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RESEARCH ARTICLE

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# Cancer mortality update with an exposure response analysis among styrene-exposed workers in the reinforced plastics boatbuilding industry

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None.

**Background:** There is sparse and inconsistent evidence of an association between styrene exposure and cancer.

**Methods:** This study examines mortality patterns in a previously studied cohort of 5201 workers employed in two Washington boat-building facilities, extending follow-up 5 years. Standardized mortality ratios (SMR) were calculated using state rates as referent. Cox regression calculated rate ratios (RR) per year employed in styrene-exposed exposed jobs.

**Results:** No excess deaths from lymphohematopoietic cancers (LHCs) were observed (SMR: 0.99, 95%CI: 0.74-1.30) when compared to the referent population; however, the relative risk increased with duration of employment in internal analyses. Conversely, lung cancer mortality was significantly elevated (SMR: 1.24, 95%CI: 1.08-1.41), but there was no evidence of a dose-response relationship.

**Conclusion:** We found evidence that occupational exposure to styrene was associated with increased LHC risk, while no such association was observed for lung cancer.

**KEYWORDS**
Cox regression, exposure response, leukemia, reinforced plastics, styrene

## 1 | INTRODUCTION

The National Toxicology Program (NTP) has concluded that styrene is reasonably anticipated to be a human carcinogen based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, and supporting data on mechanisms of carcinogenesis.[1] Likewise, the International Agency for Research on Cancer (IARC) classifies styrene as Group 2B, *possibly carcinogenic to humans*, based on limited evidence found in both humans and experimental animals.[2] Styrene primarily metabolizes to the DNA-reactive styrene-7,8-oxide, which was previously classified as *probably carcinogenic to humans* (Group 2A) by IARC[2] and *reasonably anticipated to be carcinogenic* by NTP,[1] given evidence judged sufficient in experimental animals but inadequate in humans. Because of sparse human data, an IARC advisory committee gave a high priority for styrene re-evaluation pending updates to relevant epidemiologic studies.[3]

Previous reviews[1,4] suggest that the available epidemiologic information is supportive but insufficient to declare styrene unequivocally as a human carcinogen. This is because of inconsistent results among epidemiologic studies and a paucity of exposure-response information. Among positive studies, modestly increasing exposure-related lymphohematopoietic cancers (LHCs), including leukemias and non-Hodgkin lymphoma (NHL), were reported most often.[5–9] In addition, increased lung cancer risk has also been observed in many

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styrene-exposed cohorts[8,10–12] and has also been found in a laboratory study of mice exposed to styrene.[13] Less frequent findings include elevated risk of cancers of the bladder,[11] larynx,[8] kidney,[8,11] esophageal,[14] and nasal cavities.[8]

The current study extends follow-up of previously studied workers who were employed for at least 1 day in glass fiber-reinforced plastic and composites (RPC) boat manufacturing between 1959 and 1978. Studies of RPC workers are potentially most informative because their styrene exposures are generally greater than in other industries and there are fewer potentially confounding concomitant chemical exposures.[4] For example, personal and area samples were collected in 1978[15] on workers in the two companies from this cohort and reported a mean styrene TWA of 42.5 ppm (range 12-85 ppm) in company A and a mean styrene TWA of 71.7 ppm (range 10-183 ppm) in company B. In comparison, Macaluso, Larson, Lynch, Lipton, Delzell[16] reported for workers in the styrene-butadiene rubber industry average daily exposure of 1.2-1.4 ppm at two facilities.

The most recent mortality study of this cohort reported excess lung cancer (standardized mortality ratio, SMR = 1.26; 95%CI: 0.95, 1.56) and ovarian cancer (SMR = 3.08; 95%CI: 1.00, 7.19) in the cohort compared to the US population. The leukemia SMR was not increased (SMR = 0.90 95%CI: 0.52, 1.95); however, there was some evidence of a dose-response association when comparing persons with the potential for "high-exposure" to those with "low-exposure" (standardized rate ratio, SRR = 2.97; 95%CI: 0.54, 16.20).[17] These results were tempered by observing only six leukemia deaths and the use of a crude proxy for exposure. The current study added 5 years of follow-up to the previous study. The focus of this paper is on LHCs as well as lung cancer, but results of other outcomes are also presented in an online supplement.

