Int Arch Occup Environ Health (2001) 74: 31–37

ORIGINAL ARTICLE

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Biological monitoring of workers exposed to ethylbenzene and co-exposed to xylene

Received: 6 March 2000 / Accepted: 10 June 2000

Abstract ***Objective***: Ethylbenzene is an important constituent of widely used solvent mixtures in industry. The objective of the present study was to provide information about biological monitoring of occupational exposure to ethylbenzene, and to review the biological limit values corresponding to the threshold limit value of ethylbenzene. ***Methods***: A total of 20 male workers who had been exposed to a mixture of ethylbenzene and xylene, through painting and solvent mixing with commercial xylene in a metal industry, were recruited into this study. Environmental and biological monitoring were performed during an entire week. The urinary metabolites monitored were mandelic acid for ethylbenzene and methylhippuric acid for xylene. Correlations were analyzed between urinary metabolites and environmental exposure for ethylbenzene and xylene. The interaction effects of a binary exposure to ethylbenzene and xylene were also investigated using a physiologically based pharmacokinetic (PBPK) model. ***Results***: The average environmental concentration of organic solvents was 12.77 ppm for xylene, and 3.42 ppm for ethylbenzene. A significant correlation ($R^2 = 0.503$) was found between environmental xylene and urinary methylhippuric acid. Urinary level of methylhippuric acid corresponding to 100 ppm of xylene was 1.96 g/g creatinine in the worker study, whereas it was calculated as 1.55 g/g creatinine by the PBPK model. Urinary level of mandelic acid corresponding to 100 ppm of ethylbenzene was found to be 0.7 g/g creatinine. PBPK results showed that the metabolism of ethylbenzene was highly depressed by co-exposure to high concentrations of xylene leading to a non-linear behavior. ***Conclusions***: At low exposures, both methylhippuric acid and mandelic acid can be used as indicators of commercial xylene exposures. However at higher concentrations mandelic acid cannot be recommended as a biological indicator due to the saturation of mandelic acid produced by the co-exposure to xylene.

Key words Ethylbenzene · Xylene · Biological monitoring · Biological limit value · Metabolic interaction

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Introduction

Ethylbenzene is a colorless liquid with an aromatic odor. It is found in gasoline and is produced commercially by the alkylation of benzene with ethylene. Ethylbenzene is used as an intermediate for the production of styrene, and as a solvent. Commercial xylene contains approximately 20% ethylbenzene (ACGIH 1992). Occupational exposure to ethylbenzene during the production of styrene is unlikely, whereas workers are usually exposed to ethylbenzene in connection with the use of xylene (Kerstin and Engström 1984).

Ethylbenzene is considered as an irritant to the eyes, skin and mucous membranes. Acute and possibly chronic effects on the central nervous system were also reported (ACGIH 1992). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) of 100 ppm for ethylbenzene (ACGIH 1999). The Deutsche Forschungsgemeinshaft (DFG) in Germany recommends the same value for the maximal workplace concentration [Maximale Arbeitsplatz-Konzentration (MAK)] for ethylbenzene (DFG 1999). Ethylbenzene is absorbed mainly by inhalation, and metabolism is its major elimination route. Mandelic and phenylglyoxylic acids amount to 90% of the ethylbenzene metabolites (Engström et al. 1984).

Biological monitoring has been suggested for ethylbenzene by the use of urinary metabolites. In the

United States, ACGIH recommends a concentration of urinary mandelic acid of 1.5 g/g creatinine as the biological exposure index (BEI) in urine sampled at the end of the final shift of the workweek (ACGIH 1999). The DFG in Germany recently recommended a biological tolerance value (BAT) of 0.8 g/g creatinine for ethylbenzene, expressed as the sum of mandelic acid and phenylglyoxylic acid (DFG 1999). In general, BATs are considered as ceiling values based on relationships with health effects, whereas BEIs are the expected average biological levels equivalent to inhalation exposure at the TLV. BAT would therefore be expected to be higher than BEI (Morgan and Schaller 1999). In spite of this difference in their definition and also in their recommended sampling times, BEI is not expected to be twice as high as BAT, as is the case here.

