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Field Study

Urinary Excretion of Thioethers Related to Styrene Exposure

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Abstract: Urinary Excretion of Thioethers Related to Styrene Exposure: Ginette TRUCHON *et al.* Institut de recherche en santé et en sécurité du travail, Montréal, Québec, Canada—The objective of this study was to test the suitability of styrene-specific mercapturic acids as urinary bioindicators of occupational styrene exposure. The excretion of mandelic acid (MA), global thioethers and styrene-specific mercapturic acids was measured in urine samples from 64 workers employed in three companies fabricating glass fiber-reinforced polyester products. Global thioethers were measured by a spectrophotometric method while MA and specific mercapturic acids, N-acetyl-S-(1-phenyl-2-hydroxyethyl)-L-cysteine (M1) and N-acetyl-S-(2-phenyl-2-hydroxyethyl)-L-cysteine (M2), were measured by high pressure liquid chromatography with UV detection. Excretion of M1 and M2 was qualitatively verified by gas chromatography-mass spectrometry. The environmental measurements were carried out with passive dosimeters. Workers had 8-h TWA exposure levels ranging from 0 to 667 mg/m^3. End-of-shift MA excretion ranged from 0 to 2.08 mmol/mmol creatinine and was well correlated with environmental styrene exposure ($r=0.91$, $p<0.001$). M1 and M2 were detected (i.e. above ca. 1 μmol/mmol creatinine) in urine samples of only three workers who were exposed to various concentrations of styrene. End-of-shift excretion of global thioethers was found to be significantly correlated to cigarette consumption as well as to styrene exposure, as measured by end-of-shift MA excretion. In opposition to data from rats, our results indicate that humans exposed to styrene excrete little styrene-specific thioethers. The apparent inter-individual variability in excretion of M1 and M2 suggests that they may not constitute suitable indicators of occupational styrene exposure.
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Large-scale biological assessment of exposure to styrene in the workplace is usually conducted by measuring the urinary excretion of the major metabolites mandelic acid (MA) and phenylglyoxylic acid (PA). In humans, these two substances account for approximately 90% of absorbed styrene[1, 2]. Another pathway for styrene metabolism is conjugation of styrene oxide, a reactive electrophilic metabolite, with glutathione in a reaction catalyzed by glutathione S-transferase[3]. The resulting end products of this type of reaction are thioether compounds mainly of the mercapturic acid family. Malonova and Bardodej[4] have found increases in concentrations of non-specific thioethers in the urine of workers exposed to styrene vapors. Rats exposed to styrene by inhalation (105 to 850 mg/m^3, 6h) have been shown to excrete in their urine, in a dose related manner, the two following specific mercapturic acids: N-acetyl-S-(1-phenyl-2-hydroxyethyl)-L-cysteine (M1) and N-acetyl-S-(2-phenyl-2-hydroxyethyl)-L-cysteine (M2)[5].

Compounds that are metabolized via electrophilic intermediates can be considered as potentially genotoxic substances[6]. There has been growing interest in the determination of specific thioethers or mercapturic acids in urine as markers of exposure to these potentially toxic reactive electrophilic compounds[6–9].

The object of this study was to evaluate urinary excretion of M1 and M2 in workers exposed to various doses of styrene to test the suitability of these metabolites as biological indicators of exposure.

Materials and Methods

Population

The three plants in the study were involved in the manufacture of glass fiber-reinforced polyester products. Sixty-four workers volunteered to participate in the

environmental and biological evaluations. Subjects were selected to represent a wide range of levels of styrene exposure.

Environmental and biological evaluations

The environmental measurements were carried out with passive dosimeters (3M, 3500, 3M Canada Inc., Dorval, Québec, Canada). The samples were analyzed by gas chromatography with flame ionization detection according to a standard analytical procedure[10]. Two dosimeters per worker were used to evaluate the day's exposure in the breathing zone throughout the workshift; each dosimeter covered approximately half of the workshift. An 8-h time-weighted average (TWA_{8h}) was calculated.

