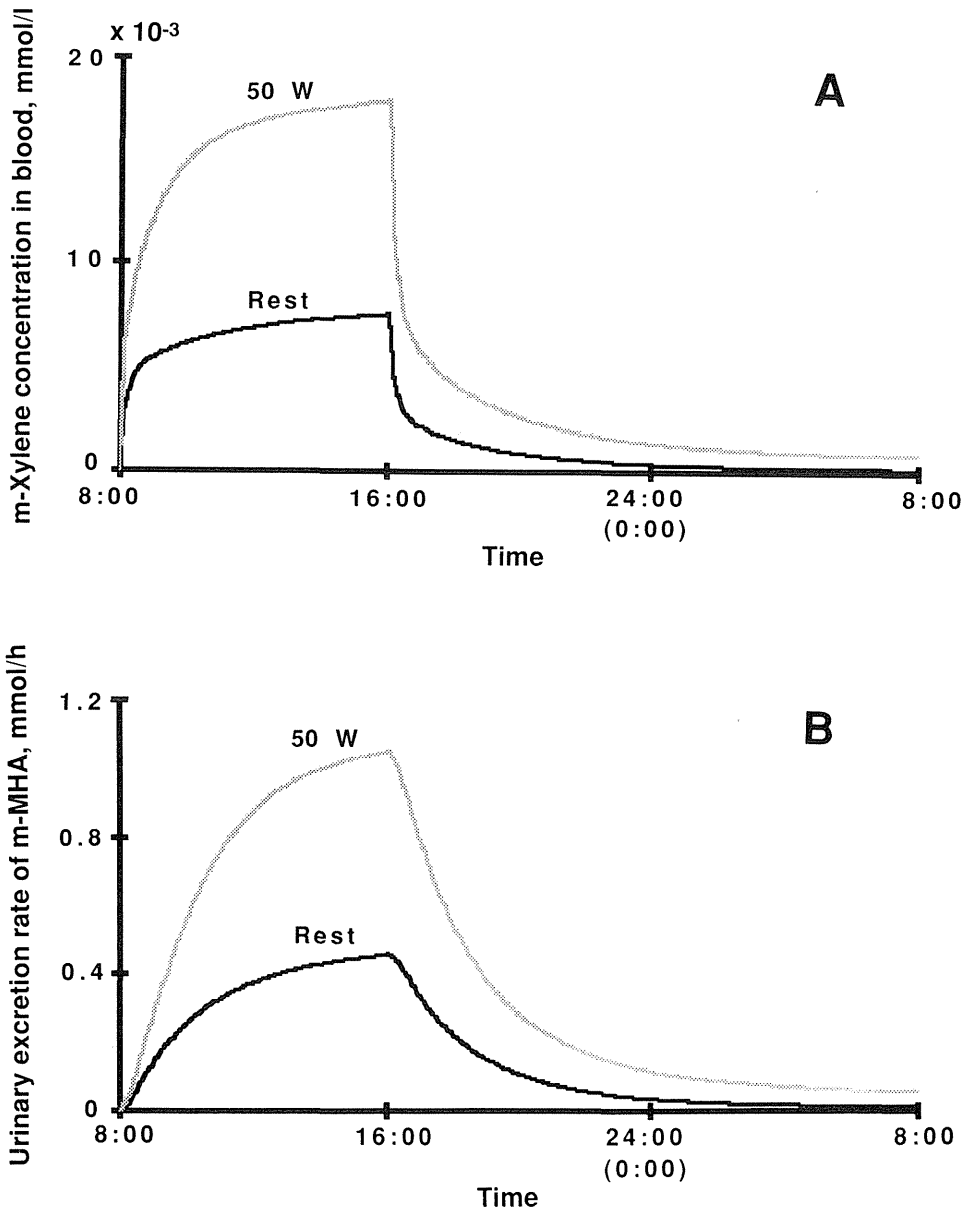

Fig. 7. Effects of physical activity on pharmacokinetics of m-xylene. These simulations assumed that a 70 kg man inhaled 50 ppm m-xylene for 8 hours either at rest or during 50 W physical exercise. The post-exposure period was spent at rest in both cases. A, m-xylene concentration in blood. B, m-MHA excretion rate in urine.

hours after the previous exposure), less precision is required, but evaluation of the results is not easy due to various factors affecting the pharmacokinetics of organic solvents (e. g. activity level during work). On the other hand, the urinary metabolite concentration is derived as a mean value over a certain period of time, precise timing of the sampling is less important. However, the effects of various environmental factors on metabolic processes may