Despite its presence in many products and workplaces, there are few reports about health effects and exposure assessment for ethylbenzene, compared with other alkylbenzenes such as toluene, xylene and styrene. Most of the studies reported on the biological monitoring of ethylbenzene were performed under experimental conditions with volunteers (Knecht et al. 2000). The BEI for ethylbenzene is based only on one controlled study with volunteers (Bardodej and Bardodejova 1970), for the correlation between ethylbenzene exposure and urinary mandelic acid excretion (ACGIH 1992).

Occupational exposure to ethylbenzene is a situation different from experimental exposure because of the presence of other constituents in the mixture, mainly xylene. The combined exposure to ethylbenzene and xylene decreases the amounts of metabolites formed, compared with separate exposures, and it further delays the excretion of the metabolites (Engström et al. 1984). Biological monitoring of urine, for exposure to mixtures, should take into account this interaction by reducing the reference biological levels (Ogata et al. 1993). Ethylbenzene was also reported to accumulate in the intestine, liver, kidney, and fat (Lauwerys and Hoet 1993), which could lead to a different situation when exposure is repeated.

In this paper we report new data on the correlation between urinary metabolites and environmental exposure among workers who were occupationally exposed to ethylbenzene as part of a mixture. The interaction between ethylbenzene and xylene, the two main constituents of the mixture, is also investigated with a physiologically based pharmacokinetic (PBPK) model. The objective of the present study is to provide more information about the biological monitoring for occupational exposure to ethylbenzene. Such information might be used to suggest biological limit values for mixed exposures to the two main constituents of the mixture.

Subjects and methods

Subjects

Twenty male workers, exposed to a mixture of ethylbenzene and xylene in a metal factory, were recruited into this study. These workers had been exposed to organic solvents through painting and solvent mixing. They were aged between 25 and 53 years and their average employment duration was 8.3 years (Table 1). Their average body height and weight were 166.9 cm and 60.6 kg respectively. Their alcohol consumption ranged between 0 and 47.13 g/day. However, all of them were asked not to drink during the period of this survey, to exclude any acute influence of alcohol consumption.

Environmental and biological monitoring

Personal air samples of ethylbenzene and xylene were collected during the entire work shift using charcoal tubes (NIOSH 1995). Sampling was performed for 5 days to obtain the workweek average exposure concentration. Environmental monitoring was also performed to check whether workers were exposed to other solvents besides xylene and ethylbenzene. Analysis of organic solvents was carried out by gas chromatography. Total xylene concentration was calculated by summing the concentrations of the three isomers.

The sampling time for urine was recommended to be at the end of the final shift of the workweek by ACGIH, and at the end of shift by DFG, respectively. To be in agreement with these recommendations, urine samples were collected at the end of the shift on every day. The urinary metabolites monitored were mandelic acid for ethylbenzene, and methylhippuric acid for xylene. Methylhippuric acid and mandelic acid were analyzed by high-performance liquid chromatography according to NIOSH method 8301(NIOSH 1995). Concentrations of urinary metabolites were corrected for creatinine. Total methylhippuric acid concentration was calculated by summing the concentrations of the three isomers.

Physiologically based pharmacokinetic model

The simulations of urinary metabolites after exposure to ethylbenzene and xylene were done using a seven-compartment PBPK model. The previously developed and used model (Droz et al. 1989; Jang and Droz 1996, 1997) was modified for the simulation of a binary chemical mixture. The model for a binary mixture consisted of two single solvent PBPK models, linked in the liver compartment where the two solvents interact through their metabolism. Interaction was considered to be competitive inhibition, which was calculated according to the equation suggested by Tardif et al. (1993b):

$$\text{Metabolite of substrate in liver compartment} = \frac{\text{Vmax}_{\text{sub}} \cdot \text{C}_{\text{sub}}}{Km_{\text{sub}}(1 + \text{C}_{\text{inh}}/Ki) + \text{C}_{\text{sub}}}$$

where C_{sub} is the concentration of substrate, C_{inh} is the concentration of inhibitor, and Ki is metabolic inhibition constant.

