

Health status of styrene-polystyrene polymerization workers

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LORIMER, W. V., LILIS, R., FISCHBEIN, A., DAUM, S., ANDERSON, H., WOLFF, M. S. and SELIKOFF, I. J. Health status of styrene-polystyrene polymerization workers. *Scand. j. work environ. & health* 4 (1978): suppl. 2, 220—226. Styrene monomer is a greatly used chemical, chiefly in the production of polystyrene. A cross-sectional health survey of 493 production workers was undertaken at the oldest and largest monomer production, polymerization, and extrusion facility in the United States. Relative exposure durations and levels were obtained from occupational histories and corroborated by spot air sampling, blood and fat styrene concentrations and levels of urinary mandelic and phenylglyoxylic acids. Statistically significant differences between the prevalence of abnormalities in high and low exposure groups were found for the following: history of acute prenarcoctic symptoms, history of acute lower respiratory symptoms, peroneal nerve conduction velocities, relative lymphocytosis, and elevated gamma glutamyl transpeptidase. The following showed no distinct pattern in prevalence when analyzed by exposure group: chest radiographic changes; indices of restrictive, obstructive, and small airway dysfunction; other hepatic and hematological parameters; carcinoembryonic antigen level; sputum cytopathology; radial nerve conduction velocities; and ophthalmological findings. Clinically significant abnormalities were rare.

Key words: cross-sectional survey, occupational health, polymerization, styrene.

Styrene monomer is a greatly produced chemical whose predominant use is in the polymerization either of classical plastics (polystyrene, butadiene-styrene, acrylonitrile-butadiene-styrene) or of polyester resins. The latter process (4, 15, 19) has been more extensively studied than the former (11). It is of interest that the concomitant chemical exposures of the two processes are quite different. Processing

classical plastics often involves steps taking place in the same facility prior to the actual polymerization, such as ethylbenzene production from benzene and ethylene and the conversion of ethylbenzene to styrene. Polyester resin use involves use of complex amines and a variety of other resin components, as well as the reinforcing agent. If similar patterns of dysfunction were found in the two sets of workers, one would have confidence in ascribing an etiologic role in the dysfunction to styrene, especially if the patterns of dysfunction were consistent with experimental animal (25) and human (1, 3) laboratory exposures.

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MATERIALS AND METHODS

A brief outline of the study design is presented in this report; more details were given in an initial publication (11).

From a review of the literature it was hypothesized that clinical effects of styrene exposure might be detected in a sufficiently large, exposed population in a cross-sectional survey. The analytical model was that of dose-response. Both dose (level and length of exposure) and response (detectable biological effects) had to be sufficiently well-defined for meaningful analysis. The statistical model used under dose-response was categorical (chi-square) for every clinical parameter, the null hypothesis being that the proportion of clinical abnormality (response) is independent of length and/or intensity of styrene exposure (dose).

A large styrene manufacturing, polymerization, and (to a limited degree) extrusion facility was selected for the study. Investigation revealed a large (over 600), stable (about 40 % employed longer than 20 years) work force, 98 % caucasian male. The plant history (fig. 1) revealed relative process stability and a manageable number of confounding chemical exposures. A total of 493 workers underwent the examination.

Dose was determined in three ways. First, from a description of the plant history and processes and from discussion with workers and management, jobs with relatively high and low exposure were determined (table 1). A detailed occupational history was recorded for each worker. A worker was assigned to the high exposure group if over 80 % of his total time since beginning employment was spent in a high exposure position; otherwise he was categorized with the low exposure group. Each of the two groups was subdivided into three intervals since employment (0—7, 7.1—20, > 20 years). Second, mandelic and phenylglyoxylic acids (in a spot urine sample), as well as blood styrene, were measured at the time of the examination (5, 18). The results provided validation (table 2) of the original classification of high or low exposure jobs. [Details on the results regarding the biological indicators of exposure were also presented at this symposium.]

Plant History

Period

Process

1943—1963

coke oven by-products
↓
benzene
↓
ethylbenzene
↓
styrene

NOTE:

Butadiene was produced until about 1950. Styrene and butadiene were polymerized elsewhere into butadiene rubber. After 1947 some polystyrene was produced in the plant. After 1951 much polystyrene was produced, and little styrene monomer was shipped.

