ORIGINAL ARTICLE

Mortality among styrene-exposed workers in the reinforced plastic boatbuilding industry

Avima M Ruder, Alysha R Meyers, Stephen J Bertke

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Industrywide Studies Branch, Division of Surveillance, Hazard Evaluations and Field Studies, The National Institute for Occupational Safety and Health, Cincinnati, Ohio, USA

Correspondence to
Avima M Ruder, Industrywide Studies Branch, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Mailstop R-16, 1090 Tusculum Ave, Cincinnati, OH 45226, USA; amr2@cdc.gov

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ABSTRACT

Background We updated mortality through 2011 for 5203 boat-building workers potentially exposed to styrene, and analysed mortality among 1678 employed a year or more between 1959 and 1978. The a priori hypotheses: excess leukaemia and lymphoma would be found.

Methods Standardised mortality ratios (SMRs) and 95% CIs and standardised rate ratios (SRRs) used Washington State rates and a person-years analysis programme, LTAS.NET. The SRR analysis compared outcomes among tertiles of estimated cumulative potential styrene exposure.

Results Overall, 598 deaths (SMR=0.96, CI 0.89 to 1.04) included excess lung (SMR=1.23, CI 0.95 to 1.56) and ovarian cancer (SMR 3.08, CI 1.00 to 7.19), and chronic obstructive pulmonary disease (COPD) (SMR=1.15, CI 0.81 to 1.58). Among 580 workers with potential high-styrene exposure, COPD mortality increased 2-fold (SMR=2.02, CI 1.08 to 3.46).

Conclusions COPD was more pronounced among those with potential high-styrene exposure. However, no outcome was related to estimated cumulative styrene exposure, and there was no change when latency was taken into account. We found no excess leukaemia or lymphoma mortality. As in most occupational cohort studies, lack of information on lifestyle factors or other employment was a substantial limitation although we excluded from the analyses those (n=3525) who worked <1 year. Unanticipated excess ovarian cancer mortality could be a chance finding. Comparing subcohorts with potential high-styrene and low-styrene exposure, COPD mortality SRR was elevated while lung cancer SRR was not, suggesting that smoking was not the only cause for excess COPD mortality.

What this paper adds

- Styrene, a widely used industrial chemical, is a neurotoxicant and classified by the International Agency for Research on Cancer (IARC) as a possible carcinogen (2B) and by the 12th Report on Carcinogens as reasonably anticipated to be a human carcinogen. IARC classifies styrene oxide, the main metabolite, as a probable carcinogen (2A).
- This paper adds 13 years of follow-up of a cohort of boat builders and assesses the cancer and other chronic disease risks.
- Styrene-exposed workers had excess mortality from lung cancer and chronic obstructive pulmonary disease (COPD). Workers with potential high-styrene exposure had a twofold increase in COPD mortality.

INTRODUCTION

Styrene is an organic solvent used to make synthetic rubber, plastics and resins. As of 2012, more than 5000 US manufacturing plants produced or fabricated styrene products and employed about 90 000 workers.[1] The current Occupational Safety and Health Administration (OSHA) permissible exposure limit is 100 ppm time-weighted average (TWA) over an 8 h workday.[2] The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit is 50 ppm.[3]

The International Agency for Research on Cancer (IARC) classifies styrene in group 2B, possibly carcinogenic to humans, and the major human metabolite, styrene-7, 8-oxide, in group 2A, probably carcinogenic to humans.[4 5] Styrene and styrene oxide have been classified as reasonably anticipated to be human carcinogens by the Report on Carcinogens.[6]

We updated a cohort mortality study of boat builders to further evaluate the carcinogenicity of styrene. Our previous analysis of all 5203 workers found excess oesophageal (standardised mortality ratio (SMR) 2.3, CI 1.2 to 4.0) and prostate (SMR=1.7, CI 1.1 to 2.5) cancer, and accidents (SMR=1.3, CI 1.0 to 1.5), and among workers highly exposed to styrene, urinary tract cancer (SMR=3.4, CI 1.3 to 7.5) and respiratory disease (SMR=2.5, CI 1.3 to 4.4).[7]

Because of the possible association of styrene exposure with bronchiolitis obliterans and because bronchiolitis obliterans is considered difficult to diagnose and confused with other causes of airway obstruction, we decided to also investigate respiratory disease, specifically chronic obstructive pulmonary disease (COPD), in this cohort.

