CORRESPONDENCE

Increase in neuropsychiatric symptoms after occupational exposure to low levels of styrene

Editor,—Recently, Edling et al. (1993; 50:843-50) presented a paper on neuro-psychiatric effects of low level exposure to styrene. Bearing in mind previous reports and our own experience with styrene exposed workers in the glass reinforced plastics industry we consider that some extra points need to be made.

Firstly, although the results of the questionnaire (Q16) seem at first glance to show differences between exposed workers and controls, they do not differ to a statistically significant degree, as the authors themselves stated. Furthermore there is no unequivocal trend in the answers given. Whereas questions No 1, 3, and 15 are rated with Yes more often by exposed workers than by controls and there is a decrease after an exposure free period, questions No 4, 6, and 8 ratings show an increase after that time. As the questions of the Q16 specific for effects presumed as neurotoxic, there seems to be some inconsistency in the results reported. For comparison, in table 1 we show the results of Q16 when presented to styrene exposed builders and non-exposed carpenters and furnishers of the same plant. Here, no trends towards an over-representation of single symptoms according to exposure and no difference in the average number of symptoms are to be seen. A major reason for that would be that the workers were presented with the questionnaire along with other questions on potential history. We specially asked them being led to believe that the symptoms asked for could be related to their daily work. We are aware, however, that our controls were matched neither in number nor age to the exposed group.

Secondly, we do not agree with the authors’ opinion that the acute symptom scores “correlated positively” with exposure parameters. It is obvious that the correlations in figs 3 and 4 are biased by two excessive values. It is easy to see that if these values are eliminated, there is no dose-response relation shown in fig 3 and even a reverse trend shown in fig 4. This outcome is then in accordance with previously reported results and with our own findings. Using a questionnaire to quantify acute irritative symptoms according to Molhave et al. (1993) we found no positive correlation between individual styrene exposure, measured in ambient air and blood, and occurrence of symptoms. In our experience, there is no evidence of a dose-response relation at exposures below 100 ppm. Nevertheless exposed workers from the same plant reported significantly more irritative symptoms than non-exposed ones. Most published reports seem to confirm these results.

Thirdly we must point out that no link has yet been established between symptoms on the one hand and diseases on the other. On the contrary, the lack of a dose-response relation between symptoms and exposure parameters suggests that the occurrence of symptoms is not a sign of neurotoxic effects but merely indicates the personal susceptibility towards chemical odours or a certain sensitivity of mucous membranes.

The decisive question seems to be again, whether each observable effect should be considered to be “handwriting on the wall” and should therefore be referred to as “toxic”. Toxic effects are synonymous with adverse effects. This term should, in our opinion, not be applied to each health complaint which is reported. One should regard an effect as such as a neutral concept, and one should distinguish between effects such as such adverse effects (= unacceptable effects).

As a consequence, future research activity should focus on possible links between early subjective symptoms and the development of objective health impairments, in order to identify risk indicators if possible, and distinguish them from simple, acute irritations that are completely reversible at the end of exposure.

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Authors’ reply

We appreciate Nasterlack’s and Triebig’s careful reading of our paper and their comments. We believe that their interpretation of our data is partly due to a misunderstanding of the Q16 and perhaps also to a different approach to occupational medicine.

In our study we used the Q16, which has been established as a sensitive screening instrument for solvent exposed workers. The Q16 was originally designed to establish the total sum of positive answers determined whether or not the worker was affected by solvent exposure. Nasterlack and Triebig make the mistake of analysing single questions or a combination of questions. Further, they compared our results with their own questionnaire results, but did not use matched controls in their study. This is unfortunate, as you have to control for age when using the Q16. There was a thorough discussion on the use of controls in our paper (p 849).

Nasterlack and Triebig want to omit the values that suggest effects (figs 3 and 4 in our paper). We prefer to present the results in full to provide the reader with the opportunity to analyse and interpret them. The reader might then, as did Nasterlack and Triebig, reach a different conclusion. We agree that the correlation coefficients are weak and are stated specifically in our paper (p 850): “these correlations must be interpreted with caution”. Other findings, more recent than those cited by Nasterlack and Triebig, support our conclusion of an effect of low level exposure to styrene.

Concerning approaches to occupational medicine we believe that one aim of our discipline is to identify of an early stage occupational exposures to toxic substances that increase the likelihood of adverse effects in a population. We believe that the worker himself is a very sensitive indicator in the first and that symptoms can and should be used to identify and measure possible effects. If the workers report effects it must be our task to find, through research, the possible causes.