Table 2 shows the parameters used in the PBPK model. Tissue-gas partition coefficients were calculated from water, olive oil, and blood-gas partition coefficients using equations suggested by Droz et al. (1989). The three isomers of xylene were assumed to behave as *m*-xylene in the first approximation. Metabolic

Table 1 Main characteristics of the workers (sample size = 20)

	Mean ± SD	Range
Age (years)	39.1 ± 9.74	25–53
Education (years)	9.3 ± 2.21	6–12
Alcohol consumption (g/day)	13.3 ± 15.87	0–47.13
Current smoker (%)	65.0	–
Smoking (cigarettes/day)	8.5 ± 9.50	0–20
Employment duration (years)	8.3 ± 3.93	2–14
Body height (cm)	166.9 ± 3.27	160–173
Body weight (kg)	60.6 ± 6.59	50–78

Table 2 Solvent-specific parameters used in the physiologically based pharmacokinetic (PBPK) model (*MA* mandelic acid)

		Ethylbenzene	Xylene
Tissue-gas partition coefficients[a]	Lungs	28.4	34
	Muscle and skin	52.7	61
	Fat	2662	3035
	Brain	108	124
	Kidneys	54	62
	Liver	99	113
	Others	69	79
Metabolic constant	Vmax (mg/h/kg)	7.3[b]	8.4[c]
	Km (mg/l)	1.39[b]	0.2[c]
	Ki (mg/l)[d]	1.50[b]	0.23[b]
Urinary excretion rate constants of metabolites (h^{-1})		0.231[e] (MA)	1.386[f]

[a] Droz et al. (1989)
[b] Tardif et al. (1997)
[c] Tardif et al. (1993a)
[d] *Ki*: metabolic inhibition constant of inhibitor
[e] Sedivec et al. (1983)
[f] Senczuk and Orlowski (1978)

parameters such as the maximum rate constants (Vmax), the Michaelis constants (*Km*), and the metabolic inhibition constants (*Ki*) for ethylbenzene and xylene were obtained from published data (Tardif et al. 1993a, 1997). Urinary excretion rate constants for mandelic (Sedivec et al. 1983) and methylhippuric acid (Senczuk and Orlowski 1978) were obtained from experiments on humans (0.231 h^{-1} and 1.386 h^{-1}, respectively). Urinary metabolite concentrations were calculated assuming a creatinine excretion rate of 1.4 g/day for a 70 kg, 170 cm man (Droz et al. 1999). Table 3 presents the physiological parameters used in the model (Droz et al. 1989, 1999; Jang and Droz 1996, 1997; Jang et al. 1999a).

Statistical analysis

Data analysis was performed with SPSS statistical software for Windows. Linear regression analysis was used to describe the correlation between environmental and biological data. Biological limit value (BLVs) were estimated as the levels of urinary metabolites corresponding to an exposure at the TLV, using the linear regression equations obtained. In the regression all daily exposures were considered. They, therefore, include both within- and between-worker variability. These components have not been separated, as the main interest is the description of the average behavior.

Table 3 Physiological parameters used in the physiologically based pharmacokinetic (PBPK) model [Droz et al. (1989)] (*BTPS* body temperature, pressure, and saturated with water vapor)

	Tissue volume (l)	Blood flow (l/min)
Lung	0.46	
Fat	15.43	0.34
Liver	2.97	1.54
Muscle	34.90	1.15
Brain	1.30	0.74
Kidneys	0.27	1.22
Others	0.52	1.48
Alveolar ventilation (l/min BTPS)[a] 0/50W	5.18/16.29	
Cardiac output (l/min) 0/50W	6.47/10.47	

[a] At BTPS

Results

The average exposure concentration for the studied workers was 12.77 ppm (range 2.5–61.6) for xylene, and 3.42 ppm (range 0.50–22.7) for ethylbenzene. The mean ratio of ethylbenzene to xylene was 0.27 (range 0.20–0.40), which is very similar to that usually observed in commercial xylene, typically 0.25, based on an average content of 20% ethylbenzene.

