Acute behavioural effects of styrene exposure: a further analysis

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ABSTRACT Studies were carried out on two groups of men exposed to styrene-based resin. Early morning urinary mandelic acid concentrations after two days without exposure correlated with reaction time measured on arrival at work. Men were found to differ considerably in their rate of clearance of mandelic acid—those with slow clearance having slow reaction times. After some months at reduced exposure, a small group of men with previously high mandelic acid concentrations has speeded up on the reaction time task.

In a recent study¹ we have shown that a group of men who had been exposed to styrene in the previous week started work on Monday morning with a reaction time that was, on average, slower than that of a non-exposed referent group. This early morning reaction time was not found to relate to years of exposure (as might be expected if the slowing were due to insidious and possibly irreversible damage), and no good explanation was found for the slower times in the exposed group. Possibly, however, this was due to the continued presence of styrene or some metabolite (such as mandelic acid) from the previous week's exposure. We report the results of a study set up to investigate this possibility on a second group of workers and the subsequent reanalysis of the original data. We then discuss the findings from two follow-up studies, one at each of the factories referred to in the early part of the paper. These further studies look at the reversibility of any slowing in reaction time, one after some months at reduced exposures, the other after a two-week factory shutdown.

Study samples

All the men included in the studies reported here were using styrene-based resin in a fibreglass process. Two factories were visited.

FACTORY A

The work at factory A has been described.¹ The men

were engaged in a strenuous process making fibreglass boats, spraying the resin, and rolling by hand. In the initial study the mean level of exposure, measured by gas diffusion buttons, was 93 parts per million (range 11-191 ppm).

FACTORY B

The men at factory B had a less strenuous task, laying fibreglass sheets by hand and painting on styrene-based resin to make coach panels. The mean level of exposure was 20 ppm (range 6-31 ppm).

Method

In each of the four studies described here urinary mandelic acid concentrations, corrected for creatinine, were measured by gas chromatography. Reaction time was measured using a portable apparatus that required the man to respond to a visual stimulus presented randomly at intervals from 3 to 12 seconds. The response was to press a button as quickly as possible, the test lasting ten minutes. The responses of each man were recorded on a cassette, and it proved practicable to test up to six men at one session.

FIRST STUDY AT FACTORY B

This study was designed to test whether the slower reaction time at the start of the Monday shift was due to the continued presence of some metabolite of styrene. Seventeen men with a mean age of 40.1 years (range 30-56) took part in this study, which was carried out in March 1980. The men were seen in groups of five to six, the testing being spread over

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three successive Mondays. As in all the studies reported here the men were given a practice session on the reaction time task on the last day at work before the day of the test. At the practice session at factory B the men were given a container in which to collect a sample of the urine passed first thing on the following Monday morning, before exposure started for the week. The ten-minute reaction time test was carried out on arrival at work. These data were used to compute the correlation between urinary mandelic acid and reaction time at the start of the shift.

All the urine passed during the day was collected by the men in the study, a separate container, labelled with the time of the sample, being used on each occasion. A further sample was collected from the first urine passed on Tuesday morning. Mandelic acid concentrations from these urine samples were used to plot excretion curves.

Results

Mandelic acid: Monday morning—The correlation between mandelic acid concentration and the reaction time for the 17 men was 0.58 ($p < 0.01$). When these results were plotted (fig 1) it was found that this correlation was due mainly to the high mandelic acid concentrations of two of the men in the sample, whose reaction times were appreciably slower than the other workers.

Fig 1 Start-of-shift reaction time related to urinary mandelic acid concentration before exposure on Monday morning; initial study factory B.

Mandelic acid: excretion curves—When the urinary mandelic acid concentrations throughout Monday and the following Tuesday morning were plotted, it was seen that the two men with slow reaction times had a high flat excretion curve (fig 2a, b) whereas other men, whose urine was all but clear on Monday morning, had excretion curves that peaked in the later afternoon and dropped to a low level by Tuesday morning. One such curve is shown in fig 2c.

The analysis of the data from factory B suggested that the incomplete excretion of styrene metabolites

Fig 2 Urinary mandelic acid excretion curves. Note: concentration plotted on a log scale.

might account for the slow reaction times found in the exposed group in the initial study, but the information from factory B, with only two men excreting appreciable amounts of the metabolite on Monday morning, did not allow an adequate test of this effect.

