Increased urinary excretion of thioether in new rubber workers

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ABSTRACT Urinary excretion of thioether before starting work and in the early work period in a rubber factory was measured in urine samples collected after one, two to four, and five or more months of starting work. The study population consisted of 84 new workers. The urinary excretion of thioether decreased after one month's exposure and increased thereafter up to five months. Measurement of urinary thioethers in groups of new workers is therefore informative of exposure to alkylating agents only after several months from starting work. This effect may be mediated by the induction of the pertinent metabolic pathway.

Exposure to electrophilic compounds can be detected in industry by measuring urinary thioether excretion.¹⁻³ In practice, the most important value of urinary thioether measurement appears to be its signal function regardless of the routes of the exposure to electrophilic compounds.¹ Urinary excretion of thioether has been shown to be increased in several industries.^{1,2,4}

Previous reports,^{2,3,5} have shown that the urinary excretion of thioethers reflects exposure in the rubber industry. The purpose of this study was to evaluate further the excretion of thioethers among new rubber workers before starting work and after one, two to four, and five or more months from the start.

Subjects and methods

The population under study consisted of 84 new workers in a tyre factory. Freshly voided urine samples were collected before starting work and during work. The samples were collected at the end of an eight-hour working day on Thursday or Friday and stored at -25°C until analysis.

EXPOSURE

Processes undertaken in the tyre factory include mixing and milling, calendering, component preparation and assembling, curing, and finishing. Exposure in the mixing and milling department is mainly to dust and the mode of exposure is through the lungs. In calendering and curing there is exposure to fumes originating from hot rubber. The mode

of exposure is again through the lungs. In component preparation and assembling the exposure originates from rubber bulk handled manually and the mode of exposure is through the skin.

ANALYSIS OF URINARY THIOETHERS

Urinary thioethers were determined after an alkaline hydrolysis as described by Vainio *et al*² and expressed as μmol of urinary thioether per mmol of creatinine in order to adjust for differences in the concentration of urine.

Results

Altogether 177 urinary thioether measurements were carried out, 84 before working and 93 during work. The mean urinary excretion of thioether was 79 ± 4 (expressed as $\mu\text{mol}/\text{mmol}$ creatinine $\pm$ SE of mean) before work. After one month's work the urinary excretion of thioether decreased to 60 ± 5 and during the second to fourth months the excretion increased to 81 ± 5 ; after the fifth month or later the excretion reached 95 ± 6 (table 1).

The excretion of urinary thioethers in different

Table 1 Mean urinary excretion of thioether by group basis before work and after one, two to four, and over five months' exposure. Values are expressed as $\mu\text{mol}/\text{mmol}$ creatinine $\pm$ SE

	No of months			
	0	1	2-4	≥ 5
Mean	79 ± 4	60 ± 5	81 ± 5	95 ± 6
No	84	32	35	26

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Table 2 Mean urinary excretion of thioether before work and after one, two to four, and over five months' exposure. Values are expressed as $\mu\text{mol}/\text{mmol creatinine} \pm \text{SE}$. (Number of subjects in parentheses)

Department	Months			
	0	1	2-4	≥ 5
Mixing and milling	86.0 $\pm$ 6.3 (24)	44* $\pm$ 5.6 (13)	72.9 $\pm$ 12 (9)	108 $\pm$ 10.7 (7)
Component preparation and assembling	74.8 $\pm$ 5.1 (41)	71.3 $\pm$ 9.2 (11)	75.0 $\pm$ 6.6 (19)	87.4 $\pm$ 8.6 (13)
Calendering and curing	88 $\pm$ 8.3 (16)	72.0 $\pm$ 9.0 (8)	94 $\pm$ 10 (6)	94 $\pm$ 7.0 (3)

*p < 0.05 (Student's *t* test).

categories of workers decreased after one month's exposure, increased during the second to fourth month, and after five months or more reached a level higher than before the current work (table 2). The highest initial decrease was detected among the mixing and milling workers (42 $\mu\text{mol}/\text{mmol creatinine}$).

Follow-up of eight individuals yielded the same results as those found in the cross-sectional study (table 3).

Table 3 Mean urinary excretion of thioether of eight individuals followed up for five months. Values are expressed as $\mu\text{mol}/\text{mmol creatinine} \pm \text{SE}$.

	No of months		
	0	1-4	5
Mean	86 $\pm$ 11	73 $\pm$ 6	118 $\pm$ 10

Discussion

The glutathione S-transferase system is one of the pathways concerned in the neutralisation of reactive intermediates formed by the mixed function oxidases in the process that aims at removing absorbed lipophilic foreign chemicals.¹ The intermediates may be epoxides or free radicals with a high chemical reactivity. Conjugation with a suitable nucleophilic acceptor such as glutathione renders them biologically less harmful. In the process a covalent bond from the glutathione sulphhydryl to the reactive electrophilic centre is formed. The resultant compound is chemically a thioether. Thus the measurement of the concentration of formed thioethers provides an indirect index of exposure to potentially alkylating agents and of activity of glutathione S-transferase. Measurements of urinary excretion of thioether in new workers, however, seem to give pertinent results of occupational exposure only after five or more months.

Several inhibitors of insect glutathione

S-transferases are known.⁶ The present data suggest that an unidentified class of rubber chemicals may appreciably inhibit the human enzyme, and this could explain the reduced excretion of conjugation products during early exposure better than, for example, a hypothetical consumption of glutathione pool. Glutathione is virtually absent in human plasma, and the intracellular pool seems to be rapidly restored in healthy subjects.⁷ At least three glutathione S-transferase isoenzymes have been isolated in rat and mouse liver and in the housefly with molecular weights of 43 000, 44 600, and 53 000 daltons without species-dependent differences.⁸ It is currently held that the transferase activity may be induced by prolonged exposure to agents with oxidative metabolism although it is not known which isoenzyme type is concerned as they show overlapping substrate specificity.⁹

The proximate inducers do not need to be highly specific compounds—for example, antioxidant deficiency in rat yields increased transferase activity.¹⁰ Thus the increase in the urinary excretion of thioether in the new rubber workers might reflect enzyme induction rather than the accumulation of reactive chemicals during the early period of current occupation. This renders the urinary thioether determination unreliable as an index of exposure to the alkylating rubber chemicals in new workers.

The greatest decrease in urinary excretion of thioether was seen in mixing and milling workers, whereas their excretion was also the highest after five months. In component preparation and assembly departments as well as in calendering and curing the decrease was smaller than in mixing and milling, and they did not increase to the same level. The results seem to show that a high exposure causes a strong depletion in the enzyme activity, and that the enzyme induction is stronger than in a lower exposure. Measurement of the urinary excretion of thioether in order to estimate exposure at work should be started only after five to six months' exposure so that the error caused by the initial decrease in the urinary concentration of thioether may be eliminated.

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