Xylene and ethylbenzene were the main air contaminants found in the studied workplaces. Although other organic solvents were sometimes detected, their environmental concentrations were much lower than those of xylene or ethylbenzene. Methylisobutylketone and 2-ethoxyethylacetate were the most frequently found compounds. However their concentrations were smaller than one fifth of ethylbenzene at the most. Styrene and other solvents that could represent a source of urinary mandelic acid were not found in any samples.

As shown in Fig. 1, a significant correlation ($R^2 = 0.503$) was found between environmental xylene concentrations and urinary methylhippuric acid excretion. The use of the regression line of Fig. 1 gives an exertion of 1.96 g/g creatinine equivalent to 100 ppm exposure. It is close to the 1.5 g/g creatinine proposed by ACGIH as a BEI and to the BAT of 2 g/l recommended by the DFG. A significant correlation was also observed between ethylbenzene and urinary mandelic acid excretions, when 1-day (Fig. 2) or 1-week time-weighted average (Fig. 3) exposures were considered. Although exposure concentration and urinary metabolite excretion might not be related in linear fashion, such a relationship was calculated in Figs. 2 and 3. The urinary mandelic acid excretion corresponding to 100 ppm of ethylbenzene in both cases was estimated to be 0.7 g/g creatinine. This is approximately half of the BEI recommended by ACGIH.

Figure 4 shows the simulation results obtained for urinary methylhippuric acid after an occupational

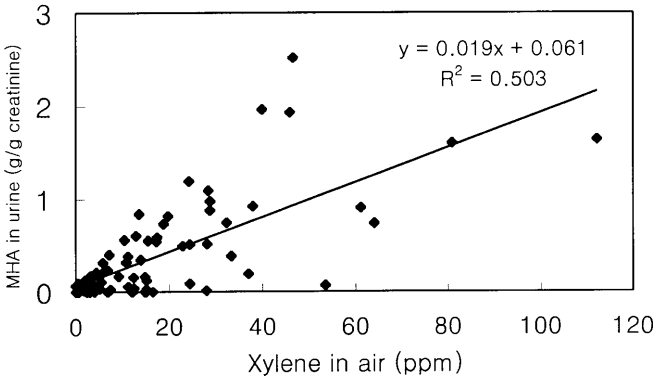

Fig. 1 Correlation between environmental xylene and urinary methylhippuric acid (MHA) in terms of daily average

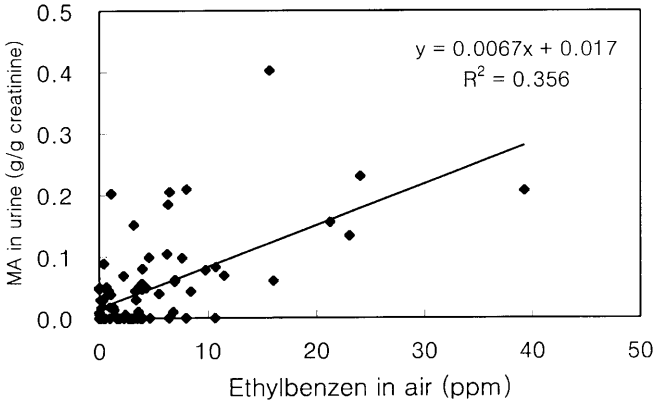

Fig. 2 Correlation between environmental ethylbenzene and urinary mandelic acid (MA) in terms of daily average. (Urine samples were collected at end of shift)

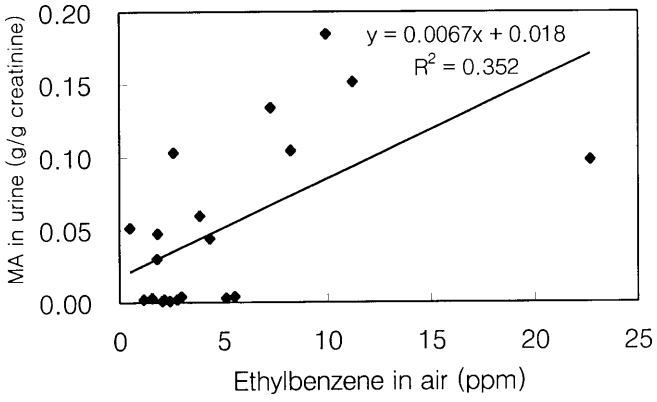

Fig. 3 Correlation between environmental ethylbenzene and urinary mandelic acid (MA) in terms of weekly average. (Urine samples were collected at end of final shift of workweek)