In previous analyses of this cohort both potential latency and statistical power to detect an increase in mortality from lymphatic and haematopoietic neoplasms, the a priori outcomes of interest, were quite limited.[7 8]

The present study updated mortality through 31 December 2011, with an additional 13 years of follow-up. Lymphatic and haematopoietic neoplasms and COPD possibly associated with bronchiolitis obliterans were the a priori outcomes of interest. Neurodegenerative diseases were also of interest because styrene is a neurotoxicant.

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MATERIALS AND METHODS

Population and data collection

Procedures were described in detail previously.[7] Briefly, the NIOSH determined that the highest potential styrene exposure levels were in boat building, where hulls were constructed by laminating fibreglass sheets together with polyester resins.[9] The NIOSH cohort included employees who worked at least 1 day between 1959 and 1978 at two plants in Washington State. Demographics and work histories (but not job titles, which were missing from many records) were abstracted from personnel records in 1978.

Based on personal and area samples collected in 1978,[9] the subcohort with potential high exposure included individuals who ever worked in the fibrous glass (company A, mean styrene TWA 42.5 ppm, range 12–85 ppm) or lamination (company B, mean styrene TWA 71.7 ppm, range 10–183 ppm). The subcohort with potential low exposure included workers who never worked in a high-exposure department (minimal styrene exposure). In addition to styrene and fibreglass (exposure levels not measured), workers were exposed to acetone (company A mean 50.6 ppm, company B mean 54.3 ppm) and (at much lower levels) to glycols, anhydrides, and cobalt hapthenate and methyl ethyl ketone peroxide or benzoyl peroxide in the hardening system. Some workers in other departments were exposed to paints and wood dust, both considered by IARC to be human carcinogens.[10 11]

When personnel and other records were obtained in 1978 there were 555 active workers. Records were not updated after 1978 and both plants ceased production (plant A in 1993, plant B in 1989) by the early 1990s. Therefore, records were incomplete for employees active in 1978 who continued working and unavailable for any employees who began working after 1978.

Data on cohort members were submitted to the National Death Index (NDI) for determination of vital status and causes of death through 2011.[12] Death was coded to the revision of the International Classification of Diseases (ICD) in effect at the time of death. For deaths from COPD we requested death certificates from state departments of vital statistics to see if the text fields mentioned bronchiolitis obliterans, as bronchiolitis obliterans does not have a unique ICD code. Workers lost to follow-up before NDI began in 1979 were classified as 'vital status unknown' and considered alive until the date last observed. Workers lost to follow-up in 1979 or later were considered alive until the study end date, as the sensitivity of NDI is greater than 95% when social security numbers are available.[13]

This study was approved by the NIOSH Human Subjects Review Board (HSRB 08-DSHEFS-02XP).

Analysis

Analyses were conducted using the NIOSH LTAS.NET life table analysis system.[14] Standard Washington State general population rate files created for LTAS.NET considered 119 cause of death categories (beginning in 1960) based on the underlying cause of death.[14a] A second version of the 119 cause rate file considered all causes listed on the death certificate (ie, multiple causes of death). In LTAS.NET, ICD codes were mapped to cause of death categories as described at http://www.cdc.gov/niosh/ltas/rates.html. As styrene is a neurotoxicant,[15] the standard LTAS causes of death were augmented with a rate file of neurodegenerative causes of death.[16] Several ICD respiratory disease codes may possibly include bronchiolitis obliterans (see online supplementary table S3). We created a special rate file to separate these from other respiratory diseases, to see if these particular diagnoses were in excess. The codes included in the special rate file for possible bronchiolitis obliterans are listed in online supplementary table S3.