Even low exposures cause serious subjective effects, such as irritation should

**Comparison of the results of Q16 questionnaire as reported by Edling et al (1993) and Nasterlack et al (unpublished results)**

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<tr>
<td></td>
<td>Exposed (n = 20)</td>
<td>Controls (n = 20)</td>
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<tr>
<td>1</td>
<td>10 (50)</td>
<td>0 (0)</td>
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<td>2</td>
<td>1 (5)</td>
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<td>3</td>
<td>6 (30)</td>
<td>2 (10)</td>
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<td>5 (15)</td>
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<td>9</td>
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<td>10</td>
<td>3 (15)</td>
<td>3 (15)</td>
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<tr>
<td>11</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Mean (SD)</td>
<td>3.1 (2.9)</td>
<td>1.5 (1.8)</td>
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Symptoms 9 and 14 were asked about in different ways and are therefore not included. Values in parentheses for numbers with symptoms are %.
Correspondence

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not Secretary of State Editor,-We note samples. quite mercury (Hg) relations number
exposure from workers. among medicine.

In fact it is one Injuries Advisory Council. In 1992;49:679-82. effects of low Neuropsychiatric

The correction of urinary mercury concentrations in untimed, random urine samples.

Editor,—We note with interest the continuing number of reports defining dose-effect relations for occupational exposure to mercury (Hg) that have used urinary Hg concentrations in untimed, random samples (spot urine) either as a cumulative exposure dose or a simple dose index.¹

These studies often use spot urinary Hg concentrations readily available from routine biological monitoring strategies in the chloralkali and other Hg utilizing industries. Diurnal variation in the metal's excretion has been noted,² but the higher concentrations found in morning samples compared with afternoon and evening samples have been suggested as being of no practical relevance to biological monitoring scheme.³ Urinary Hg concentrations are said to reflect integrated exposure over the preceding weeks or months in workers with long term exposure. There has been debate about whether correction of urinary mercury concentration would be better in reducing intra individual variation of urinary Hg and thus making a single spot measurement more closely reflect true Hg exposure.⁴ With workers at the same time of day on each day of the working week (five days). The samples from this study were uncorrected or corrected for creatinine concentration or for an SG of 1-016.³

The mean urinary mercury concentrations in the workers from the within day and between day studies were 58 (4-268) and 32 (6-50) mmol/mmol creatinine respectively. The table shows the calculated mean and standard deviation (SD) of the interindividual coefficients of variation (CVr) for urinary Hg results in the two studies and, the comparison by ANOVA, of the mean CVs of corrected urinary Hg results with uncorrected results. The data from the within day study confirmed the previously reported diurnal variation.³,⁴ A low mean and SD of interindividual CVs derived from multiple spot urinary Hg samples would imply that single urine sample closely reflects the true Hg excretion in that individual subject. Creatinine correction of Hg concentration satisfactorily, reduced intra individual variation, both between and within day, to about 50% of the variation in uncorrected urine values.⁴ Although the mean interindividual CVr, both within and between day, was less with creatinine correction than with SG correction, the difference did not reach significance (ANOVA, Bonferroni multiple comparison test). There was some evidence from F tests, however, that creatinine correction may be more reproducible between subjects than SG correction. It should be noted that, even with creatinine correction, the mean CVr of around 15% with the imprecision of our method implies that two consecutive daily spot urine samples, taken at a time to reduce the intra individual variation, could statistically be around 45%-50% apart (t=1.2/2CVr). It has been widely accepted in clinical pathologic that acceptable analytical imprecision should be less or equal to half the average intra-individual biological variation (CVr).⁴ This value for urinary Hg corrected for creatinine can be derived from the formula CVr' = CVr + CVr × CVr.³ Thus we suggest that the combined analytical precision of urinary Hg and creatinine method should be less than 7.3%.

Correction for creatinine and, perhaps slightly less satisfactorily, correction for SG reduce the uncertainty of spot urinary Hg concentration in reflecting accurately the true Hg excretion in an individual subject. Corrected spot urinary Hg results have proved their use both in routine biological monitoring and in studies describing dose-effect relations that may aid in setting standards. It is important, however, that the limitations and errors associated with their use as dose measures are understood.

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