REANALYSIS OF THE DATA FROM THE ORIGINAL SAMPLE (FACTORY A)

Exposure at factory A was, in the initial study, close to the threshold limit value, and it might be expected that Monday morning mandelic acid concentrations in men at this factory would be much higher than at factory B. Unfortunately the men had not been asked for early morning urine samples in the initial study but they had collected all the urine passed after arrival at work, noting the time of each collection. Experimental exposure to styrene under laboratory conditions had shown that, in previously unexposed subjects, appreciable concentrations of mandelic acid were not present in the urine until three hours after the start of exposure. It was therefore decided to accept a first urine specimen passed before 1030—that is, up to three hours from the start of the shift—as reflecting the concentration of mandelic acid in the urine at the start of the shift. Fourteen men had given a sample of urine before 1030; the correlation between the mandelic acid concentration in their urine and the start-of-shift reaction time was 0.75 ($p < 0.001$). These data are shown in fig 3.

INTERPRETATION OF THE RESULTS

It appears from figs 1 and 3 that the urinary mandelic acid concentration after two days without exposure to styrene was related to start-of-shift reaction time when mandelic acid concentrations exceeded about 50 $\mu\text{mol}/\text{mmol}$ creatinine in the older men at factory

Fig 3 Start-of-shift reaction time related to urinary mandelic acid concentration collected before 1030; initial study factory A.

B or about 100 μmol in the younger men at factory A. It also appeared (fig 2) that the pattern of excretion of mandelic acid differed among workers. The data presented so far, however, give no information on possible mechanisms. They do not enable us to say whether the slowing of reaction time (if indeed it is a real phenomenon) is reversible nor, if it is reversible, how soon this might occur.

FOLLOW-UP STUDY AT FACTORY A

Factory A was revisited some 21 months after the initial study when changes in the volume of work (and hence exposure levels) allowed some investigation of the effects of reduced exposure on performance. Because of the economic recession only 11 of the 27 men in the exposed group in the initial study were still employed, and these 11 had been on short-time work for several months. Even when working a full week (as they had in the week before the follow-up) mean exposure levels had reduced considerably; on the day the men were tested, the mean exposure, from gas diffusion buttons, was 23 ppm, less than a quarter of that (93 ppm) in the initial study.

Eight of the 11 men still employed had produced urine samples before 1030 in the initial study; these men collected early morning urine on a Monday and their reaction time was tested immediately on their arrival at work.

In these eight men mandelic acid concentrations had fallen from a mean of 273 $\mu\text{mol}/\text{mmol}$ creatinine to a mean of 61 μmol 21 months later. In the same period mean reaction time had speeded up by 10 msec from 239 msec to 229 msec, a difference that could well have been due to chance.

Inspection of the individual changes in reaction time indicated that speeding up was not uniform but was confined to the three men (among eight) with the highest mandelic acid concentrations in the initial study. The early morning concentrations for these three men had ranged from 218–973 $\mu\text{mol}/\text{mmol}$ creatinine with a mean concentration of 549 μmol . The initial mean reaction time for these men was 278 msec; 21 months later, with a mean mandelic acid concentration of 60 μmol , their reaction time had speeded up significantly ($t = 5.5$, $p < 0.05$) to 237 msec. None of the other five men had speeded up. Their mean initial reaction time was 215 msec, and they had a slightly slower time (223 msec) at follow-up. For these men, however, the mean mandelic acid concentrations were relatively low both initially (108 μmol) and at follow-up (62 μmol).

It thus appears that at least part of the slowing in reaction time associated with high mandelic acid concentration in the initial study may have resulted from the acute effects of exposure to styrene; if this is so the speeding up in reaction time would follow

immediately on the excretion of accumulated metabolites. The results are, however, also consistent with the hypothesis that repeated exposure causes an insidious slowing in reaction time, which is at least partially reversible but which takes longer to recover than the elimination of metabolites. The follow-up study at factory A gives no information on how long a period might be needed for recovery; at this factory the men had been working at low exposures for several months.