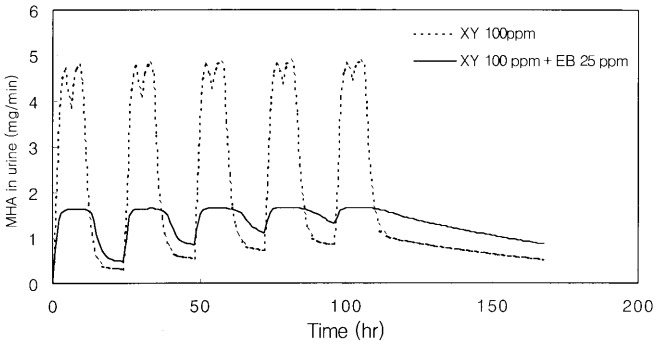

Fig. 4 Simulation results for urinary methylhippuric acid (MHA) from exposure to xylene with and without co-exposure to ethylbenzene

exposure to xylene, with and without co-exposure to ethylbenzene. Exposures in PBPK simulations were 100 ppm for xylene, and 25 ppm for ethylbenzene. These values gave a solvent ratio close to that usually found in commercial xylene, and are coherent with exposure results in the present study. The simulation results of Fig. 4 indicate that urinary methylhippuric acid is reduced by co-exposure to ethylbenzene. Urinary methylhippuric acid excretion was predicted to be 4.94 g/g creatinine when workers were exposed to 100 ppm of pure xylene, and 1.55 g/g creatinine when they were exposed to a mixture of 100 ppm of xylene and 25 ppm of ethylbenzene (Table 4).

Figure 5 shows the simulation results obtained for urinary mandelic acid after occupational exposure to ethylbenzene, with and without co-exposure to xylene. Exposure scenarios for PBPK simulations were 100 ppm for ethylbenzene and 400 ppm for xylene, to take into account a ratio of 0.25 as above. Simulation results indicate that metabolism of ethylbenzene is highly depressed by co-exposure to high concentrations of xylene. The urinary mandelic acid corresponding to 100 ppm of ethylbenzene was calculated to be 1.73 g/g creatinine for pure ethylbenzene, and 0.06 g/g creatinine when workers were exposed to a mixture of ethylbenzene and xylene.

Figure 6 presents the urinary excretions of mandelic acid obtained by the PBPK model as a function of the exposure to ethylbenzene in a constant binary mixture. The total concentration was changed in the exposure scenario, but its content of ethylbenzene remained the same, i.e., 20%. The concentrations of urinary mandelic acid at end of shift reached a maximum at 20 ppm and then decreased slightly at higher concentrations. For samples taken prior to the last shift, it remained proportional to the exposure concentration until 75 ppm of mixtures and then leveled off.

Discussion

Biological monitoring is a very useful tool for assessing workers' exposure to chemicals. However, the variability observed in biological monitoring results is often considered to be a major drawback (Droz 1989). Metabolic processes and their associated interactions due to mixed exposure can be an important source of variability in biological monitoring (Ogata et al. 1993). Co-exposure to another chemical can influence the levels of biomar-

Table 4 Predicted [physiologically based pharmacokinetic (PBPK)] and measured biological levels of urinary biomarkers corresponding to an exposure at the threshold limit value (TLV) for ethylbenzene and xylene (g/g creatinine) (*BLV* biological limit value, *BEI* biological exposure index, *ACGIH* American Conference of Governmental Industrial Hygienists, *BAT* biological tolerance value, *DFG* Deutsche Forschungsgemeinshaft)

