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Lung Cancer Mortality and Styrene Exposure in the Reinforced Plastics Boatbuilding Industry: Evaluation of Healthy Worker Survivor Bias

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Abstract

The evidence of styrene as a human lung carcinogen has been inconclusive. Occupational cohorts within the reinforced plastics industry are an ideal population to study this association due to relatively high levels of exposure to styrene and lack of concomitant exposures to other known carcinogens. However, healthy worker survivor bias (HWSB), where healthier workers stay employed longer and thus have higher exposure potential, is a likely source of confounding bias for exposure-response associations, in part due to styrene's acute effects. We studied a cohort of 5163 boatbuilders exposed to styrene in Washington state employed between 1959 and 1978; prior regression analyses demonstrated little evidence for an exposure-response between styrene exposure and lung cancer mortality. Based on estimates of necessary components of HWSB, we found evidence for a potentially large HWSB. Using g-estimation of a structural nested model to account for HWSB we estimated that one year of exposure >30 ppm accelerates time to lung cancer death by 2.3 years (95% Confidence intervals=1.53, 2.94). Our results suggest possibly strong HWSB in our small cohort and indicate that large, influential studies of styrene exposed workers may suffer similar biases, warranting a re-assessment of the evidence of long-term health effects of styrene exposure.

Keywords

Styrene; Lung Cancer; Healthy worker survivor bias; g-estimation

Styrene is a high production monomer used in the manufacture of polystyrene plastics and resins. The primary route of occupational exposure is via inhalation; however, styrene is also readily absorbed through skin. Health effects from styrene have been studied extensively. The International Agency for Research on Cancer classified styrene as *probably carcinogenic to humans* (Group 2A) based on limited evidence in humans and sufficient evidence in experimental animals (1). In making this determination, the International Agency for Research on Cancer also considered strong mechanistic data on styrene-7/8-

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oxide (a major metabolite) indicating genotoxicity and human relevance. Human data stem mostly from modest but inconsistent associations between styrene exposure and cancers of the lymphohematopoietic, respiratory, and digestive systems in reinforced plastics industry workers (2–7).

Evidence of increased lung cancer risk proceeds from multiple studies reporting similar estimates of excess mortality and incidence in reinforced plastics workers compared to external referent populations, but generally lacking indication of an exposure-response (4–7). Absent of this evidence, the excess lung cancer risk might be due to causes other than styrene, such as smoking. However, it is also possible that the exposure-response is masked by biases from sources unaccounted for in previous analyses (8). For example, styrene is a skin and respiratory irritant, which may affect continued employment (and future exposure) resulting in a potential bias in exposure-response analyses from confounding by health status because workers with stronger propensity for disease outcomes may work shorter tenures and thus have lower cumulative exposures (9, 10). In addition, the consistent evidence across multiple occupations suggests that workers who stay employed are less prone to a myriad of health outcomes (i.e., are healthier than those with shorter work tenures or those who are unemployed). This survivor effect can bias estimates of the exposure-response towards and possibly across the null, which has been referred to as a healthy worker survivor bias (HWSB) (11).

HWSB cannot be adequately accounted for in standard regression or standardization approaches in the presence of a strong association between high exposure and leaving work (12). The choice of analytic approach depends on two factors: the choice of study question (e.g. estimating a regression function versus contrasts of exposure levels) and the strength of the “component” associations underlying HWSB. Naimi, et al. (13) demonstrated an approach to quantify three components of HWSB that determined a) whether there was likely to be bias that could be controlled through employment status and b) whether standard regression methods could adequately control such confounding. These associations were between prior exposure and employment status, current status and subsequent exposure, and employment status and the outcome of interest (13). When all three associations are present, two methods have been commonly used to control bias: g-estimation of structural nested models (14–17) and g-computation (18, 19). The current study examines these component associations in a large cohort of boatbuilders employed in Washington, where previous analyses indicated significant excess lung cancer mortality in workers compared to the state population [standardized mortality ratio (SMR) =1.37, 95%CI: 1.19 to 1.57] (7), but conversely provided weak, non-statistically significant evidence of an *inverse* exposure-response association [(hazard ratio (HR) at 50 ppm-years vs. 0 ppm-years=0.87, 95% CI: 0.69 to 1.05)] (20). In addition to examining the component associations, we then demonstrate g-estimation of a structural nested model for controlling for a HWSB in exposure-response models.