Race-specific and gender-specific person-years at risk (PYAR) were accumulated for each eligible worker across 5-year age and calendar year intervals beginning with the date of first exposure or the rate file begin date, whichever was later, and ending with the date of death, the date last known alive, or 31 December 2011, whichever was earlier. Mortality rates differ from state to state; the use of state rates controls for regional variations that may have no association with occupational exposures.

Strata-specific PYAR were multiplied by general population gender, race and cause-specific mortality rates to calculate the expected number of deaths for each stratum. The expected numbers were summed across strata to obtain cause-specific and total expected numbers of deaths. The SMR is the ratio of observed to expected deaths.

Latency began at the date of first exposure and ended with the date of death, the date last known alive, or on 31 December 2011, whichever was earlier. The statistical significance of the SMR was determined by a two-tailed test based on the Poisson distribution. The 95% CI was calculated for each SMR estimate.

A multiple cause of death (MCOD) analysis using Washington State rates was done to investigate possible excesses in non-malignant chronic diseases.[17] Separate LTAS runs were completed for male and female workers.

Based on industrial hygiene measurements,[9] daily exposure was estimated for styrene-exposed (department 1 plant A, 42.5 ppm/day; department 1 plant B, 71.7 ppm/day; all other departments, 5 ppm/day) and cumulative estimated potential styrene exposure for workers ever in the styrene departments was grouped in tertiles for comparisons (0 to <3500, 3500 to <1 582 000, ≥82 000 ppm) with roughly equal numbers of deaths in each tertile. Standardised rate ratios (SRRs) were calculated for each potential styrene exposure tertile relative to the lowest tertile and 95% CIs were calculated based on a Taylor series approximation of the variance.[18] A test for linear trend was based on a weighted regression of the standardised rates.[19]

In other internal comparisons, we used a method to adjust for unmeasured confounding proposed by Richardson[21] by calculating SRRs comparing subcohorts with potential high versus potential low styrene exposure for lung cancer, COPD and COPD adjusting for smoking using lung cancer risk as a surrogate. The adjustment assumes that lung cancer is not associated with styrene exposure and that the effect of smoking is the same for COPD and lung cancer.[20] With these assumptions, the adjusted-COPD rate ratio (RR) is calculated as (COPD−RR)/(lung cancer−RR).[21]

RESULTS

Cohort description

The cohort included 5203 employees from two plants. This analysis excluded the 3585 employees (63% of the cohort) who worked less than 1 year. As our previous analysis showed, workers employed <1 year had a different profile, with excess mortality from alcoholism, accidents and homicides.[7]

Table 1 shows the composition of the analysed subcohort by race, gender, updated vital status and other descriptive characteristics. Online supplementary table 2 presents results for all workers. By the end of the observation period (31 December 2011), the cohort had a total of 58 594 PYAR and 598 (36%) were deceased. Among those still alive on 31 December 2011, the average age was 66 years.

Table 1 The National Institute for Occupational Safety and Health (NIOSH) styrene cohort: composition of the analysed study population as of 31 December 2011

Characteristic	Entire analysed population (n=1678)	Potential low styrene exposure (n=1098)*	Potential high-styrene exposure (n=580)
Race/gender/vital status (deaths, % dead)†			
Females, races other than Caucasian	18 (3, 17%)	6 (2, 33%)	12 (1, 8%)
Females, Caucasian	290 (67, 23%)	93 (19, 20%)	197 (48, 24%)
Males, races other than Caucasian	56 (14, 25%)	38 (9, 24%)	18 (5, 28%)
Males, Caucasian	1314 (514, 39%)	961 (415, 43%)	353 (99, 28%)
Total	1678 (598, 36%)	1098 (445, 41%)	580 (153, 26%)
Median age at first employment (IQR)	28.3 (22.8, 38.8)	30.1 (23.8, 42.7)	25.3 (21.2, 33.5)
Median years of employment (IQR)	2.56 (1.49, 5.63)	2.69 (1.49, 6.00)	2.40 (1.49, 5.13)
Mean years of employment (SD(s))	4.34 (4.17)	4.62 (4.55)	3.83 (3.30)
Person-years at risk	58 594	37 586	21 007

*Never worked in a high-styrene department.
†'Alive' includes five persons lost to follow-up before the National Death Index was initiated.