## 2 | METHODS

### 2.1 | Study population

Institutional review for the protection of human subjects was conducted in accordance with current federal regulations.

Procedures for cohort enumeration were previously described.[15,17,18] Briefly, the cohort included all salaried and non-salaried employees who worked at least 1 day between January 1, 1959 and September 31, 1978 at one of two RPC boat manufacturers located in Washington State (WA). Two "workers" were removed, one missing a birth date and another found to be a duplicate entry. At the time of records collection in 1978, 772 workers were currently employed. The two facilities ceased production in 1989 and 1993, respectively, and as a result, no records were available to update work histories after 1978. There were 67 workers hired before 1959 included in this study, and their work history information, going back to 1957, is included.

Vital status through 2011 was as described previously,[17] for additional follow-up through 2016 we matched records to data from the National Death Index (NDI). NDI Plus provided underlying and contributing causes of death for deceased workers. All deaths were coded according to the revision of the International Classification of Diseases (ICD) in effect at the time of death. Workers lost to follow-up before NDI began in 1979 ($n$ = 28) or known to have emigrated out of the United States ($n$ = 19) were classified as "vital status unknown" and considered alive until the date last observed. Workers known to be alive in 1979, with a valid Social Security number, and not known to have emigrated were considered alive until the study end date, as the sensitivity of NDI is greater than 95% when Social Security numbers are available.

### 2.2 | Exposure assessment

The exposure assessment has been previously presented.[15,19] Work history information was used to construct an exposure index based on employment duration and exposure potential. Exposure potential was assessed based on industrial hygiene surveys conducted at each plant to characterize airborne styrene concentrations. Combining this information with job titles, department codes, and work period, Okun et al[15] classified individual employment histories according to time spent in five categories of work based on exposure potential: (i) Fiberglass or plasticians, comprising mostly skilled labor directly working with styrene; (ii) Minimally exposed workers, which included a mix of skilled and unskilled labor, and supervisory personnel having a much lower potential for exposure (eg, upholsterer, general laborer, foreman); (iii) Plant wide workers, which included security, maintenance, and janitorial workers who may have been intermittently exposed; (iv) Assembly workers, comprising a skilled labor force that was essentially unexposed; and (v) Administrative staff, which consisted of unexposed office workers (eg, managers, secretaries, and administrative assistants).

### 2.3 | Analysis

Standardized mortality ratio (SMR) analyses, comparing the mortality experience of the cohort to that of the WA population, were conducted using the NIOSH Life Table Analysis System for Windows, LTAS.net.[19] Person-time at risk began at the latest of the following dates: (i) 1 day after the first date of employment between 1959 and 1978 and (ii) the date the referent rate file began (January 1, 1960). Person-time ended at the earliest of the following dates: (i) the worker's date of death for the deceased members of the cohort; (ii) the date last observed for those lost to follow-up; and (iii) December 31, 2016. Person-time at risk was stratified by age and calendar period (in 5-year intervals) and multiplied by the corresponding gender, race, age, and calendar period specific rate in the reference population to generate expected numbers of deaths. The SMR was defined as the ratio of the observed to the expected number of deaths and was indirectly standardized based on age and calendar period. Reference rates were based on death rates of the WA population (1960-2014) for 119 cause-of-death categories (NIOSH 2016). The references rates for 2010-2014 were used to calculate expected numbers of deaths during 2015-2016.

In addition to SMRs, Cox regression was performed to calculate rate ratios (RR) internally comparing the mortality experience of the cohort by exposure. For internal analyses, persons employed in the administrative group (Group 5) were removed because potentially confounding lifestyle and socioeconomic factors likely differed greatly from other cohort members.