Biological determinant	Exposure conditions	BLV calculated		BEI of ACGIH	BAT of DFG
		PBPK simulation	Field study		
Methylhippuric acid	Pure xylene[a]	4.94	–	1.5	2.0 (g/l)
	Commercial xylene[b]	1.55	1.96		
Mandelic acid	Pure ethylbenzene[c]	1.73	–	1.5	0.8
	Occupational exposure to ethylbenzene[d]	0.06	0.70		

[a] 100 ppm of xylene alone
[b] Binary mixture of 100 ppm of xylene and 25 ppm of ethylbenzene
[c] 100 ppm of ethylbenzene alone
[d] Binary mixture of 100 ppm of ethylbenzene and 400 ppm of xylene

kers by altering the metabolism or the elimination. The results obtained here can be used to assess the significance of this interaction in the case of ethylbenzene and xylene.

Exposures to mixtures of organic solvents are so common that, in principle, all components should be evaluated. In order to estimate the total exposure to mixtures of organic solvents, cumulative exposure indices are usually calculated by adding the ratios of biological monitoring results to the respective BLV (Jang et al. 1999b). BLV developed without considering a possible interaction could produce an underestimation or overestimation in exposure assessments. Therefore, it is especially important to review the BLV of organic solvents concerning the metabolic interaction.

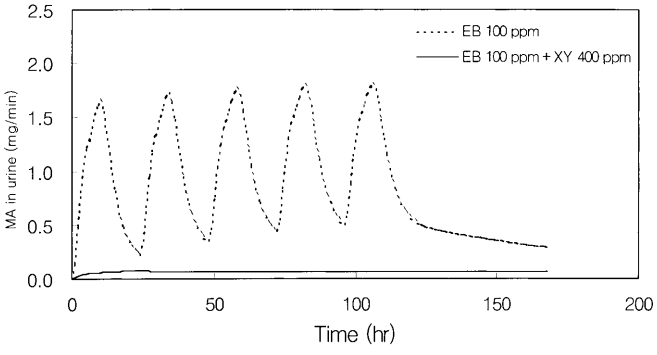

Fig. 5 Simulation results for urinary mandelic acid (MA) from exposure to ethylbenzene with and without co-exposure to xylene

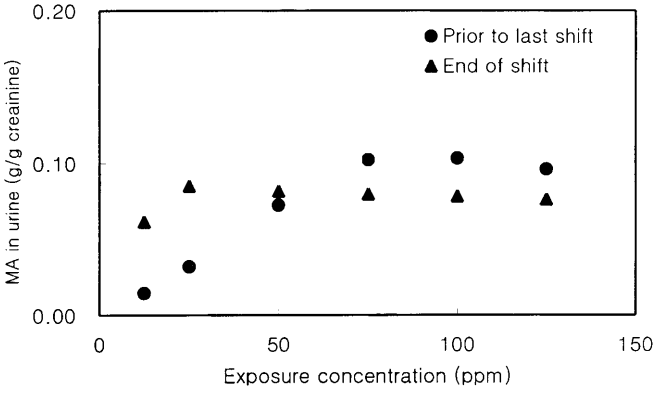

Fig. 6 Correlation between urinary mandelic acid and environmental exposure to binary mixture of ethylbenzene and xylene simulated by a physiologically based pharmacokinetic (PBPK) model. (The content of ethylbenzene in mixtures was constant at 20%) *prior to last shift* concentrations of mandelic acid in urine sampled prior to last shift, *end of shift* concentrations of mandelic acid in urine sampled at end of final shift of workweek

For xylene, the PBPK model developed here to describe the metabolic interaction (Fig. 4) gave results consistent with what was published before. A BLV of 4.94 g/g creatinine could be simulated for experimental exposure to xylene at 100 ppm. A BLV of 1.55 g/g creatinine was, however, predicted by simulation of exposure to commercial xylene. Results obtained from workers were close to this figure (1.96 g/g creatinine, Fig. 1). Both field and simulation data agree and show an important reduction of the BLV in mixed exposure compared with exposure to pure xylene. This is similar to the range of values of 1.3–2.3 g/g creatinine reported in other occupational exposure studies (Engström et al. 1978, Lundberg and Sollenberg 1986; Schaller and Triebig 1987), and to the recommendations of ACGIH and DFG, 1.5 g/g creatinine and 2.0 g/l respectively. These two recommended values seem, therefore, adequate and useful for the monitoring of exposure to commercial xylene.