METHODS

Cohort Description

Cohort enumeration, vital status ascertainment, and exposure assessment are discussed elsewhere (7, 20–22). Briefly, the cohort comprises 5,163 workers employed in one of two Washington boatbuilding facilities for at least one day from January 1, 1959 through September 31, 1978 with sufficient information available for planned analyses. Workers were considered at risk beginning on the date of cohort entry and continued to the earliest of the date of death, date last observed, or study end (December 31, 2016). Employment and exposure information was available through September 1978. As was done in previous analyses of this cohort (7, 23), there were 772 workers still employed at end of records collection who were censored on the last date of records availability (October 1, 1978) and treated as lost to follow-up. As a sensitivity analysis, we replicated analysis without censoring active employees. Lung cancer mortality was determined from the underlying cause of death coded according to the revision of the International Classification of Diseases in effect at the time of death.

The assessment of individual exposures was conducted by exposure assessors blinded to case status. A job-exposure matrix was constructed using individual employment histories linked to exposure data from personal air-samples collected in each plant during operations in 1978 (24, 25). Measurements were recorded as 8-hour time weighted average styrene concentrations in parts per million (ppm). General area air-sampling data also collected during the same surveys were used in job locations with inadequate personal measurement data. Individual jobs were collapsed into similar exposure groups by plant, resulting in 19 groups for Plant 1 and 13 Groups for Plant 2. Exposures were reduced by 50% for supervisors in styrene departments to account for time spent in tasks other than styrene work.

In addition, a variable indicating socioeconomic status was developed in a previous analysis of this cohort (23). This variable, known as the prestige score, is a continuous variable based on the first job held by each worker and is based on the work of Nakao and Treas (26).

Component Analysis

We addressed three component associations that underlie one potential mechanism for HWSB (Figure 1)(27). Let j be the index time of the study (e.g., age). The first component association, c_1, represents the effect of prior exposure, X_{j-1} on work status (actively employed at time j, yes or no), W_j. c_2 is between W_j and subsequent exposure, X_j, and c_3 is between W_j and lung cancer mortality, here represented as disease status, D_j. The unknown factor, U, may represent disease latency or unmeasured risk factors (e.g., smoking). Component association c_2 is present by definition due to the fact that we investigate exposures that occur at work only. To investigate c_1 and c_3, two sets of stratified Cox regressions were performed: 1) matching risk-sets on attained age, 2) matching on risk-sets attained age, race, sex and birth date (+/− 5 years from the index case) and controlling for socioeconomic status prestige score as a spline (28).

For c_1, time to end of employment was the outcome of interest. Three approaches were used to investigate c_1. First, following the approach in Naimi et al (13), the association between time-varying past cumulative exposure and the time-to-end of employment was considered. Second, because cumulative exposure is largely dependent on duration of employment, the effect of average exposure intensity (defined as past cumulative exposure divided by duration of exposure) on employment termination was also considered. Third is the effect of current exposure, while controlling for past exposure, on leaving employment. Current exposure was a time-varying variable defined as the ppm of exposure on the current day of observation, and past exposure defined as a time-varying variable of duration in a job with >30 ppm exposure, which was modeled as a restricted cubic spline. While Naimi et al (13) did not employ this last approach, we note that it directly coincides with the hypothetical underlying mechanism of HWSB given in their analysis and the directed acyclic graph presented in Figure 1. In addition, these last two approaches are also similar to more recent approaches, such as Neophytou, et al. (29), in which the effect of average daily exposure on employment termination was modeled with an accelerated failure time (AFT) model in a cohort of miners exposed to diesel exhaust. All three metrics were modeled categorically so as not to impose any particular parametric exposure-response shape.

Similarly, for c_3, time to lung cancer mortality was modeled with stratified Cox regression. Three time-varying exposure metrics were considered: currently employed, ever employed within the past 5 years and duration of employment (regardless of exposure).

For completeness, time to lung cancer by exposure was also evaluated and results can be found in the Web Table 1.