FOLLOW-UP STUDY AT FACTORY B

The possibility of a short-term recovery after the elimination of metabolites was investigated at factory B, which closed down completely for a two-week holiday period in July 1980. The group of men with the highest exposure (the laminators) in the first study at the factory were briefed on the Friday before the shut down (to renew their familiarity with the test) and asked to come straight to the testing room when they returned to work. Twelve men gave samples of urine on arriving at work and then completed the ten-minute reaction time task. It was found, unexpectedly, that two of the 12 men were still excreting mandelic acid after 16 days without exposure and, as the interest was in the effect of clearing styrene and its metabolites, they were excluded from the performance study. For the other ten men, the mean reaction time from a Monday following normal exposure was compared with the Monday reaction time after the two-week break. On the Monday after exposure a mean reaction time of 250 msec was recorded; after the two week break the mean was 262 msec. This difference was small and may well have arisen by chance. At this factory, where none of the ten men had morning urinary mandelic acid concentrations after exposure greater than 50 $\mu\text{mol}/\text{mmol}$ creatinine, the two-week break (with complete elimination of metabolites) was not sufficient to counter any adverse effects of a delay between rebriefing and testing or the lack of motivation on returning to work from the holiday.

This post-holiday study did, however, allow one further set of observations to be collected; these were the afternoon reaction times on the first day back at work. Here afternoon reaction times for the ten men whose urine was free of mandelic acid on return to work could be related to the mandelic acid concentration in the urine passed at the end of the day. In this analysis it was found that a low mandelic acid concentration was related to a slow reaction time ($r = -0.69$, $p < 0.05$). This finding, shown in fig 4, may be interpreted in several ways but is not consistent with the hypothesis that circulating mandelic acid (as least as reflected by urinary mandelic acid) has an acute effect on the reaction

Fig 4 End-of-shift reaction time related to urinary mandelic acid concentration on first day back at work after a two-week break; follow-up study factory B.

time. It may be that a low urinary mandelic acid concentration at the end of the first day back at work indicates slow clearance and hence a high plasma concentration of styrene or some compound other than mandelic acid in the metabolic pathway.

Discussion

We have reported four studies. From the first studies at factories A and B it appears that start-of-shift reaction time is related to early morning urinary mandelic acid concentrations (figs 1 and 3), but it also appears (fig 4) that this relationship may not be a direct one, the concentration of mandelic acid indicating only the speed of clearance of some compound earlier in the metabolic pathway. It is apparent (fig 2) that men differ considerably in the way in which they clear styrene and its metabolites, and there is also some suggestion (from the follow-up study at factory A) that those with an initially high urinary mandelic acid concentration may, if exposure is reduced, speed up on a reaction time task.

Many questions remain unresolved. If a speeding up of reaction time does occur after reduced exposure, it is not known how long this may take nor whether the effect of reducing exposure would be the same for those with slow clearance (shown by high Monday morning mandelic acid concentrations even after comparatively low exposure) as for those whose high urinary concentrations may reflect only exceptionally high exposure in the previous week. There is also no clear evidence on the point at which clearance is slowed nor on the identity of the compound that is related to poor performance in the reaction time test. To be consistent with the data presented here, however, it appears that the substance must be one that has a rapid effect on reaction time (fig 4) but which can persist for at least two days

without further exposure (figs 1 and 3).

Although the observations reported in this paper are based only on two small groups of styrene workers, measured on more than one occasion, the associations reported are unlikely to have arisen by chance. The findings extend our earlier report¹ by showing that an easily measured metabolite, urinary mandelic acid, may act as a marker of individuals who are slow to clear the solvent and whose reaction times are impaired, at least temporarily.

Before considering the implications of these results for the health and safety of workers exposed to the solvent, the apparently clear-cut results in, for example, fig 3 need to be replicated and further information collected on patterns of excretion and the prevalence of men with slow excretion after

permitted exposures. It would also be of considerable interest to discover whether metabolites of other solvents show a differential pattern of excretion and, if so, whether the differences are also related to behavioural changes.

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Reference

- ¹ Cherry N, Waldron HA, Wells GG, Wilkinson RT, Wilson HK, Jones S. An investigation of the acute behavioural effects of styrene on factory workers. *Br J Ind Med* 1980;37:234-40.