Urine samples were collected immediately after the workshift as well as in the late evening and the following morning upon waking up. The urinary concentrations of MA, M1 and M2 were determined by high pressure liquid chromatography (HPLC) with UV detection[11]. Acidified urine samples (<pH2) were extracted with ethyl acetate, the organic layer was evaporated to dryness, and the residues were dissolved in water-acetonitrile (1:1). Samples were analysed with a Supelco C_{18} - reverse phase column and a water (pH6, 5 mM tetrabutylammonium dihydrogen phosphate) - acetonitrile gradient. p-Hydroxybenzoic acid was used as an internal standard. Programmable ultraviolet detection was operated at 220 nm (p-hydroxybenzoic acid and MA) and 208 nm (M1 and M2). Samples in which M1 and M2 were detected by the HPLC procedure and those with negative results for M1 and M2 but presenting end-of-shift urinary concentrations of MA≥0.6 mmol/mmol creatinine were subjected to a qualitative confirmatory determination by gas chromatography coupled to mass spectrometry (GC-MS). Sample preparation was the same as for the HPLC procedure. Separation was done on a DB-5 capillary column. The quadrupole mass spectrometer was operated in the electron impact mode, with multiple ion detection. The characteristic ion and the confirmation ion were at 104 and 161 respectively. The detection limits of the HPLC and the GC-MS methods for M1 and M2 were in the order of 10 μmol/L (HPLC) and 1.5 μmol/L (GC-MS) which, for an average urine sample, corresponds to approximately 1 μmol/mmol creatinine (HPLC) and 0.15 μmol/mmol creatinine (GC-MS). Global thioethers were determined by the classical method developed by Van Doorn *et al.*[12] The concentration of creatinine was also determined for each urine sample[13].

Questionnaire

A self-administered questionnaire filled out at the end of the work shift was used to elicit information on the job title, tasks, wearing of respirators, the number of cigarettes smoked during that day, and previous 24-h consumption of coffee and of certain other food items that have been reported or suggested to increase thioether excretion (number of times consumed): horseradish, onion, garlic, turnip, pineapple, beans, broccoli, radish, mustard, white cabbage, red cabbage, kale, brussels sprouts, cauliflower and kohlrabi[14].

Results

Results of the environmental and biological evaluations for the three companies are summarized in Table 1. Workers had 8-h TWA exposure levels ranging from 0 to 667 mg/m^3 and end-of-shift MA excretion ranging from 0 to 2.08 mmol/mmol creatinine. Chopper-gun operators and laminators were the most highly exposed workers with mean environmental styrene concentrations well above the current ACGIH[15] threshold limit value (TLV) recommendation of 213 mg/m^3. In total, 13 workers had exposure levels above the TLV. End-of-shift urinary MA for workers not wearing a mask was significantly correlated to environmental styrene exposure (Pearson's correlation coefficient $r=0.91$, $p<0.001$). Based on the regression equation calculated in this study ($y=0.00367x - 0.0816$), exposure at the TLV would be expected to correspond to an MA excretion level of 0.7 mmol/mmol creatinine, close to the biological exposure index (BEI) of 800 mg/g creatinine (0.6 mmol/mmol creatinine) recommended by the ACGIH[15]. In total eight workers

Table 1. End of shift mandelic acid and average ambient styrene concentrations

Task	N	Ambient concentrations of styrene - TWA (8 h)[a] (mg/m^3)[b]	End of shift mandelic acid concentrations[a] (mmol/mmol creatinine)
Laminator	16	315 (147–667)	0.81 (0.13–2.08)
Chopper-gun operator	3	341 (188–496)	1.18 (0.43–1.75)
Painter	4	107 (50–166)	0.11 (0.04–0.18)
Other tasks[c]	41	40 (0–204)	0.07 (0–0.25)

[a] Arithmetic mean (range). [b] 1 mg/m^3=0.235 ppm. [c] Carpenter, plumber, plastic welder, foreman, trimmer, office worker.

had end-of-shift urinary MA excretion above that level. Urinary MA for other collection periods was also correlated with environmental styrene exposure, but linear regression slopes and correlation coefficients were lower than for end-of-shift MA (late evening; r=0.69, y=0.00188x − 0.0694 and next morning; r=0.81, y=0.000755x − 0.204).

The specific thioethers M1 and M2 were detected in urine samples of only three workers. One was a painter exposed to 50 mg/m^3 of styrene (end-of-shift MA at 0.05 mmol/mmol creatinine) for whom metabolites were detected in all urine samples. Another worker was a laminator exposed to 237 mg/m^3 (MA at 0.31 mmol/mmol creatinine) for whom M1 and M2 were detected in end-of-shift urine. The third worker was a chopper-gun operator exposed to 339 mg/m^3 (MA at 1.36 mmol/mmol creatinine) who excreted M1 and M2 in all urine samples. M1 and M2 were quantifiable only in the third worker's end-of-shift urine, with levels of 8.4 and 7.5 μmol/mmol creatinine, respectively. GC-MS analysis confirmed the presence of M1 and M2 in these various samples; M1 and M2 were not detected by GC-MS in the urine samples of the seven other workers whose end-of-shift MA excretion was above the 0.6 mmol/mmol creatinine BEI level (actual range: 1.03 to 2.08 mmol/mmol creatinine).

