Exposure to styrene and mortality from non-malignant respiratory diseases

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Abstract

A cohort of 34 560 men and 6128 women employed in 660 European factories manufacturing reinforced plastic products, followed up originally to assess the risk of cancer, was used to assess the risk of non-malignant respiratory diseases associated with exposure to styrene. Mortality from pneumonia was associated with intensity of exposure to styrene, but this may have been due to chance. Mortality from bronchitis, emphysema, and asthma was not associated with styrene exposure.

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Styrene (C_8H_8) is an aromatic hydrocarbon produced in substantial quantities. Worker exposure occurs during its production and polymerisation, and in the manufacture of glass reinforced plastics, resins, and synthetic rubber.¹ Styrene is taken up through the lung and the skin, and causes irritation of the respiratory tract, even at low levels of exposure (about 20 ppm). Pulmonary lesions due to styrene have been reported in humans and animals, but data on possible long term morbidity and mortality from non-neoplastic diseases associated with exposure to styrene are scanty. The effects of styrene on the respiratory tract of workers exposed to concentrations above 100 ppm (433 mg/m^3) include chronic bronchitis and obstructive pulmonary changes.¹ Cases of asthma induced by styrene have also been reported.¹ In experiments with rats, morphological damage occurred after exposure to styrene in the upper, and to a less extent, in the lower respiratory tract.² Respiratory effects of styrene in rats are thought to be associated with glutathione depletion in the lungs accompanied by inhibition of cytochrome P450 dependent oxidative drug metabolism.³ We examined mortality from non-malignant respiratory diseases in relation to exposure to styrene in a large international cohort study of workers in the glass reinforced plastics industry, where high workroom concentrations of styrene were encountered. The cohort had been established initially to assess the risk of cancer associated with exposure to styrene.⁴

Materials and methods

The cohort consisted of 34 560 men and 6128

women ever employed in 660 European factories to manufacture reinforced plastic products. The subjects were identified through eight research centres in Denmark, Finland, Italy, Norway, Sweden, and the United Kingdom. Cohort recruitment has been described in detail elsewhere.⁴ We excluded subjects unexposed or with unknown exposure to styrene ($n = 5245$). A total of 35 443 exposed subjects remained for the external comparisons with national reference rates. They accumulated 446 784 person-years during an average of 12.6 years of follow up. For internal comparisons, we excluded 2641 additional subjects with incomplete job data, leaving 32 802 subjects (405 975 person-years). Follow up for mortality was initiated at first exposure to styrene (1945-91), or on the first date for which complete payrolls were available, whichever was later. A styrene exposure database was constructed from personal, environmental, and biological measurements. An exposure matrix was developed by country and calendar period. It used job titles, types of product, and methods of production. Estimates of individual exposure were reconstructed by applying the matrix to personal occupational histories. Exposures decreased in all countries from around 200 ppm in the early 1960s to 20-40 ppm in the late 1980s.

For external comparisons, standardised mortality ratios (SMR) and 95% confidence intervals (95%CI) were calculated with the program PERSON-YEARS.⁵ The WHO mortality data bank provided national mortalities by sex, age, and calendar period.

Poisson regression models were used for the internal comparisons among exposed subjects. Relative risks (RR) and 95%CI were estimated with the program GLIM.⁶ We examined mortality from all non-malignant respiratory diseases (ICD-9 460-519), and from two subcategories (pneumonia ICD-9 480-486; and bronchitis, emphysema, and asthma ICD-9 490-493), in relation to variables of exposure to styrene. Country, sex, age (five levels,) and calendar period (four levels) were included in all models. Time since first exposure, duration of exposure, cumulative (ppm-years) and average exposure (ppm) were analysed as categorical variables as in the analysis on cancer risk.⁴

Results

All cause mortality among exposed workers was lower than expected from national rates (2196 observed deaths, SMR 96 (95%CI