Overall mortality

Observed deaths, corresponding SMRs using Washington State rates, and the SMR CIs are presented in table 2 for those who worked at least 1 year, and those with high and low potential styrene exposure, as well as the SRRs comparing high-exposed and low-exposed subcohorts. Mortality was not increased overall (598 deaths, SMR=0.96, CI 0.89 to 1.04), but was higher in the high-exposure (153 deaths, SMR=1.17, CI 0.99 to 1.37) than in the low-exposure (445 deaths, SMR=0.91, CI 0.83 to 1.00 subcohort. When stratified by sex, overall mortality was not significantly elevated for men or women (male: 528 deaths, SMR=0.95, CI 0.87 to 1.04; female: 70 deaths, SMR 1.07, CI 0.84 to 1.36).

Cancer mortality

An elevation in cancer deaths was observed overall (n=181, SMR 1.07, CI 0.92 to 1.23) and in the high-exposure (n=54, SMR 1.35, CI 1.01 to 1.76) subcohort (table 2).

There was no increase in deaths due to leukaemia or lymphoma, as hypothesised a priori, in the cohort or either exposure subcohort. SMRs for several cancer sites not considered a priori to be cancers of interest were elevated (table 2). Lung cancer mortality was in excess overall (SMR=1.23, CI 0.95 to 1.56) and increased in the subcohort with potential high-styrene exposure (SMR=1.54, CI 0.92 to 2.40; table 2). Both men (53 deaths, SMR=1.10, CI 0.83 to 1.44) and women (14 deaths, SMR=2.15, CI 1.18 to 3.62) had excess lung cancer mortality, with a more than doubled rate among women in the subcohort with potential high-styrene exposure (12 deaths, SMR=2.65, CI 1.37 to 4.63). Ovarian cancer mortality was elevated among women in the high-exposure subcohort (SMR=3.62, CI 0.99 to 9.28).

Almost 90% of the cancer deaths in the cohort occurred at least 15 years after first exposure to styrene. However, the CIs for all-cancer-death SMRs associated with workers with less than 15 years latency and those with 15 or more years of latency overlapped: latency <15 years, n=20, SMR=0.85, CI 0.52 to 1.32; latency ≥15 years, n=161, SMR=1.10, CI 0.94 to 1.60. Similar results were found for lung cancer (latency <15 years, n=9, SMR=1.16, CI 0.53 to 2.20; latency ≥15 years, n=58, SMR=1.24, CI 0.94 to 1.60). Ovarian cancer mortality was in borderline excess overall (5 deaths, SMR=3.08, CI 1.00 to 7.19) and elevated in the subcohort with potential high-styrene exposure (SMR=3.62, CI 0.99 to 9.28).

Respiratory disease

Both men and women had excess COPD (men: 32 deaths, SMR 1.10, CI 0.75 to 1.56; women: 6 deaths, SMR 1.49, CI 0.55 to 3.25). Deaths from respiratory diseases overall and COPD were in excess in the subcohort with potential high-styrene exposure (13 COPD deaths, SMR 2.02, CI 1.08 to 3.46; table 2), although numbers of deaths were sparse.