G-Estimation of a Structural Nested Model

The details of the approach taken in this paper to account for the HWSB are described in the appendices of Hernán, et al. (30) and Chevrier, et al. (31). In short, an accelerated failure time (AFT) model for survival times (using time on study as the time scale) was assumed and counter-factual survival times under different exposure scenarios are generated for each person as:

$$T(\psi,\ A(t)) : = \int_0^{T_A} e^{\psi A(t)} dt$$

Where T_A is the observed survival time, and $T(\psi, A(t))$ is the potential survival time under the counter-factual scenario of no exposure, which depends on the parameter ψ. ψ defines the exposure-response by quantifying the extent to which exposure experienced at time t, $A(t)$, contracts/expands one's survival time over the period of exposure dt. Here, time was measured in discrete units of days, so, for example if $\psi = \log(2)$, a single day of being exposed (versus unexposed) is assumed to shorten one's overall lifespan by $e^{\log(2)} - e^0 = 1$ day. For this study, exposure was dichotomized as $A(t) = 1$ if the exposure at time t was > 30 ppm and $A(t) = 0$ otherwise. The cut-point of 30 ppm was roughly the mean of the average exposure intensity of exposed individuals and is also above the subjective irritation threshold of 105 mg/m3 (25 ppm) reported in Geuskens, et al. (32). As in the prior

examples, administrative censoring (i.e., those alive as of 12/31/2016) was accounted for by artificial censoring and loss-to-follow-up (including those currently employed at record collection) and competing risks were accounted for via inverse probability of censoring weights.

The identifying assumption of g-estimation is that any potential survival time, $T(\psi, A(t))$, for a subject is independent of the observed exposure experience, conditional on time-fixed and all prior values of time-varying confounders. This assumption is often referred to as "no unmeasured confounding" and cannot be checked in any given observed cohort. G-estimation leverages this assumption to estimate the exposure-response parameter, ψ, through a grid search. In particular, at each proposed value of ψ in the grid search, $T(\psi, A(t))$ is calculated for each person and used as a predictor in a pooled logistic regression to estimate the probability of exposure at any time t. This model includes terms for past exposures, race, gender, age, calendar period, and SES prestige score. Employment history was adjusted for by conditioning the model on employed time only. G-estimation is based on hypothesis tests of the coefficient for $T(\psi, A(t))$ in the logistic model for exposure, denoted by β. The value of ψ that results in an estimated potential survival time that does not predict exposure (i.e. β=0 and not significant) is chosen as the point estimate of ψ. We estimated 95% confidence intervals by taking the minimum and maximum values of ψ at which the p-value for β was >0.05.

In addition, it is worth noting the AFT model treats time to lung cancer as inevitable and simply models how exposure extends or contracts this time.

Additional details of the g-estimation procedure can be found in Web Appendix 1 as well as Web Tables 2 through 4 and Web Figures 1 and 2.

RESULTS

Table 1 and Table 2 provide basic demographics of the cohort as well as a summary of their exposures. The majority of the cohort were white males, and most were relatively young when they were first hired. Among 2,095 deaths, there were 187 lung cancer deaths. Less than 1% was lost to follow-up. The majority of the cohort worked on the plant floor with an almost even split between the highly exposed plasticians, who directly handled and applied the styrene resin, and those in other plant operations. Table 2 also highlights the effect of exposure on employment, with those routinely exposed to higher styrene concentrations (time weighted average >30 ppm) typically working almost half as long as those in a lower exposed job.

Table 3 and Table 4 give the results of the component analyses. c_1, which evaluates past exposure on future employment, suggests two different relationships. That is, those with higher cumulative exposure were *less* likely to leave employment, whereas those with higher average exposure intensity higher current exposures were *more* likely to leave employment. In either case, the results of Table 3 suggest that c_1 is satisfied.

The results of Table 4, investigating a relationship between employment and lung cancer mortality, are a little less conclusive. There were less than 5 lung cancer deaths that occurred

during employment, and the estimated risk during this time is almost a fourth smaller than unemployed person-time [HR: 0.24 95% CI: (0.01, 1.22)]. Only five deaths occurred within five years of employment. Both of these results are imprecise due to the rarity of lung cancer at younger ages but suggest that employment is an indicator of lower lung cancer mortality risk, even up to five years after employment termination. Additionally, there is a subtle trend of decreasing risk with increasing duration of employment.