1963—1975

ethylbenzene
↓
styrene
↓
polystyrene

NOTE:

Significantly less benzene exposure occurred during this period.

Fig. 1. Plant history of styrene and polystyrene processing.

Table 1. Occupational distribution of high and low styrene exposure.

Exposure	Number of workers
Low	
Retired, quit	41
Power house	22
Sheet plant (salvage extrusion)	41
Packaging expandable polystyrene	25
Warehouse of transportation	38
Maintenance, low exposure	22
Other	11
Total low	200
High	
<i>Production</i>	
Styrene manufacture	16
Styrene purification	14
Polymerization	108
Miscellaneous	39
<i>Maintenance</i>	
Pipe fitters	29
Millwrights	19
Electricians	15
Laborers	13
Welders	11
Miscellaneous	24
Total high	288

Table 2. Urinary mandelic acid and blood styrene in styrene-exposed workers less than 4 h from end of shift.

Exposure group	Mandelic acid (≥ 7 mg/g creatinine)		Blood styrene (≥ 5 ppb)		Both elevated	
Low	1/ 55	(1.8 %)	1/ 42	(2.4 %)	0/ 41	(0 %)
High	38/ 94	(40 %)	16/ 70	(23 %)	9/ 65	(14 %)
Total	39/149	(26 %)	17/112	(15 %)	9/106	(8.5 %)

Table 3. Clinical parameters used in the evaluation of the dose-response model.

Parameter	Categorical borderline
Mucous membrane irritation (eyes, nose or throat)	
Ophthalmological	
Irritation	
Optic neuritis	
Hematological	
Anemia	< 14.0 g %
Leucopenia	$< 4,800/\text{mm}^3$
Thrombocytopenia	$< 180,000/\text{mm}^3$
Increased lymphocyte percentage	≥ 45 %
Hepatic	
Alkaline phosphatase	> 41 I.U.
Serum glutamic pyruvic transaminase	≥ 70 I.U.
Serum glutamic oxaloacetic transaminase	≥ 50 I.U.
Gamma glutamyl transpeptidase	≥ 45 I.U.
Pulmonary ^a	
Radiographs	Pneumoconiosis, ILO U/C, $\geq 1/0$
Restriction	< 80 % VC
Obstruction	
Large airway	$\text{FEV}_1/\text{FVC} < 75$ %
Small airway	$\text{FEF}_{75}/\text{FVC} < 0.30$ and $\text{FEV}_1/\text{FVC} \geq 75$ %
Diffusion defect	< 75 % pred.
Neurological	
Acute prenarcois	
Sensory changes	
Nerve conduction studies	
Radial	< 55 m/s
Peroneal	< 40 m/s
Carcinoembryonic antigen level and sputum cytology	
Mutagenesis	
Chromosome abnormalities	

^a FEV_1 = Forced expiratory volume in 1 s; FVC = Forced vital capacity;
FEF = Forced expiratory flow.

sium (18)]. Third, limited air sampling data, available from the National Institute for Occupational Safety and Health (13) and from the company, were used that

indicated that the mean styrene concentrations in the styrene purification and polymerization areas (highest exposure) were on the order of 20 ppm (time-

weighted average) with very wide excursions. Ethylbenzene levels were roughly an order of magnitude less. Areas with somewhat less exposure (~ 5 ppm) were still classified as high exposure for purposes of this analysis; low exposure was generally < 1 ppm (18).

Chronic toxic effects of styrene on the ophthalmological, hematological, hepatic, pulmonary, and neurological systems, as well as mutagenic effects, have been described or hypothesized in the literature. In addition, acute irritative effects on mucous membranes (conjunctivas, upper respiratory and bronchial mucosa) have been described. In a previous report (11) the specific investigative techniques used in this study have been summarized. Clinical parameters were selected which were well validated and for which the

limits for normal were fairly well defined. Job-related symptom histories were recorded by trained interviewers. Table 3 gives a list of effects to which the dose-response model was applied, together with the categorical borderline (of abnormality) used.