In the MCOD analysis, mortality from COPD was similar to that in the underlying cause of death analysis. The cohort had 93 COPD-related deaths when all causes of death were considered (MCOD 1.24, CI 1.00 to 1.52); there were 64 COPD-related deaths in the subcohort with potential low styrene exposure (MCOD=1.05, CI 0.81 to 1.34) and 29 deaths in the subcohort with potential high-styrene exposure (MCOD 2.05, CI 1.37 to 2.94)

Mean age at death for those with COPD as the underlying cause of death was 72 (range 49–94). Among those younger than 70 at death the COPD SMR was 1.40 (0.81 to 2.24). To address the concern that our findings for COPD might be due to smoking, we compared lung cancer and COPD SRRs for high versus low potential styrene exposure assuming that lung cancer was not caused by styrene exposure or by being in the styrene cohort, and that the effect of smoking was the same for COPD and lung cancer[21] (table 2). The COPD SRR of 1.76 (0.80 to 3.92) is greater than the lung cancer SRR (0.77 (0.42 to 1.41)), indicating that not all the excess COPD mortality can be attributed to smoking.

Other causes of death

Although styrene is a neurotoxin, we found no statistically significant excess of deaths due to any of the neurodegenerative diseases of interest (results not shown). The styrene cohort had no statistically significant increased SMRs for other non-cancerous diseases.

Internal comparisons

Among workers ever employed in departments with potential high-styrene exposure, there was no positive association between all causes of death and tertiles of estimated cumulative potential styrene exposure. Deaths due to ovarian cancer, pancreatic cancer and cardiomyopathy were concentrated in the highest tertile, and the trends for pancreatic cancer and cardiomyopathy showed significant increases with increasing levels of exposure, but numbers were small (data not shown).

Table 2 Mortality in the NIOSH styrene cohort and exposure subcohorts for selected causes, WA State rates for 1960–2011, and standardised rate ratios for selected causes with >5 deaths or statistically significant excess mortality, comparing high-exposed and low-exposed workers