The value of the exposure-response term, ψ, calculated from the g-estimation procedure for an AFT model was significantly positive (1.19, 95% CI: 0.93, 1.37), indicating that styrene exposure is associated with a shorter time to lung cancer death in a model adjusting for HWSBs. The direct interpretation of this parameter is the log of the ratio of a survival time of no exposure to exposure > 30ppm. Additionally, this result implies that one year of exposure >30 ppm accelerates time to lung cancer death by 2.3 years. While this is a large estimated effect, its realization within this particular cohort is limited by the fact that most workers were exposed less than a year. In practical terms of this cohort, of the 176 lung cancers, a third had exposure >30ppm, which lasted on average 8.5 months. This would have the effect of accelerating their time to lung cancer death by 1.6 years (8.5months * ($e^{1.19} - 1$)), or put alternatively, removal of this exposure would extend their time to lung cancer death by 1.6 years. The sensitivity analysis, in which actively employed workers at records collection were assumed to be unemployed and unexposed after 10/1/1978 (the date of records collection), also gave a significantly positive value of ψ (1.30, 95% CI: 1.23, 1.35). See Web Appendix 2 as well as Web Figures 3 through 6 for additional discussion of the model and sensitivity analyses.

DISCUSSION

This study found evidence of an exposure-response association (defined as a contrast to the effect of an intervention) between styrene exposure and lung cancer. Previous studies of this cohort (7) showed excess lung cancer mortality in styrene workers compared to an external referent population; however, internal comparisons did not reveal an exposure-response association (defined as an increasing trend in lung cancer risk with exposure). The lack of an exposure-response is consistent with other studies of workers in the reinforced plastic industry. Analyses of Danish (5) and other US (6) reinforced plastics worker studies reported elevated lung cancer rates compared to referent populations, however, the rates decreased with increasing duration of employment and estimated cumulative exposure. In contrast, a study pooling data on workers from eight British glass-reinforced plastics companies reported the greatest risk of lung cancer deaths among workers with more than a year of employment at a high styrene exposure level; however, this result was based on SMR analyses and internal comparisons were not performed (4).

Information on smoking is not available for this cohort, so potential confounding by smoking cannot be evaluated directly. However, a previous analysis of this cohort(22) reported elevated SMRs for the smoking related outcomes of stomach cancer, intestinal cancer, kidney cancer, bladder cancer, ischemic heart disease and other respiratory diseases among the high exposed sub-cohort, but not the low exposed sub-cohort. This suggests prevalence of smoking may have been higher among this sub-group. In addition, previous

analyses of this cohort (7) observed that those workers who were employed less than a year were more likely to have died of alcoholism and accidents indicating this subgroup may have a riskier lifestyle and, therefore, potentially be more likely to smoke. It is possible that this uncontrolled confounding may also influence our component analysis.

The component association analysis suggests that the lack of an exposure-response trend observed in these cohorts may be a result of the HWSB. Styrene is a known skin and lung irritant (33–35) and symptomatic workers may have been reassigned to jobs with lower exposure or sought employment elsewhere as a means to reduce symptoms. This is supported by the c_1 analysis in which those with higher exposure intensities were more likely to end employment. In addition, a review of employment records uncovered several instances where workers listed acute symptoms related to styrene exposure as reasons for reassignment or termination.

The c_1 analysis suggested two seemingly contradictory associations, where those with higher cumulative exposure were *less* likely to leave employment while those with a higher exposure intensity, both averaged over the entire work history as well as current exposure intensity while controlling for past exposure history, were *more* likely to leave. However, this could also be explained by HWSB, where workers sensitive to exposure leave earlier and accrue a smaller cumulative exposure. The c_1 association simply requires *any* association between exposure and subsequent employment termination, which is true within this cohort. However, for the reasons just stated, cumulative exposure may not be an ideal metric when evaluating the c_1 association.