RESULTS

The prevalence of a history of selected symptoms in high and low exposure groups is given in table 4. On categorical analysis the prevalence of prenarcotic symptoms (styrene-induced lightheadedness, dizziness, headache) and of lower

Table 4. Prevalence of reported acute symptoms in 488 styrene-exposed workers.

Symptom	Low exposure (N = 200)	High exposure (N = 288)	p value
Prenarcotic symptoms (lightheadedness, etc.)	10 %	19 %	$0.001 < p < 0.01$
Mucous membrane irritation	17 %	20 %	$p > 0.05$
Lower respiratory symptoms (cough, wheezing, or tightness in chest)	7.2 %	19 %	$p < 0.001$
Recurrent lower respiratory symptoms (averaging at least once a month)	4.9 %	12 %	$0.001 < p < 0.01$
Eye irritation	17 %	25 %	$p > 0.05$

Table 5. Relative lymphocytosis (≥ 45 %) in 342 styrene-exposed workers by intensity and duration of exposure.^a

Intensity of exposure	Duration of exposure			Total
	0.1—7.0 years	7.1—20 years	> 20.0 years	
Low ^a	23/60 (38 %)	15/44 (34 %)	9/60 (15 %)	47/164 (29 %)
High ^b	7/46 (15 %)	12/46 (26 %)	22/86 (26 %)	41/178 (23 %)
Total	30/106 (28 %)	27/90 (30 %)	31/146 (21 %)	88/342 (26 %)

^a Low exposure group shows decrease over time of lymphocytosis prevalence ($\chi^2 = 8.86$, $0.02 > p > 0.01$).

^b High exposure group shows increase over time (highly significant difference in the two patterns).

respiratory irritation (cough, wheezing, or tightness in the chest) is significantly higher in the group with higher exposure.

The general ophthalmological examination was unremarkable; no evidence of optic neuritis was found (8).

Styrene is thought to have minimal hematological effects (11). The prevalence of hemoglobin below 14.0 g% was 13.6 %, of white blood count below 4,800/mm³ was 2.7 %, and of platelet count below 180,000/mm³ was 7.4 %. No dose-response relationship could be documented. For relative lymphocytosis (≥ 45 %) opposite trends were observed in the low and high exposure groups (table 5). The presence of benzene in the facility, especially in the past, is a confounding factor in the interpretation of the hematological findings.

As indices of hepatic function serum levels of four enzymes (glutamic pyruvic transaminase, alkaline phosphatase, glutamic oxalocetic transaminase and gamma glutamyl transpeptidase) which may reflect hepatic dysfunction were studied. All four showed a prevalence of 3 to 6 % for abnormal values; this percent-

age did not differ from the 4 % found in a comparison group (11). The high and low exposure groups were not significantly different in this respect, except for gamma glutamyl transpeptidase (GGTP), for which the high exposure group had a significantly elevated prevalence of abnormal values, even when alcohol intake was taken into account (1.7 % vs. 7.2 %; $0.01 < p < 0.02$).

The respiratory system is of interest because styrene is a known pulmonary irritant in animal experiments (16) and may have acute and/or chronic effects. Chmielewski and Renke (2) found irritation and obstruction to airflow in styrene workers. The analysis was made more complex by confounding factors (cigarette smoking, occupational exposure to coal or asbestos, other chest disease) which needed to be taken into account. Standard postero-anterior chest radiographs were read by a panel of five readers; consensus reading was used for analysis. Forty-one of the 417 workers (9.8 %) had small opacities (rounded and/or irregular corresponding to ILO/UC pneumoconiosis category 1/0 or higher (ILO/UC classification), and 10 fitted category 2/1 or higher. No dose-response relationship with styrene exposure was noted; many of the abnormal chest radiographs were attributable to previous coal or asbestos exposure in the styrene facility (table 6). The prevalence of ventilatory restrictive dysfunction ($FVC < 80$ % predicted)² was only 4.2 %. Large airway obstruction to flow ($FEV_1/FVC \leq 74$ %) was 30 % in nonsmokers and 36 % in smokers. Isolated small airway obstruction ($FEV_1/FVC \geq 75$ % and $FEF_{75}/FVC < 0.30$) was found in 15 % of the nonsmokers and 16 % of the smokers. No dose-response relationship with styrene exposure could be established for these changes. A total of 78 carbon monoxide diffusion tests were performed; in 8 cases (10 %) a decrement (less than 75 % predicted) was found; 7 of these workers were smokers.