			Low exposure		High exposure		High vs low
Cause of death	n	WA SMR (95% CI)	n	WA SMR (95% CI)	n	WA SMR (95% CI)	SRR (95% CI)
All causes	598	0.96 (0.89 to 1.04)	445	0.91 (0.83 to 1.00)	153	1.17 (0.99 to 1.37)	1.41 (0.86 to 2.30)
All cancers	181	1.07 (0.92 to 1.23)	127	0.98 (0.82 to 1.16)	54	1.35 (1.01 to 1.76)	1.51 (0.96 to 2.38)
digestive and peritoneum	38	0.94 (0.67 to 1.29)	27	0.87 (0.57 to 1.26)	11	1.21 (0.60 to 2.17)	2.71 (1.07 to 6.86)
pancreas	10	1.08 (0.52 to 1.98)	7	1.00 (0.40 to 2.05)	†	1.33 (0.27 to 3.90)	1.65 (0.41 to 6.64)
trachea, bronchus, lung	67	1.23 (0.95 to 1.56)	48	1.14 (0.84 to 1.51)	19	1.54 (0.92 to 2.40)	0.77 (0.42 to 1.41)
ovary	5	3.08 (1.00 to 7.19)	†	1.93 (0.05 to 10.73)	4	3.62 (0.99 to 9.28)	4.16 (0.46 to 37.35)
prostate	17	1.20 (0.70 to 1.92)	15	1.19 (0.66 to 1.96)	†	1.31 (0.16 to 4.72)	0.49 (0.11 to 2.25)
kidney	6	1.37 (0.50 to 2.97)	†	1.19 (0.32 to 3.04)	†	1.95 (0.24 to 7.06)	1.30 (0.19 to 8.97)
bladder, other urinary site	5	1.06 (0.35 to 2.48)	†	1.02 (0.28 to 2.61)	†	1.28 (0.03 to 7.15)	1.40 (0.16 to 12.54)
other and unspecified sites	10	1.11 (0.53 to 2.04)	7	1.01 (0.41 to 2.08)	†	1.45 (0.30 to 4.25)	2.27 (0.52 to 9.98)
lymphatic, haematopoietic	16	0.90 (0.52 to 1.47)	11	0.80 (0.40 to 1.43)	5	1.26 (0.41 to 2.94)	2.09 (0.55 to 7.88)
Multiple myeloma	6	1.82 (0.67 to 3.96)	5	1.93 (0.63 to 4.50)	†	1.41 (0.04 to 7.86)	2.45 (0.28 to 21.09)
Leukaemia	6	0.90 (0.33 to 1.95)	†	0.57 (0.12 to 1.68)	†	2.07 (0.43 to 6.06)	2.97 (0.54 to 16.20)
Diabetes mellitus	17	1.04 (0.60 to 1.66)	13	1.05 (0.56 to 1.80)	†	0.99 (0.27 to 2.52)	0.90 (0.27 to 3.03)
Mental and psychiatric disorders	11	1.19 (0.59 to 2.13)	9	1.22 (0.56 to 2.31)	†	1.10 (0.13 to 3.97)	0.55 (0.12 to 2.55)
Nervous system disorders	17	0.75 (0.44 to 1.20)	14	0.77 (0.42 to 1.29)	†	0.66 (0.14 to 1.93)	0.49 (0.13 to 1.86)
Heart diseases	148	0.82 (0.69 to 0.97)	113	0.76 (0.62 to 0.91)	35	1.15 (0.80 to 1.60)	1.71 (0.55 to 5.31)
Ischaemic heart disease	122	0.83 (0.69 to 0.99)	94	0.77 (0.62 to 0.94)	28	1.15 (0.77 to 1.67)	1.03 (0.36 to 2.94)
Other circulatory system diseases	57	1.08 (0.82 to 1.39)	46	1.05 (0.77 to 1.41)	11	1.18 (0.59 to 2.11)	0.97 (0.46 to 2.02)
Cerebrovascular disease	38	1.11 (0.78 to 1.52)	30	1.06 (0.71 to 1.51)	8	1.36 (0.59 to 2.68)	1.15 (0.48 to 2.75)
Diseases of arteries, veins, lymphatics	15	0.95 (0.53 to 1.56)	13	1.00 (0.53 to 1.71)	†	0.70 (0.08 to 2.52)	0.70 (0.16 to 3.12)
Respiratory system diseases	56	0.99 (0.75 to 1.28)	39	0.84 (0.60 to 1.15)	17	1.64 (0.96 to 2.63)	1.93 (0.84 to 4.47)
Pneumonia	8	0.64 (0.28 to 1.27)	6	0.56 (0.21 to 1.23)	†	1.12 (0.14 to 4.04)	4.04 (0.51 to 32.19)
COPD	38	1.15 (0.81 to 1.58)	25	0.94 (0.61 to 1.39)	13	2.02 (1.08 to 3.46)	1.76 (0.80 to 3.92)
Other respiratory diseases	9	0.99 (0.45 to 1.88)	7	0.95 (0.38 to 1.95)	†	1.16 (0.14 to 4.20)	0.68 (0.14 to 3.31)
Digestive system diseases	24	0.95 (0.61 to 1.42)	22	1.14 (0.72 to 1.73)	†	0.33 (0.04 to 1.20)	0.17 (0.04 to 0.76)
Cirrhosis and other liver diseases.	15	1.21 (0.68 to 2.00)	14	1.55 (0.85 to 2.60)	†	0.30 (0.01 to 1.66)	0.16 (0.02 to 1.24)
Genitourinary system diseases	7	0.98 (0.40 to 2.02)	†	0.69 (0.19 to 1.77)	†	2.27 (0.47 to 6.62)	3.12 (0.63 to 15.47)
Transportation injuries	17	1.05 (0.61 to 1.68)	12	1.09 (0.56 to 1.90)	5	0.97 (0.31 to 2.25)	0.64 (0.22 to 1.89)
Falls	6	1.02 (0.37 to 2.22)	5	1.06 (0.34 to 2.47)	†	0.87 (0.02 to 4.87)	0.19 (0.02 to 1.67)
Other injury	16	1.17 (0.67 to 1.90)	9	0.95 (0.44 to 1.81)	7	1.65 (0.66 to 3.40)	3.09 (1.02 to 9.33)
Violence	14	0.96 (0.52 to 1.61)	13	1.26 (0.67 to 2.16)	†	0.23 (0.01 to 1.31)	0.13 (0.02 to 1.03)
Other and unspecified causes	16	1.10 (0.63 to 1.78)	12	1.13 (0.58 to 1.98)	†	1.01 (0.28 to 2.59)	0.56 (0.17 to 1.86)