The c_3 analyses provide evidence of an association between current employment and lung cancer death. However, this analysis is limited in power due to the short duration of employment as well as the young age of cohort members while employed. There were only five deaths from lung cancer within five years of employment within either facility, but this rate is less than half of the rate of among person-time five years or more after leaving employment based on internal analyses. While this large association was underpowered in this study, Steenland and Stayner (11) demonstrated employment status is generally an important confounder in any occupational cohort. Their study looked at 10 large occupational cohorts, and all showed a strong association between active employment and lower rates of all-cause mortality, with SMRs ranging from 0.29 to 0.61, consistent with the results from this study. An alternative framing of the HWSB is that duration of *employment* is an indicator of susceptibility with those employed longer having a lower rate of lung cancer. There is again evidence this is the case in this cohort with those working 5+ years having 70% of the lung cancer rate as those working <3 months.

It is worth noting that the mechanisms of styrene-induced cancer are not clear. However, a possible non-genotoxic mode of action is through chronic inflammation from respiratory irritation. For example, multiple studies of workers exposed to styrene have reported changes in immune cells that are consistent with a proinflammatory response. Nevertheless, the current evidence of chronic inflammation as an important pathway in styrene carcinogenesis is weak (36). More research is needed to elucidate this pathway.

G-methods provide tools to help address the potential for HWSB by providing alternative approaches to control confounding via employment status that does not result in inducing additional biases, which may occur with traditional regression analyses in the presence of the 3 components described by Naimi, et al. (13). One method, referred to as g-estimation, was used in this study. This analysis suggested a positive association between styrene exposure and lung cancer mortality. Additional methods, such as the g-formula (18, 19) or inverse probability weighting could be used to evaluate this relationship. However, in the latter case, inverse probability weighting would not be possible in our cohort due to lack of measurement of health status, for which employment is a proxy. The g-formula, or g-computation, is more sensitive to model specification due to the need for an additional model for employment and a more stratified model for lung cancer. Specifically, under model misspecification and time-varying confounding, g-computation will be guaranteed to reject the null hypothesis of no exposure effect in large samples(37). This “g-null paradox” is not present in our approach, although we still rely on correct model specification for our estimates to be asymptotically consistent(38). Additionally, it is difficult within the g-formula to characterize the exposure effect in a single exposure-response parameter, unlike g-estimation of structural nested models and thus was not considered for the current analysis. The choice of analytic approach can be dictated by study question in which g-formula is more suited for comparisons of hypothetical interventions (18, 19) while g-estimation directly estimates an exposure-response parameter.

This analysis relies on the identifying assumption that the potential survival times under no exposure are independent of exposure, after accounting for observed confounders. This assumption is referred to as “conditional exchangeability” or sometimes simply “no unmeasured confounding.” The intuition for this assumption is that if one were given a list of theoretical survival times of a cohort under an exposure scenario in which no one was ever exposed (that is, $A(t) = 0$ for all t and for all persons) then a researcher should not be able to identify those persons who were indeed actually exposed (accounting for other factors such as race, gender, age and calendar period). We note that this assumption is not limited to our statistical approach – making causal inferences from any set of observational data requires some variation of this assumption. However, the effects of a violation of this assumption are unclear. We emphasize that it is untestable in a given dataset and relies on background knowledge to assess its plausibility. For example, if smoking were related to exposure intensity assignment, we would be subject to bias from uncontrolled confounding by smoking.

Finally, the current analysis used duration in a job with >30 ppm of exposure. A binary exposure metric was chosen for practical purposes since g-estimation becomes much more computationally intensive for continuous exposure metrics, such as cumulative exposure. The interpretation of modeling a continuous exposure with a dichotomous variable is to model the effect of an intervention on the observed continuous dose distribution truncated this exposure metric is to model the effect of an intervention on the observed continuous dose distribution truncated above or below 30 ppm(39). The purpose was to highlight the potential effect of confounding by the HWSB, but future studies should consider additional, more biologically relevant exposure metrics.

CONCLUSION

This paper demonstrated a potential bias in analyses of associations between styrene exposure and lung cancer mortality in a cohort of boatbuilders in Washington state resulting from a special form of time-varying confounding. To correct for this bias, special methods are required outside of standard analytic procedures. G-methods offer an approach to correct for this bias, and for this cohort, g-estimation of a structural nested model procedures suggest a positive association between styrene exposure and lung cancer not seen in previous analyses of this cohort or other cohorts within the reinforced plastics industry. Evaluation of the potential for HWSB in other, larger cohorts in this industry should be evaluated. If the effect of this bias is as large as seen in this cohort, this may warrant a re-evaluation of the carcinogenicity of styrene to account for this bias.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY

The data in this paper contains death certificate data and is protected by an assurance of confidentiality granted under Section 308(d) of the Public Health Service Act, (42 U.S.C. 242 m (d)). The data can only be accessed through a National Center for Health Statistics (NCHS) Research Data Center (RDC) upon written request to and approval by NIOSH.