An interesting observation was the higher prevalence of detectable urinary mandelic acid in workers with obstructive

Table 6. Radiologic abnormalities ($s \geq 1/0$, ILO U/C International Classification of Radiographs of Pneumoconioses) in 41 styrene-exposed workers according to occupational history.

History in this facility	Number of workers
≥ 5 years	
Power house worker (coal/asbestos)	6
Insulator	2
Welder	3
Other maintenance (laborer, carpenter, pipefitter, millwright)	7
Total	18
≥ 20 years (not included above)	
High styrene exposure	7
Low styrene exposure	6
Total	13
Other history	10
Total	41

Note: Those with exposure to coal and/or asbestos dust prior to work at the facility were excluded. Half of the current insulators and about 20 % of the current power-house workers are included.

² FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 s; FEF = forced expiratory flow.

ventilatory dysfunction when these workers were compared to those without obstruction (table 7). This result provides some evidence for an acute irritative and obstructive effect of styrene.

Neurological findings have been reported from occupational exposure to styrene (4, 6, 7, 15). The physical findings of distal hypoesthesia and hypoactive deep tendon reflexes were about 4 and 6 %, respectively, and did not follow a dose-response pattern. Radial and peroneal nerve conduction velocity abnormalities (table 3) were present in 15 of 80 and 12 of 73 workers, respectively. There was a consistent decrement in peroneal nerve conduction velocity with duration of styrene exposure. Details of the neurological findings and possible confounding factors to be considered have been published earlier (10).

Elevated carcinoembryonic antigen levels (CEA titer > 2.5 ng/ml) have been reported in a number of malignant and nonmalignant conditions, such as cigarette smoking and a history of a significant intake of alcohol. When the analysis concerned only those individuals free of any such condition, only 73 individuals of 442 remained and only 4 had an elevated titer (3 % prevalence in general nonsmoking population). It was thus concluded that styrene has little if any effect on the prevalence of elevated carcinoembryonic antigen titers. No severe atypia or malignant changes and only three cases of moderate atypia were found in the 225 sputum cytology specimens examined.

The finding that styrene oxide is almost certainly an obligatory metabolite of styrene, and that it is mutagenic (9, 12, 17), made the study direct some attention to possible alterations in genetic material.

Since styrene oxide is a known base-substitution mutagen (12, 17) and a metabolite of styrene, 21 urine and 21 blood samples from workers just completing work for the day were tested with the Ames/Salmonella auxotroph reversion test (12). Sixteen of these men had detectable mandelic acid in their urine and/or styrene in their blood. No mutagenic activity was detected in any of the samples tested with test strains previously sensitive to mutagenesis by styrene oxide (Garro and Phillips, unpublished data).

Table 7. Relationship of FEV/FVC < 0.75 ^a to urinary mandelic acid in actively working non-smoking styrene-exposed workers.^b

	Mandelic acid	
	Detectable	Not detectable
FEV/FVC < 0.75	12/29 (41 %)	13/62 (21 %)

^a FEV = forced expiratory volume; FVC = forced vital capacity.

^b Chi-square for large airway obstruction (FEV₁/FVC < 0.75) detectable mandelic acid compared with nondetectable = 4.13 0.05 > p > 0.02.

Karyotyping was attempted on 17 individuals; seven were successful including two controls. Two of the five test cases had a high number of gaps and breaks. In 50 cells one had five gaps and a break; in the other there were three gaps and seven breaks. These two men had been under high exposure for over 20 years. The other three test cases had been exposed for seven or less years, two being of a low level. These three had three gaps and one break among them. In the two controls only one gap was found. The results are fragmentary and confounded by possible past benzene exposure. Further studies would probably help valid conclusions be drawn concerning this problem.

DISCUSSION

An extensive cross-sectional survey of a working population in a styrene manufacturing, polymerization, and polystyrene extrusion facility was undertaken. About 25 clinically plausible hypotheses were tested under the dose-response model. Of these, six revealed statistically significant differences between the high and low exposure groups. Some were acute effects; i.e., a history of prenarctic syndrome and a history of lower respiratory symptoms. Airway obstruction as related to mandelic acid presence in the urine indicated the possibility of both acute and long-term effects. Three hypotheses were positive

under the chronic dose-effect model: relative lymphocytosis, elevated GGTP, and decreased peroneal conduction velocity. No chronically, clinically disabling effect on any individual was noted.