*Never worked in a department with potential high-styrene exposure.
†Sparse numbers of deaths not reported to protect worker confidentiality.
COPD, chronic obstructive pulmonary disease; NIOSH, National Institute for Occupational Safety and Health; SMR, standardised mortality ratio; SRR, standardised rate ratio; WA, Washington.

DISCUSSION

Recent reviews of studies of styrene-exposed worker cohorts, conducted in Europe and the USA, have not shown statistically significant excess mortality overall.[4 22] In other studies, statistically significant excess overall mortality generally has been found only among styrene-exposed workers employed less than 1 year;[23–25] the mortality excess in those studies did not appear to be related to styrene exposure. Our study, however, found excess overall and cancer mortality, especially among workers who were employed in departments with potential high-styrene exposure (table 2), independent of duration of employment.

As in our previous analyses,[7 8] this update found no evidence for an excess risk of lymphatic and haematopoietic mortality associated with exposure to styrene in the boat building facilities studied. Previous reviews and studies of lymphatic and haematopoietic neoplasm in styrene-exposed workers[4 22] have varied widely, including a statistically significant deficit of cancer deaths,[26] a lack of association with styrene,[27] and a moderate association of increased lymphoma and leukaemia mortality with longer latency and higher average level of exposure.[28] Incidence studies are preferred over mortality studies for cancers with relatively high survival rates, such as lymphohaematopoietic cancers.[29 30] Our investigation of cancer incidence in this cohort is currently under way, and may prove more informative.

Our previous update found significant elevated mortality (6 deaths, SMR 3.44, CI 1.26 to 7.50) from cancer of the urinary tract (kidney and bladder) among workers in the subcohort with potential high-styrene exposure.[7] No additional urinary tract deaths have occurred, and these causes of death are no longer in excess. Our previous analysis found a slight elevation in multiple sclerosis mortality;[7] 10 additional years of follow-up added only one multiple sclerosis death and the SMR decreased. Prostate cancer mortality remained elevated but was not related to potential cumulative styrene exposure.

Lung cancer mortality was significantly elevated in the cohort and higher in the subcohort with potential high-styrene exposure. COPD mortality was also elevated and at a twofold increase

in the subcohort with potential high-styrene exposure. Neither lung cancer nor COPD mortality was associated with estimated cumulative styrene exposure, possibly because, lacking specific job titles, we could not accurately estimate workers' relative potential exposure levels. Almost 80% of the COPD deaths were in subcategories that possibly include bronchiolitis obliterans, with similar SMRs for those subcategories than those for COPD. However, no deaths occurred from other (non-COPD) respiratory diseases that may possibly include bronchiolitis obliterans. Comparing the lung cancer and COPD SRRs in the subcohorts with potential high-styrene and low-styrene exposure using the Richardson method,[21] we observed a higher ratio for COPD adjusted for smoking than for lung cancer, indicating that the elevated COPD is unlikely to be due solely to smoking.