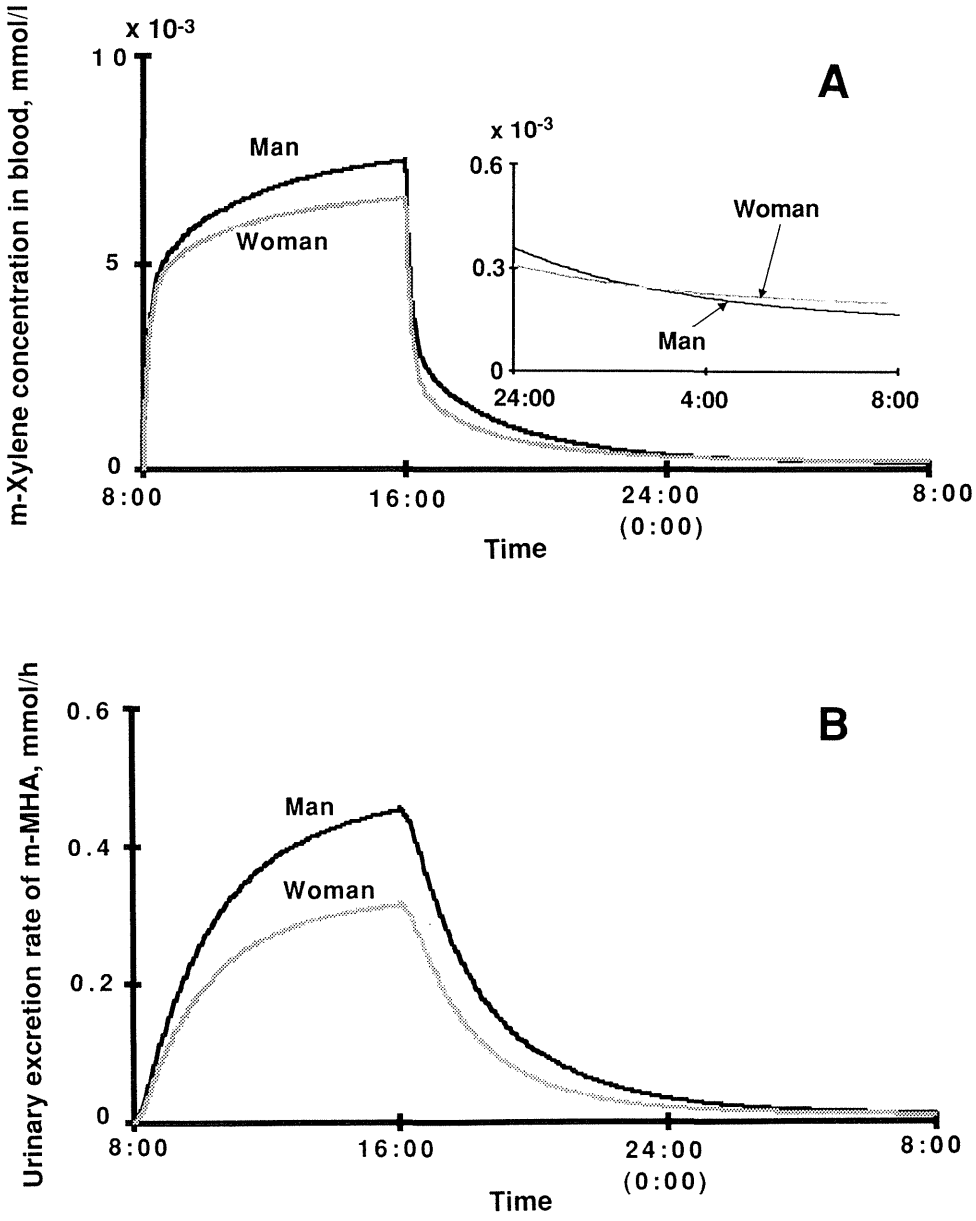

Fig. 8. Sex difference in pharmacokinetics of m-xylene. These simulations assumed that a 70 kg man and a 55 kg woman were exposed to 50 ppm m-xylene for 8 hours. A, m-xylene concentration in blood. B, m-MHA excretion rate in urine.

cause very large individual variations in urinary metabolite concentrations.

2. The health effects of low-concentration, long-term exposure to organic solvents have emerged as a major issue in modern industries. However, the urinary metabolite concentration as well as the blood concentration merely reflects the state of exposure on the day of sampling or on the day before because of the short half-life of organic solvents. The chronic

health effect is more closely related to the sum or the mean of the internal dose over long period of time. It should be noted that a single determination of blood solvent or urinary metabolite concentration does not represent the internal dose resulting from chronic exposure. Such determination leads to overestimation of total exposure if the exposure on the previous day happened to have been high and underestimation if it was low. The values obtained by a single determination should not be immediately connected with workers' complaints or symptoms. If abnormal values are measured, repeated measurements on different days are indicated, and it is also necessary to check the working conditions for possible percutaneous absorption, etc.

3. The blood concentration and urinary metabolite excretion show marked interindividual variations even at the same level of exposure, because these values are greatly affected by many physiological factors. These values should be employed to assess the working environment and work conditions at the group level rather than to evaluate health effects on individuals.

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