The risk-sets for Cox regression consisted of those persons at risk as of the attained age of the case. In addition, risk-sets also matched on race, gender, birth date (within 2.5 years), and employment duration (<1 year and > = 1 year of employment) of the case. Risk-sets were matched on employment duration because previous analyses[16,17] found an excess of deaths from outcomes indicative of a different lifestyle profile (such as alcoholism, homicides, and accidents) among those employed less than a year.

Two exposure metrics were considered in internal analyses: ever/never worked in highly exposed jobs (Group 1) and employment duration in Group 1 jobs. The duration analyses also included workers in employment Groups 2-4. In an attempt to avoid exposure misclassification of the active workers in 1978, person-time for active workers was truncated at October 1, 1988 (10 years after record collection) in the duration metric analyses only since a 10 year lagged duration of employment after this date would be uncertain. In addition, the distribution of employment duration in a high-exposed employment group was very skewed and therefore, to reduce the influence of outlying data, duration was also modeled with a two-piece linear spline with a knot at 10 years (approximately the 99th percentile).[20] Duration was lagged 10 years and all results are presented with 95% confidence intervals. All analyses were repeated following restriction to person-time with at least 1 year of employment.

## 3 | RESULTS

This study added 5-years, 16 297 person-years of follow-up and 418 deaths to the previous analysis. Table 1 shows basic statistics for the cohort. Nearly two-thirds of workers were employed for less than a year. Those who were employed for less than a year were slightly more likely to be among those employed in the high-exposed employment group (42% vs 35%).

Table 2 presents overall SMRs for all causes of death and all cancers by longest held employment category. The 293 administrative workers were generally much healthier than the rest of the cohort, suggesting a strong healthy worker selection compared to other exposure groups.

Table 3 presents results for mortality risk of lung cancer and LHCs for the entire cohort, and results of analyses restricted to persons with at least a year of employment can be found in Supplemental Table S1. Full mortality results, as compared to WA rates, can be found in Supplemental Table S2. As of December 31, 2016, 2111 (40.6%) members of the cohort were known to be deceased. Overall mortality was significantly higher than expected for the full cohort (SMR: 1.19 [1.14, 1.24]) when compared to the WA state. However, this increase in overall expected mortality appears to be concentrated among those with less than a year of employment. When restricted to those employed 1 or more years, overall mortality was as expected (SMR: 0.99 [0.92, 1.06]). In fact, as seen previously, among those employed less than a year, there were excess deaths from diseases associated with generally adverse lifestyle factors such as diabetes mellitus (45 deaths, SMR: 1.42 [1.03, 1.89]), alcoholism (15 deaths, SMR: 2.13 [1.19, 3.52]), and accidents (124 deaths, SMR: 1.43 [1.19, 1.70]).

Overall cancer was also not elevated for person-time with > = 1 year of employment (SMR: 1.07 [0.93, 1.23]). However, among this subgroup, there was a slight excess of lung cancer (SMR: 1.20 [0.95, 1.51]). On the other hand, there were fewer deaths than expected from all LHCs (SMR: 0.85 [0.51, 1.35]) and in particular leukemia (SMR: 0.88 [0.35, 1.81]).

Cox regression analyses, which controlled for employment duration either by matching (Table 3) or restriction to person-time with employment > = 1 year (Supplemental Table I), gave similar findings. For lung cancer, risk was not elevated among person-time ever having worked in a high-exposed employment group and actually decreased with increasing duration in a high-exposed employment group. In contrast, for LHCs and leukemia, risk was elevated for person-time ever having worked in a high-exposed employment group (RR: 1.2 [0.6, 2.2] and 1.6 [0.5, 4.5], respectively] and this risk increased with increasing duration in a high-exposed employment group (RR per year: 1.4 [1.1, 1.7] and 1.6 [1.2, 2.2], respectively), suggestive of an exposure-response.

Table 4 summarizes the number of LHCs and leukemia cases by duration employed in a high-exposed employment group. While fewer than expected LHCs and leukemia cases were observed for the entire cohort, risk does appear to increase with duration.