Questionnaire information showed that 50% of the workers had smoked during the sampling day. Of these, 80% had smoked between 1 and 20 cigarettes/day and the other 20% between 21 and 40. Seventy-nine percent of the workers had drunk coffee, of whom 81% had consumed between 1 and 5 cups/day and 19% had more than 5. Consumption of the individual foodstuff items enumerated in the questionnaire was generally low (less than 10 % of the workers) except for onions (27%), mustard (23%) and broccoli (14%), so that answers were combined in one category. When all items were aggregated, 58 % of the workers had consumed one or more of these foodstuffs on at least one occasion in the last 24 h.

End-of-shift global thioethers varied from 1.2 to 14 μmol/mmol creatinine. In simple linear regressions, exposure to styrene and cigarette consumption was observed to be significantly associated with this measure (Table 2) but consumption of coffee (number of cups) and of specific foodstuffs was not. In a multiple regression analysis (Table 2) exposure remained significant and the number of cigarettes was nearly significant (p=0.052). Inclusion of coffee consumption and of specific foodstuff consumption did not improve the fit significantly; the regression coefficients were very similar. It is worth noting that exposure to styrene and the number of cigarettes smoked explained only 17% of the variation in the thioether concentration. The slope of the regression line between global thioethers and MA excretion, in the order of 10^{-3}, indicated a very low level of excretion of styrene-related thioethers. No attempt was made to correlate thioether excretion at other urine collection times with these different variables as questionnaire information was relevant only to the period preceding the end of the shift.

Discussion

Urinary excretion of styrene thioethers

In the present study, workers subjected to a wide range

Table 2. Linear regression of thioether excretion[a] as a function of styrene exposure[b] and cigarette consumption[c]

Independent variables	Regression coefficient	Standard error	p	R^2
Single linear models				
styrene exposure				0.114
Intercept	5.0	0.38		
MA[b]	0.0016	0.006	0.008	
cigarette consumption				0.094
Intercept	5.0	0.41		
NC[c]	0.086	0.037	0.020	
Multiple linear model				0.173
Intercept	4.6	0.42		
MA	0.00136	0.006	0.022	
NC	0.070	0.036	0.052	

[a] End-of shift thioether excretion in μmol/mmol creatinine. [b] MA: end-of-shift mandelic acid excretion in μmol/mmol creatinine. [c] NC: number of cigarettes smoked that day.

of styrene exposure levels were found to have excreted very small quantities of thioethers related to styrene. Styrene-specific thioethers, M1 and M2, were found in only three workers at levels ranging from 1 to 8 μmol/mmol creatinine. These results showed that the end-of-shift excretion of styrene-related thioethers is approximately three orders of magnitude lower than the end-of-shift MA excretion. This is consistent with the results that we obtained by the global thioethers method, and the fact that, in contrast to rats, man is less efficient at forming glutathione conjugates[5, 16, 17].

The present results also confirm data presented by Malonova and Bardodej[4] who were the first to show an increase in the excretion of global thioethers in workers exposed to styrene. In the latter study, workers exposed to styrene up to 560 mg/m^3 (environmental exposure was extrapolated based on end-shift urinary mandelic acid excretion) showed global thioethers excretion up to 14 μmol/mmol creatinine. Our results are also in agreement with recent data of Aringer *et al.*[18] who studied global thioether excretion in 18 styrene-exposed workers (8 h × 27–208 mg/m^3) and 6 volunteers (2 h × 210 mg/m^3). They estimated that only about 1% of absorbed styrene was excreted as thioethers in humans over a period of 43 h, and end-shift global thioethers excretion in exposed workers ranged from 4 to 11 μmol/mmol creatinine.

And in a study by Norström *et al.*[19], urine samples from six individuals who had been experimentally exposed to styrene (205–220 mg/m^3, 2 h) were analysed for M_2. The compound could not be identified in the urine collected during the exposure and up to 5 h from the end of exposure. Samples were not analysed for M1. The analysis was performed by HPLC with electrochemical detection (detection limit of 32 μmol/L i.e. approximately 3 μmol/mmol creatinine). Their higher detection limit (less sensitive method), and their moderate exposure doses (25% of the 8 h-TLV) combined with the small number of individuals tested make these results compatible with ours as we found M2 excretion above 3 μmol/mmol creatinine in only one worker, exposed to much higher levels (above the TLV). Our results are also compatible with those of Hallier *et al.*[20] who reported that out of 20 workers exposed to styrene levels ranging from 124 to 175 mg/m^3, only one was found to excrete styrene-specific mercapturic acids, at 3.5 μmol/L (approximately 0.28 μmol/mmol creatinine), the detection limit of their thin-layer chromatographic method.