Mortality from respiratory diseases and exposure to styrene (internal comparisons (Poisson regression); all relative risks (RR) and adjusted for country, age, calendar year, sex)

<i>All respiratory diseases (ICD-9 460-519)</i>				<i>Pneumonia (ICD-9 480-486)</i>				<i>Bronchitis, emphysema, asthma (ICD-9 490-493)</i>			
<i>Indicator</i>	<i>Deaths</i>	<i>RR</i>	<i>(95% CI)</i>	<i>Indicator</i>	<i>Deaths</i>	<i>RR</i>	<i>(95% CI)</i>	<i>Indicator</i>	<i>Deaths</i>	<i>RR</i>	<i>(95% CI)</i>
<i>Time since first exposure (y)</i>				<i>Time since first exposure (y)</i>				<i>Time since first exposure (y)</i>			
< 10	23	1.00*		< 10	9	1.00*		< 10	11	1.00*	
10-19	58	2.06	(1.20-3.54)	10-19	9	1.24	(0.43-3.52)	10-19	35	2.19	(1.02-4.69)
> 20	31	2.50	(1.28-4.89)	> 20	7	2.98	(0.81-11.0)	> 20	13	1.82	(0.69-4.79)
P for trend = 0.01				P for trend = 0.08				P for trend = 0.22			
<i>Duration of exposure (y)</i>				<i>Duration of exposure (y)</i>				<i>Duration of exposure (y)</i>			
< 1	53	1.00*		< 1	11	1.00*		< 1	28	1.00*	
1-3	25	0.76	(0.47-1.22)	1-3	6	0.82	(0.30-2.23)	1-3	14	0.85	(0.45-1.62)
4-9	22	0.83	(0.50-1.40)	4-9	5	0.87	(0.29-2.62)	4-9	9	0.75	(0.35-1.63)
> 10	12	0.71	(0.37-1.38)	> 10	3	1.91	(0.24-3.52)	> 10	8	1.09	(0.47-2.53)
P for trend = 0.16				P for trend = 0.48				P for trend = 0.58			
<i>Average exposure (ppm)</i>				<i>Average exposure (ppm)</i>				<i>Average exposure (ppm)</i>			
< 20	9	1.00*		< 60	3	1.00*		< 20	6	1.00*	
20-59	17	0.37	(0.16-0.83)	60-119	8	2.07	(0.53-8.04)	20-59	10	0.32	(0.12-0.90)
60-119	39	0.55	(0.26-1.17)	120-199	7	3.20	(0.79-13.0)	60-119	20	0.39	(0.16-0.99)
120-199	26	0.67	(0.31-1.47)	> 200	7	6.10	(1.44-25.8)	120-199	13	0.50	(0.18-1.33)
> 200	21	0.86	(0.38-1.93)	P for trend = 0.01				> 200	10	0.54	(0.19-1.52)
P for trend = 0.08								P for trend = 0.58			
<i>Cumulative exposure (ppm-y)</i>				<i>Cumulative exposure (ppm-y)</i>				<i>Cumulative exposure (ppm-y)</i>			
< 10	22	1.00*		< 10	4	1.00*		< 10	10	1.00*	
10-74	31	0.88	(0.51-1.51)	10-74	6	0.90	(0.25-3.21)	10-74	16	1.01	(0.46-2.24)
75-199	17	0.66	(0.35-1.24)	75-199	4	0.78	(0.19-3.16)	75-199	11	1.01	(0.43-2.40)
200-499	19	0.66	(0.35-1.23)	200-499	6	1.08	(0.30-3.97)	200-499	11	0.92	(0.39-2.21)
> 500	23	0.62	(0.34-1.14)	> 500	5	0.69	(0.17-2.77)	> 500	11	0.76	(0.31-1.84)
P for trend = 0.05				P for trend = 0.48				P for trend = 0.96			

*Reference category.