By contrast to our results, a large (N=40 688) IARC study of European styrene workers found a slight increase in lung cancer mortality for laminators, who would have had the highest exposures[28] and no increase in non-malignant respiratory disease mortality.[31] The recently updated British styrene cohort also had an excess of lung cancer deaths, especially among workers with high-styrene exposure, and, like us, no leukaemia or lymphoma excess.[27] However, a recent update of a large (N=15 826) US study of workers in the reinforced plastics industry originally studied by Wong and colleagues[32 33] found an increase in lung cancer mortality, but with an inverse trend with exposure,[26] and a previous update had found an increase in mortality from 'other respiratory diseases', but only in short-term (<1 year) or low-exposure workers.[33] The difference in findings between our cohorts and others could be due to differences in styrene levels or lifestyle or other differences between the cohorts. Estimated potential styrene exposure to laminators in the IARC study varied by country, and were as high as 200 ppm in the 1960s and 1970s in Denmark, but dropped to about 80 ppm by 1980.[24 28] Lower average potential styrene exposures of 25 ppm in 1977 and 35 ppm in 1967 were reported for the Wong-Collins cohort.[26]

In our cohort, styrene and other exposures varied widely within the high-exposure departments. At plant A, the 8 h TWA range, as measured in 1978 varied from 7.3 to 84.7 ppm. At plant B, the 8 h TWA range varied from 14.5 to 183 ppm.[9] As many of our work history records did not indicate specific job title, we were unable to determine which styrene-exposed workers within highly exposed departments had the highest potential exposure levels. Because of this, all workers in the styrene departments were assigned the same daily potential exposure score (company A, mean styrene TWA 42.5 ppm) or lamination (company B, mean styrene TWA 71.7 ppm), although exposure levels were known to vary within those departments;[9] and we have no information on styrene levels after 1978 in either plant.

Our finding in the high-styrene-exposed subcohort of increased ovarian cancer might be related to asbestos exposure at other jobs (asbestos was widely used in naval shipyards in the state of Washington through the 1970s.[34])

As in most occupational cohort studies, we have no information on lifestyle factors or other employment. The lack of information on previous or subsequent employment is a significant limitation, even though we excluded from this analysis the 3585 cohort members who worked less than 1 year, because median years employed is still less than 3 (table 1). Our cumulative potential styrene exposure estimates are not job-specific because job titles were missing for many workers and are underestimated because they do not include any exposure after 1978 (when measurements were conducted and records obtained). We have no exposure data on levels of fibreglass (which could have differed for different jobs within the styrene departments), solvents, wood dust or wood finishing agents, all known to have been present in the plants. The lack of work history information after 1978 means that our exposure estimates for potential cumulative styrene exposure and duration of exposure are underestimates for workers employed after 1978, and would bias results towards the null.

In conclusion, we found no evidence for excess mortality from leukaemia and lymphoma, our a priori hypotheses. There was excess mortality from lung cancer and COPD. It should be noted that COPD mortality was also in excess for short-term workers (see online supplementary table S1), as has been found for other styrene-exposed cohorts.[35] Among workers employed in departments with potential high-styrene exposure, there was excess ovarian cancer, but these results were based on small numbers of deaths. Unanticipated excess ovarian cancer mortality is difficult to interpret and could be chance findings or due to employment elsewhere.[34] There were no strong associations between cumulative potential styrene exposure and a priori or elevated causes of death and none of the excess mortality was for causes of death considered likely a priori. The COPD excess points to a need for an in-depth investigation of respiratory disease and occupational styrene exposure, particularly in light of recent reports associating styrene reinforced plastic manufacturing with the lung disease bronchiolitis obliterans.[36 37] Our study of cancer incidence in this cohort may clarify some of the cancer mortality results.

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Contributors AMR directed the implementation of the study and wrote the draft paper. SJB conducted the statistical analyses. SJB and AM edited the manuscript and contributed to the conception and design of the study, the acquisition of data, or the analysis of the data in a manner substantial enough to take public responsibility for it. AMR attest to the fact that all authors have reviewed the final version of the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission.

Declaration The findings and conclusions in this reports are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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Avima M Ruder, Alysha R Meyers and Stephen J Bertke

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