Abbreviations:

AFT	Accelerated Failure Time
HR	Hazard Ratio
HWSB	Healthy Worker Survivor Bias
ppm	parts per million
SMR	Standardized Mortality Ratio

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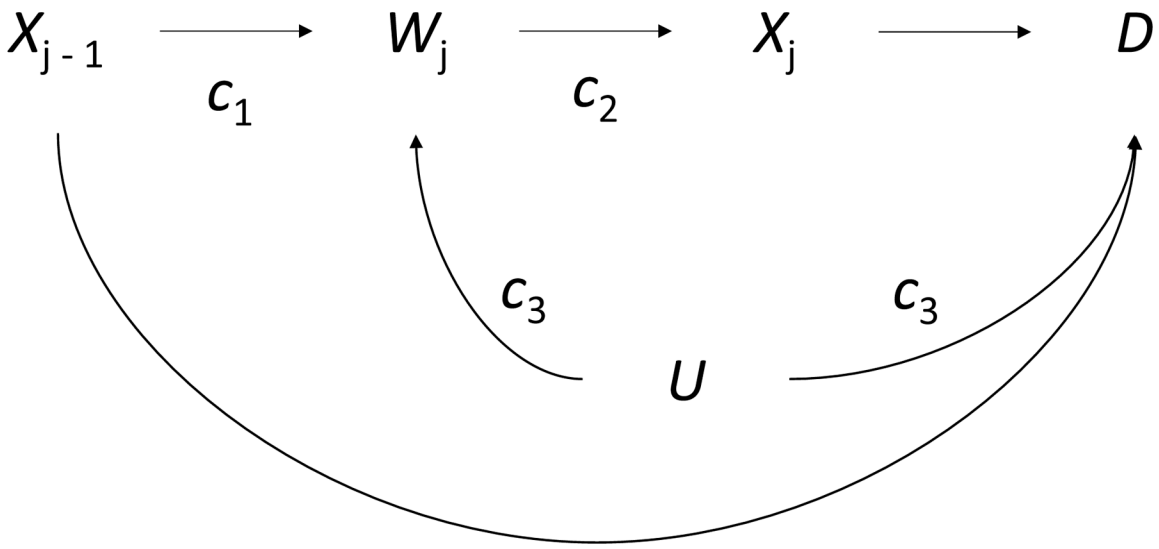

Figure 1.

Directed acyclic graph representing healthy worker survivor effects. Let j be index age, X is styrene exposure, W is work status, U is an unmeasured common cause of W and T, and T is survival time. The three component associations expressing work status as a time varying confounder are shown as c_1, c_2, and c_3 (adapted from Naimi et al, 2013).

Table 1:

Characteristics of study participants, Washington state boatbuilders cohort, 1959–2016

Characteristic	N	%
Gender		
Male	4,493	87
Female	670	13
Race		
White	4,811	93
Other	289	6
Unknown	63	1
Vital status		
Alive	3,068	59
Deceased	1,830[a]	41
Lung Cancer	176[b]	
Facility employment		
Plant 1	1,679	33
Plant 2	3,481	67
Worked in both plants	5	<1
Follow up		
Person-years	175,929	
Age at hire[c]	24 (21, 33)	
Age at date last observed[c]	66 (58, 72)	
Year hired[c]	1970 (1967, 1974)	

[a] – excludes 265 deaths among those who were currently employed at record collection

[b] – excludes 33 lung cancer deaths among those who were currently employed at record collection

[c] – Values are expressed as median (interquartile range)

Table 2:

Summary of employment duration and styrene exposures, Washington state boatbuilders cohort, 1959–2016