**TABLE 1** Descriptive statistics of the cohort

| | Full cohort | Employed <1 yr | Employed > = 1 yr |
|---|---|---|---|
| *N* | 5201 | 3523 | 1678 |
| Number of deaths (%) | 2111 (41%) | 1383 (39%) | 728 (43%) |
| Median age at first employment (IQR) | 24 (20, 32) | 23 (20, 30) | 27 (21, 37) |
| Median years employed (IQR) | 0.4 (0.1, 1.5) | 0.2 (0.1, 0.4) | 2.6 (1.5, 5.6) |
| Number worked in high-exposed dept | 2063 | 1483 | 580 |
| Median years employed in high-exposed dept (IQR)[a] | 0.3 (0.1, 1) | 0.2 (0.1, 0.4) | 2.1 (1.3, 4.4) |
| Median year of birth (IQR) | 1946 (1936, 1950) | 1946 (1940, 1950) | 1943 (1930, 1950) |
| Person-years at risk | 203 404 | 137 650 | 65 754 |

[a]Among those employed in high exposed department.

**TABLE 2** Standardized mortality ratios (SMRs) for all causes of death and all cancers by longest held employment category. Analyses were replicated restricting to person time with more than a year of employment

| | Full cohort | | | | | Person-time with >1 yr employment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | All deaths | | All cancers | | | All deaths | | All cancers | |
| Employment category | *N* | Obs[a] | SMR (95%CI) | Obs[a] | SMR (95%CI) | *N* | Obs[a] | SMR (95%CI) | Obs[a] | SMR (95%CI) |
| 1) Fiberglass or plasticians | 1960 | 667 | 1.21 (1.12, 1.31) | 197 | 1.27 (1.10, 1.46) | 514 | 180 | 1.07 (0.92, 1.24) | 59 | 1.22 (0.93, 1.58) |
| 2) Minimally exposed | 2003 | 889 | 1.03 (0.96, 1.10) | 250 | 1.09 (0.96, 1.23) | 651 | 318 | 0.89 (0.79, 0.99) | 92 | 0.99 (0.80, 1.22) |
| 3) Plant wide | 717 | 325 | 1.04 (0.93, 1.15) | 92 | 1.10 (0.88, 1.34) | 284 | 126 | 0.85 (0.70, 1.01) | 33 | 0.84 (0.58, 1.19) |
| 4) Assembly | 229 | 134 | 1.33 (1.11,1.57) | 45 | 1.75 (1.27, 2.34) | 78 | 47 | 1.08 (0.79, 1.44) | 15 | 1.41 (0.79, 2.3) |
| 5) Administrative | 293 | 96 | 0.73 (0.59, 0.89) | 28 | 0.77 (0.51,1.12) | 151 | 57 | 0.70 (0.53, 0.90) | 18 | 0.83 (0.49, 1.30) |

[a]Number of observed deaths.

## 4 | DISCUSSION

The results of this study suggest a dose-response between styrene exposure and LHCs, and in particular, leukemia. While SMRs indicated there were fewer than expected leukemia deaths, the internal analyses suggested that the leukemia cases were more likely to occur among the high styrene exposed employment group, and leukemia risk increased with increasing duration. The relationship between duration in a styrene-exposed employment group and leukemia mortality was strongest when modeled as a two-piece spline. In this study, the distribution of duration was highly skewed with a maximum duration of 21 years but only 22 persons had worked more than 10 years in Group 1. The range of 10-21 years of employment in Group 1 contains only 0.4% of the total person-time but makes up over half of the dose range. As a result, since there is likely to be no cases for rare outcomes in this range, overall exposure-responses from traditional linear models will likely be attenuated. By placing a knot at 10 years, the influence of the sparse data among person-time in the top half of the dose distribution is reduced.