The increase in relative lymphocytosis is suggestive of a hematological effect of styrene; it is nevertheless not conclusive since it may reflect a benzene effect. The prevalence of elevated GGTP is not unexpected since one of the metabolic pathways of styrene detoxification in the liver requires this enzyme (14). The borderline higher prevalence in decreased nerve conduction velocities may partially be an age effect (diabetics, ethanol drinkers, and lower back injuries were eliminated from the analysis), and is consistent with the work of Seppäläinen (15).

In conclusion, styrene monomer is confirmed as an irritant to mucous membranes, including bronchial epithelium, and as a cause of prenarcotic types of central nervous effects and possible peripheral neuropathy. An hepatic (sub-clinical) effect may result in GGTP elevation. At least at the moderate level of styrene exposure of a few tens of parts per million or less, the time-weighted average found in this facility, no other dose-response relationships were documented.

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Comments made at the end of the session

Dr. Compertz:

Today we have heard several papers correlating clinical findings and symptoms with urinary mandelic acid measurements, using these measurements as a measure of styrene exposure. I am somewhat worried about the use of random urinary specimens for the measurement of mandelic acid in this assessment. Using personal monitoring equipment — charcoal tubes with personal monitoring pumps — we undertook a small study to investigate the relationship between styrene exposure and mandelic acid excretion. The exposures, as measured by the sampling apparatus, were limited to between 50 and 150 ppm of styrene, with many of the workers having a time-weighted average very near 100 ppm. However, the range of mandelic acid excretion was extremely large. To analyze this data, we made an initial working assumption that there is a linear relationship between exposure and excretion over this exposure range. The urinary mandelic acid results were then corrected for exposure to a figure of 100 ppm of styrene, and the results were plotted out as a frequency histogram. When the results were presented in this manner, the distribution of mandelic acid excretions adjusted to this specific exposure level was extremely large. It is obvious that this variability is reflected in other studies in the literature. The next question we asked was: What was the cause of this variability? Obviously there are wide genetic differences between individual workers, but it seemed from studies in other fields that the variability that we were looking at was too large to be accounted for in this way. If one looks at the data of Engström et al. (1), one sees that the range of half-times for the clearance of mandelic acid is quite wide. This would be reflected by a great variability in excretion rates at specific times after exposure. Data that we had been studying previously were for samples taken towards the end of work exposure, and we had no idea whether this reflected the exposure during that day or whether there was a lag period.

The studies presented earlier today by Ms. Engström showed in fact that there is a lag period between the end of exposure at the end of the shift and the maximum excretion

of mandelic acid. We have similar findings. Our colleagues, the industrial hygienists of the Health and Safety Executive, devised a ventilation study for the construction of fiber glass reinforced boats, and two experienced technicians built the same sized boat daily (hull in the morning, deck in the afternoon) on a 5-day cycle with different degrees of ventilation. With the cooperation of these technicians, we analyzed every urine sample they excreted for a 7-day period. The interesting result from this study was that one worker had a peak mandelic acid excretion 8 h after the end of exposure, whereas the other worker had peak excretion 4 h after the end of exposure.

If we had measured either the last urine specimen after the end of exposure or the first specimen the next morning, we would have had no indication of the peak levels that would have been related to that shift. It seems that mandelic acid excretion measured during the workday has a minimal relationship to the peak of excretion observed between 4 and 8 h later after the end of the shift, and we suggest that a much better correlation between exposure and mandelic acid excretion could be made if this peak excretion could be monitored. However, biological differences in the half-time of mandelic acid excretion makes it difficult to forecast where this peak will occur. We suggest it would be reasonable to collect all urine samples from the end of one shift until the beginning of the next shift, i.e., overnight, and so include the period containing the maximum mandelic acid excretion. This may correlate better with exposure and be a better marker for other clinical and epidemiologic studies. In the next survey that we have planned, we intend to attempt a correlation between exposure and the overnight production of mandelic acid.

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