Ghittori *et al.*[21] have also analysed specific thioethers of styrene (M1 and M2) with a sensitive HPLC method incorporating fluorescence detection. M1 and M2 were found in the urine of all 22 workers exposed to various styrene levels (mean 113 mg/m^3, SD 57 mg/m^3). The sum of M1 and M2 concentrations averaged 1.24 μmol/mmol creatinine (SD 1.27 μmol/mmol creatinine). Significant correlations were found between either urinary PA, urinary styrene or ambient styrene and mercapturic acids specific for styrene. Our results on styrene-specific thioethers are compatible with theirs, if we take into account the different sensitivities of the methods. Furthermore our finding of a significant correlation between urinary MA and global thioethers supports this association.

In our study, the fact that global thioether excretion is related to styrene exposure while the specific thioethers M1 and M2 are not detected in the vast majority of our samples could be explained partly by the different sensitivities of the methods (global vs. specific thioethers) and partly by the possible excretion in humans of other styrene-derived thioethers, such as mercaptolactic and mercaptoacetic acids, as was suggested by Norstrom *et al.*[19] With M1 and M2 detected in only three workers' urine, little can be concluded regarding excretion kinetics for theses metabolites. Altogether, our results, with the finding of the other studies mentionned above, confirm that styrene-specific thioethers are quantitatively minor metabolites in humans.

The global thioether method

Our results obtained with the global thioethers method confirm those of Aringer *et al.*[18] who found that smoking and styrene exposure were significant when modeling thioethers in afternoon urine by means of linear regression. They did not report, however, regression parameters. Our findings concerning the effect of smoking are also consistent with several other studies that have shown that global thioethers excretion was higher in smokers than non-smokers[4, 14, 22–24].

The importance of diet on global thioether excretion[14] is revealed by the fact that exposure to styrene and smoking in our model explained only 17% of the variation, compared to 80% in Aringer's study for workers submitted to a standard diet[18]. The fact that the inclusion of specific foodstuff items did not significantly change our model could be due to the low level of consumption of these foodstuffs in these workers. It could also indicate that other foodstuffs, not on the list, could be important contributors to thioethers and that only a standardized diet may be able to control these. In this study, the last 24 h coffee consumption was not associated with thioether excretion. Aringer and Lidums[14] reported a moderate increase in thioethers after coffee consumption which subsided, however, after several hours.

Inter-individual variability

In our study specific thioethers of styrene, M1 and M2, were found in the end-of-shift urine of three workers exposed to very different levels. Out of the 8 workers excreting MA above the BEI only one was found excreting M1 and M2. Observations of high inter-individual variability have been reported for the excretion

of other specific thioethers such as those derived from methyl chloride[12], acrylonitrile[25] and benzene[26]. In the case of styrene, one possible explanation for inter-individual variability is the polymorphism of the isoenzyme glutathione S-transferase μ, which is responsible for the conjugation of epoxides to glutathione in the liver, and which has been shown to be active in only half of the population[27, 28]. Pacifici *et al.*[29] have demonstrated that conjugation of styrene oxide with glutathione was five times less important for individuals without glutathione S-transferase μ than for those having this enzymatic activity, so that thioether excretion in workers exposed to styrene could depend not only on exposure levels but also on the metabolic capacity to conjugate epoxides. This hypothesis is supported also by the results of Ghittori *et al.*[21] who found a high inter-individual variability in the excretion of M1 and M2 in styrene exposed workers, reflected in rather poor correlation coefficents (ca. 0.5) between mercapturic excretion and styrene exposure, which they explain by the possible existence of two groups corresponding to rapid and poor metabolizers. Because of the limited number of highly exposed individuals in our study and the fact that M1 and M2 were detected in only a few samples, our results cannot be directly compared with those of these authors or used to evaluate the prevalence of metabolic polymorphism. More work should therefore be done to measure these metabolites with sensitive methods in order to better understand inter-individual variability in the metabolism of styrene in humans and its potential impact on health. Because of the poor overall correlations with exposure, and the existence of other good bioindicators, we do not consider that styrene specific thioethers can be recommended as routine bioindicators of styrene exposure.

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