In fact, the BEI of methylhippuric acid was developed for commercial xylene with the consideration of metabolic interaction between xylene and ethylbenzene (ACGIH 1992). The urinary level of methylhippuric acid corresponding to 100 ppm of pure xylene was found to be higher than 3 g/g creatinine in several experimental studies (Campbell et al. 1988; Riihimaki et al. 1979a, b; Senczuk and Orlowski 1978), which was also much higher than results in occupational exposure studies.

For ethylbenzene, the ACGIH recommendation of 1.5 g/g creatinine of mandelic acid is mainly based on results obtained in controlled studies with volunteers (Bardodej and Bardodejova 1970). With the present

PBPK model, mandelic acid excretion was estimated to be 1.73 g/g creatinine for experimental exposure at 100 ppm, which is in agreement with the recommended BEI. However, results obtained from workers (Figs. 2 and 3) indicate a much lower mandelic acid excretion of 0.70 g/g creatinine for occupational exposure to 100 ppm.

Ethnic differences could possibly be an explanation for this difference, as this study was performed on Asian workers (Jang et al. 1997). However, the effect of ethnic difference was reported to be rather small for urinary metabolites of chemicals that are highly metabolized. Furthermore, mandelic acid excretion (from exposure to styrene) was not different between Asian and Caucasian groups by simulation (Jang and Droz 1997). This discrepancy is therefore certainly due to metabolic interaction and this should thus be taken into account when estimating a BLV.

The BLV predicted by the PBPK model for 100 ppm mixed ethylbenzene exposure (400 ppm xylene) was 0.06 g/g creatinine, a much lower value than the BEI and also than the extrapolated result obtained in the present study (Fig. 3). It should, however, be noticed that ethylbenzene exposures were here below 40 ppm, and that due to interaction the extrapolation should not be done linearly. This relationship is further explored with the PBPK model in Fig. 6, which shows that at rather low exposures, mandelic acid is no longer proportional to the exposure level. The non-linearity is less pronounced for urine taken before the next shift. This is due to the fact that at this time xylene has been largely eliminated, reducing the interaction with ethylbenzene. Figure 6 shows that at high exposures, concentrations before the next shift are even higher than just after the shift. As far as linearity is concerned, it would be beneficial to sample urine before the next shift rather than at the end of shift.

When monitoring exposure to a mixture of chemicals having additive effects but no toxicokinetic interaction, the BLVs can be applied as such and the rule of the ''biological hazard index'' followed (Ogata et al. 1993). If exposure to one chemical alone is unlikely, such as here, and co-exposure is common in most occupational exposures, metabolic interaction should be considered in applying and developing BLV.

The BEI for methylhippuric acid was developed in this context, reducing its concentration to take into account interaction between xylene and ethylbenzene (ACGIH 1992). For ethylbenzene a similar approach should, in principle, be used. However, the data gathered in the present study indicate another difficulty: a non-linear behavior of mandelic acid. This fact reduces the usefulness of this metabolite to monitor over-exposure. It should, therefore, not be used when exposure is elevated. It might also be difficult to develop other biomarkers for ethylbenzene, as metabolic inhibition was shown to be so high that non-linearity could be present in all cases. One solution would be to use urinary methylhippuric acid as biological monitoring determinant for the binary mixture of xylene and ethylbenzene and not for xylene alone. In that case, the BLV of methylhippuric acid should be reduced to about 80% of current BLV considering the biological hazard index of the mixture. It is probably worth developing a BLV specific for this mixture which is very common in occupational exposure situations.

Acknowledgements This study was funded by a grant from the Ministry of Environment of the Republic of Korea. The authors thank Dr. J. Roh for his discussion and Y. Kim, J.S. Lee, K.W. Lee, and K.J. Lim for their technical assistance.

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