92-100)). Mortality deficits were found for all non-malignant respiratory diseases (118 deaths, SMR 81 (67-96)), pneumonia (27 deaths, SMR 62 (41-90)) and bronchitis, emphysema, and asthma (63 deaths, SMR 86 (66-110)). Mortality from all non-malignant respiratory diseases increased with increasing time since first exposure (SMR 58 (38-85) for < 10 years, SMR 89 (68-115) for 10-19 years, SMR 92 (63-129) for > 20 years).

Six workers who died of respiratory diseases were excluded from the internal comparisons because of incomplete exposure data. Mortality from respiratory diseases increased significantly with time since first exposure (P for trend 0.01). An inverse trend with cumulative exposure (0.05) was found. Respiratory mortality dropped from RR 1.00 (reference category < 20 ppm) to 0.37 for 20-59 ppm average exposure. An increasing trend was found for average exposure higher than 60 ppm. Duration of exposure to styrene was not associated with respiratory mortality (table). Mortality from pneumonia increased with time since first exposure (0.08) and average exposure to styrene (0.01), but was not associated with cumulative exposure (0.48) nor duration of exposure (0.48). The significant trend for average exposure remained after adjustment for time since first exposure. The trend in risk of pneumonia by time since first exposure was confounded by average exposure (P for trend after adjustment 0.65). Average exposure remained the only variable consistently associated with pneumonia. Mortality from bronchitis, emphysema, and asthma increased slightly with time since first exposure but was not associated with other indices of exposure (table).

Discussion

Mortality from all non-malignant respiratory diseases increased significantly with increasing

time since first exposure, although no association was found with other indicators of exposure to styrene. This pattern is likely to be due, at least in part, to the gradual diminution of the healthy worker effect.

Average exposure to styrene was significantly associated with mortality from pneumonia, though no overall excess was found when using national mortalities for comparisons. Pneumonia has been associated in humans with exposure to solvents, such as petrol,⁷ but we do not know of other findings linking long term exposure to a solvent with pneumonia. The causal pathway associating styrene exposure with pneumonia is not well understood. Infection is a necessary cause for the occurrence of pneumonia. Continuous exposure to irritants of the respiratory tract may damage the architecture of the lung parenchyma, allowing the action of infectious agents. Extraneous substances may be accumulated in the lungs by infiltration. These may induce multiple pathogenic entities, such as diffuse infiltrative diseases, and produce structural damage and alterations in pulmonary function, so facilitating the induction of pneumonia.⁸ Of all the 25 deaths from pneumonia, 22 occurred after the end of work in the glass reinforced plastics industry. For these subjects, a significant increasing trend for average exposure was found (P for trend 0.03). This suggests that subjects exposed to high average exposures may have higher risks of dying from pneumonia even long after the end of exposure. The association between average styrene exposure and pneumonia may be a chance finding but may also suggest that high exposures damage the lung parenchyma and increase the long term risk of pneumonia. Even in recent years, when average exposures have been considerably lowered, peak exposures of 200-300 ppm are regularly encountered in the lamination processes.⁹

The possible confounding effect of other

exposures present in the reinforced plastic industry should be considered. There is some evidence that it is unlikely that other agents are responsible for the increased risk of respiratory diseases. The most important agents to which exposure occurs in the reinforced plastic industry, apart from styrene, are mineral fibres, in particular glass wool, and resin dust.¹⁰ Although mineral fibres are released, mainly in the handling of mats, their diameter is too large to make them respirable. Exposure to resin dust occurs, mainly in the finishing of the product: workers with the highest exposure to resin dust may therefore not be those with the highest exposure to styrene; however, in small workshops workers may perform different tasks. Exposure to other respiratory irritants, such as asbestos, is not documented in this industry.¹⁰

In conclusion, mortality from pneumonia was associated with intensity of exposure to styrene. The excess risk occurred in one of the target systems for the acute effects of styrene. This finding may be due to chance, however, and will have to be verified in further studies.

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