The previous mortality analysis,[16] which was restricted to workers with more than 1 year of employment, also suggested an elevation of leukemia cases among workers with high styrene exposure, which internally compared those in Group 1 to all others, reporting an SRR, of 2.97 (95%CI: 0.54, 16.20). This is similar to the equivalent RR of 3.6 (95%CI: 0.5, 23.5) reported in Supplemental Table S1, which added 5 years of follow-up but removed administrative workers (Group 5). While these estimates are elevated, they are very imprecise likely due to the lack of power in analyzing only seven cases. However, estimates of the exposure-response between leukemia risk and duration of employment in a styrene-exposed employment group was more exact indicating that risk increased by 60% (RR: 1.6; 95%CI: 1.1, 2.2) per year worked in a high styrene-exposed employment group (Group 1).

Other studies of workers in RPC have shown mixed results with regard to styrene exposure and leukemia risk. Twoseparate, recent studies considering RPC workers in the United States[11] and Britain[10] did not find an association between styrene exposure and leukemia mortality in external comparisons nor in internal comparisons by styrene exposure.

**TABLE 3** Mortality of cohort in comparison with general Washington state population, and risk estimates from internal Cox regression analyses

| | External comparison | | Internal comparison-Cox regression[a] | | | |
|---|---|---|---|---|---|---|
| | | | | Ever never | Log-linear[b] | 2 Piece spline[b,d] |
| Outcome | Obs[e] | SMR (95%CI) | Obs[e] | RR (95%CI) | RR[c] (95%CI) | RRc (95%CI) |
| All cancers | 611 | 1.23 (1.13, 1.33) | 584 | 1.2 (1.0, 1.4) | 1.0 (1.0, 1.1) | 1.1 (1.0, 1.2) |
| MN trachea, bronchus, lung | 211 | 1.37 (1.19, 1.57) | 204 | 1.0 (0.8, 1.4) | 0.9 (0.7, 1.1) | 0.9 (0.8, 1.1) |
| MN lymphatic & hematopoietic | 52 | 0.99 (0.74, 1.30) | 49 | 1.2 (0.6, 2.2) | 1.2 (1.0, 1.4) | 1.4 (1.1, 1.7) |
| Non-Hodgkin's lymphoma | 19 | 0.91 (0.55, 1.42) | 18 | 0.3 (0.1, 1.2) | 0.9 (0.2, 1.4) | 0.9 (0.2, 1.6) |
| Multiple myeloma | 13 | 1.33 (0.71, 2.27) | 11 | 2 (0.5, 7.0) | 1.1 (0.6, 1.5) | 1.3 (0.6, 1.9) |
| Leukemia | 18 | 0.91 (0.54, 1.45) | 18 | 1.6 (0.5, 4.5) | 1.3 (1.0, 1.5) | 1.6 (1.2, 2.2) |

Cox regression internally compared the mortality experience by duration employed in a high exposed employment category (employment category 1) as: (a) Ever versus never employed in employment category 1; (b) duration employed in employment category 1 as a continuous variable; and (c) duration employed in employment category 1 as a two-piece spline with a knot place at 10 years.

[a]Duration of employment in a high exposed employment category was lagged 10 years. The Cox regression analyses removed persons employed in employment group 5 (Administrative). Regressions matched on attained age, gender, race, birth date (±2.5 years), and employment duration (< = 1 or >1 yr).

[b]For analyses where duration was treated as a continuous variable, those currently employed during record collection had their person-time censored at January 10, 1988, 10 years after records collection.

[c]Results are presented as rate ratio (RR) per 1 year employment in a high exposed employment category.

[d]Two piece linear spline with a knot placed at 10 years. The results represent the slope of the first piece of the spline.

[e]Obs, observed number of deaths.

**TABLE 4** Standardized mortality ratios (SMRs) for outcomes of a priori concern by duration in a high exposed employment group, Washington State rates as referent

| | | Lung | | LHC | | Leukemia | |
|---|---|---|---|---|---|---|---|
| Duration in high exposed employment Group 1 | PYAR[a] | Obs[b] | SMR (95%CI) | Obs[b] | SMR (95%CI) | Obs[b] | SMR (95%CI) |
| Never high | 140 440 | 143 | 1.30 (1.10, 4.53) | 36 | 0.95 (0.66, 1.31) | 11 | 0.77 (0.38, 1.37) |
| >0-<2 yrs | 59 010 | 58 | 1.67 (1.27, 2.16) | 11 | 0.93 (0.46, 1.67) | 4 | 0.93 (0.25, 2.38) |
| 2+ yrs | 8954 | 10 | 1.13 (0.54, 2.07) | 5 | 1.81 (0.59, 4.22) | 3 | 2.95 (0.61, 8.63) |

[a]PYAR, person years at risk.
[b]Obs, observed number of deaths.