	Duration of employment (n = 5,163)				
Percentile	**Duration of employment (n = 5,163)**	**<30 ppm[a] (n=3,269)**	**30+ ppm[a] (n=1,894)**	**Cumulative Exposure, ppm-years (n = 5,163)**	**Average Exposure Intensity, ppm (n = 5,163)**
Minimum [b]	2	2	3	<0.1	0.7
5th percentile [b]	7	8	6	0.2	4
25th percentile [c]	1.4	1.7	1	1.3	4
50th percentile [c]	5.2	6	3.7	5.7	15
75th percentile [d]	1.4	1.7	1	24.5	45.5
95th percentile [d]	7.7	9.1	5.7	149.2	73.9
Maximum [d]	26.8	26.8	20.8	1259.5	80.2

ppm = parts per million

[a] – These columns summarize duration of employment of cohort members stratified by overall average exposure intensity (lifetime cumulative exposure divided by duration of employment).

[b] – Duration expressed in days

[c] – Duration expressed in months

[d] – Duration expressed in years

Table 3:

Component 1 (c_1) analyses evaluating the effect of past exposure on ending employment, Washington state boatbuilders cohort, 1959–2016

Exposure metric	HR[b]	(95% CI)	aHR[c]	(95% CI)
Cumulative Exposure				
≥0 but <5 ppm-years	1	referent	1	referent
≥5 but <25 ppm-years	0.44	(0.41, 0.47)	0.44	(0.41, 0.48)
≥25 but <150 ppm-years	0.27	(0.25, 0.29)	0.26	(0.24, 0.29)
≥150 ppm-years	0.14	(0.12, 0.17)	0.12	(0.10, 0.15)
Average Exposure Intensity				
≥0 but <15 ppm	1	referent	1	referent
≥15 but <45 ppm	0.88	(0.81, 0.95)	0.94	(0.86, 1.02)
≥45 but <70 ppm	0.96	(0.86, 1.06)	1.02	(0.91, 1.13)
≥70 ppm	1.54	(1.41, 1.67)	1.28	(1.17, 1.40)
Current Exposure[a]				
≥0 but <15 ppm	1	referent	1	referent
≥15 but <45 ppm	1.18	(1.09, 1.28)	1.27	(1.17, 1.38)
≥45 but <70 ppm	3.07	(2.73, 3.44)	3.35	(2.95, 3.79)
70 ppm	3.31	(3.00, 3.64)	2.87	(2.59, 3.17)

HR = Hazard Ratio; aHR = adjusted Hazard Ratio

[a] - Current exposure is a time-varying variable representing the current day's exposure intensity. This model also controlled for duration of time in a job with > 30 ppm of styrene exposure.

[b] - Results of Cox regression modeling time to end of employment at either facility. Matched on age only.

[c] – Results of Cox regression modeling time to end of employment at either facility. Matched on age, birth year (+/− 5yrs of index case), race, sex and controlled for SES prestige score with a spline.

Table 4:

Component 3 (c_3) analyses evaluating time-dependent employment status on lung cancer mortality, Washington state boatbuilders cohort, 1959–2016

Exposure metric	Ncases[a]	HR[b]	(95% CI)	aHR[c]	(95% CI)
Employment Status					
Not Employed (0 lag)	>171	1.00	referent	1.00	referent
Employed (0 lag)	<5	0.43	(0.03, 1.94)	0.25	(0.01, 1.30)
Employed last 5 years					
Not Employed (5 lag)	171	1.00	referent	1.00	referent
Employed (5 lag)	5	0.78	(0.28, 1.75)	0.42	(0.12, 1.20)
Duration of Employment					
<3 months	79	1.00	referent	1.00	referent
≥3 months but <1 year	47	0.86	(0.59, 1.23)	0.89	(0.61, 1.27)
≥1 year but <5 years	38	0.89	(0.60, 1.30)	0.93	(0.62, 1.37)
5 years	12	0.69	(0.35, 1.22)	0.64	(0.33, 1.17)

HR = Hazard Ratio; aHR = adjusted Hazard Ratio

[a] – Number of lung cancer mortality cases. Cells with less than 5 observations censored to protect identity.

[b] – Results of Cox regression modeling time to death from lung cancer. Matched on age only.

[c] – Results of Cox regression modeling time to death from lung cancer. Matched on age, birth year (+/− 5yrs of index case), race, sex and controlled for SES prestige score with a spline.