However, analysis of a cohort of Danish RPC workers[8] did find higher standardized incidence ratio (SIR) values for myeloid leukemia with longer duration of employment and higher styrene exposure probability. In addition, the Danish cohort found excess Hodgkin lymphoma incidence with longer duration of employment.

The results of this study do not support a causal link between styrene exposure and lung cancer. While there were more than expected deaths from lung cancer in this cohort compared to the WA population, this did not appear to be related to styrene exposure since internal comparisons by exposure did not show a positive exposure-response trend. In fact, lung cancer risk was negatively related to duration of employment in Group 1. This is consistent with other studies of workers in the RPC industry. The analyses of the above Danish[8] and US[11] RPC cohorts both reported elevations of lung cancer risk compared to referent populations, however, risk appeared to decrease with increasing duration of employment and estimated cumulative exposure, respectively. On the other hand, analysis of the British cohort of companies making glass-reinforced plastics suggest that the highest risk of lung cancer deaths were among workers with more than a year of employment at a high styrene exposure level.[10] However, this result was based on external SMR analyses and was not verified by an internal comparison.

Previous analysis of this cohort had suggested an association between styrene exposure and ovarian cancer. Results from this site as well as other outcomes can be found in the supplemental tables. With nine cases of ovarian cancer, there were more cases than expected in this cohort and six deaths occurred in women employed in the styrene-exposed employment Group 1. However, a majority (63%) of the 679 women in the full cohort were employed in employment Group 1. As a result, a lack of variability in exposure and few cases limited the power to examine the exposure-response for this outcome.

Study limitations include small sample size and imperfect exposure information. Because duration in styrene-related jobs was used as a proxy for exposure, exposure misclassification is unavoidable given that the metric does not account for within-group differences in exposure intensity and only crudely classifies workers by exposure potential. However, there is little evidence that measurement error is differential with respect to the outcome; therefore, the potential bias is likely to be toward a null association.

In addition, the distribution of exposure was narrow among those exposed. For example, there were 2063 workers considered occupationally exposed to styrene, and the median duration of employment is only 4 months. Only 580 of these high-exposed workers were employed more than a year at either facility.

Another study limitation is the use of mortality as opposed cancer incidence, especially given the high survival rates of LHCs. Ruder and Bertke (2017)[21] conducted a cancer incidence analysis of this cohort with follow-up through 2007. However, the study was underpowered due to WA state's cancer registry not beginning until 1991.

Finally, there is a lack of information on smoking as a potential confounder. However, in the online supplement, analyses of smoking-related solid cancers showed a slight positive trend with employment duration in employment Group 1. This suggest that the negative results of lung cancer is not likely due to confounding by smoking. However, this is speculative and results should be interpreted cautiously.

## 5 | CONCLUSION

The analyses presented here support an association between occupational styrene exposure and LHC, in particular leukemia, mortality. However, the literature investigating this relationship gives inconsistent results and, therefore, results from this single population, which has limited power for LHC, should be considered cautiously. On the other hand, this study does not support an association between styrene exposure and lung cancer, an outcome in which power was less of an issue.

### AUTHORS' CONTRIBUTIONS

All authors meet the authorship criteria: (i) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (ii) drafting the work or revising it critically for important intellectual content; (iii) final approval of the version to be published; and (iv) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

## DISCLOSURE (AUTHORS)

The authors declare no conflicts of interest.

## DISCLOSURE BY AJIM EDITOR OF RECORD

Steven B. Markowitz declares that he has no conflict of interest in the review and publication decision regarding this article.

## DISCLAIMER

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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