1,3-Butadiene, Styrene and Selected Outcomes Among Synthetic Rubber Polymer Workers: Updated Exposure-Response Analyses

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ABSTRACT

Objective – To evaluate exposure-response relationships between 1,3-butadiene and styrene and selected diseases among synthetic rubber polymer workers.

Methods – 21,087 workers (16,579 men; 4,508 women) were followed from 1943 through 2009 to determine mortality outcomes. Cox regression models estimated rate ratios (RRs) and 95% confidence intervals (CIs) by quartile of cumulative exposure to butadiene or styrene and exposure-response trends for cancers of the bladder, lung, kidney, esophagus and pancreas, and for all nonmalignant respiratory disease (NMRD), chronic obstructive pulmonary disease (COPD) and pneumonia.

Results – Bladder cancer RRs were 2.13 (95% CI=1.03 to 4.41) and 1.64 (95% CI=0.76 to 3.54) in the highest quartiles of cumulative exposure to butadiene and styrene, respectively, and exposure-response trends were positive for both monomers (butadiene, trend p=0.001; styrene, trend p=0.004). Further analyses indicated that the exposure-response effect of each monomer on bladder cancer was demonstrated clearly only in the subgroup with high cumulative exposure (at or above the median) to the other monomer. Lung cancer was not associated with either monomer among men. Among women, lung cancer RRs were above 1.0 in each quartile of cumulative exposure to each monomer, but exposure-response was not seen for either monomer. Male workers had COPD RRs slightly above 1.0 in each quartile of cumulative exposure to each monomer, but there was no evidence of exposure-response among the exposed. Monomer exposure was not consistently associated with COPD in women or with the other cancer outcomes.

Conclusions – This study found a positive exposure-response relationship between monomer exposures and bladder cancer. The independent effects of butadiene and styrene on this cancer

could not be delineated. In some analyses, monomer exposure was associated with lung cancer in women and with COPD in men, but inconsistent exposure-response trends and divergent results by sex do not support a causal interpretation of the isolated positive associations.

Key words: Butadiene, styrene, bladder cancer, lung cancer, nonmalignant respiratory disease, synthetic rubber polymer

1 INTRODUCTION

Synthetic rubber polymer manufacturing workers are exposed to 1,3-butadiene and styrene monomers [1]. The International Agency for Research on Cancer (IARC) and other agencies have classified butadiene as a human carcinogen causing lymphohematopoietic cancer (LHC), especially leukemia [1,2,3], and in 2019, the United States (US) Environmental Protection Agency listed butadiene as a high-priority for risk evaluation [4]. The US National Research Council concluded in 2014 that there was limited evidence of styrene carcinogenicity in humans based on reported associations with LHCs and with esophageal, pancreatic and kidney cancers [5]. IARC recently classified styrene as probably carcinogenic to humans (Group 2A), based on limited evidence of an association with LHCs in humans and on sufficient evidence of carcinogenicity in experimental animals [6].

Our previous investigation [7] of an updated cohort of North American synthetic rubber polymer workers found associations with leukemia and bladder/other non-renal urinary tract cancer and with lung cancer among female but not male employees. Here, we present further internal analyses of the exposure-response relation between each monomer and mortality from cancers of the bladder, lung, esophagus, pancreas and kidney among workers in the updated cohort. We also analyzed mortality from nonmalignant respiratory disease (NMRD) and two of its major subtypes, chronic obstructive pulmonary disease (COPD) and pneumonia, for two reasons. Positive associations between exposure to styrene and these conditions have been reported inconsistently [8,9,10,11,12,13]. Tobacco smoking is the main cause of COPD [14] in the US and is associated with the cancers [15] assessed in this study. Thus, analyses to determine the relation between monomer exposure and COPD mortality could provide indirect information on the likelihood that any observed association between monomers and these cancers is

confounded by smoking.

New data in this paper include the results of analyses by quartile of cumulative exposure to monomers, with beta coefficients (β) for the slope of the exposure-response curve and corresponding 95% confidence intervals (CIs); results pertaining specifically to bladder cancer, rather than to bladder cancer combined with other non-renal urinary tract cancers, which was the outcome analyzed previously [7]; results for each monomer and bladder cancer, stratified by exposure to the other monomer; results for COPD and pneumonia, as well as for all NMRD; and results of analyses using lagged monomer exposure data. The present analyses provide quantitative data on exposure-response trends that could be useful for risk assessments by regulatory agencies.

2 METHODS

Sathiakumar et al. [7] described in detail the methods used to update the cohort study of mortality among workers employed at eight North American synthetic rubber polymer plants, with follow-up extended through 2009. The updated cohort included 17,924 men classified as having worked, between 1943 and 1 January 1992, for at least one year at any of eight synthetic rubber polymer plants, seven in the US and one in Canada; and 4,861 women classified as having worked for at least one day during the same time period at any of the plants. The male cohort was restricted to men employed for at least one year in order to avoid the use of project resources to develop data on the large number of men who were short-term workers and in order to maximize the informativeness of the study. A similar restriction was judged unnecessary for the much smaller number of female employees. Quantitative butadiene and styrene monomer exposure estimates previously were developed for five of seven US plants and for the Canadian plant [16]. All current analyses were restricted to the 21,087 workers from those six plants.

2.1 Exposures

Synthetic rubber polymer manufacturing began at the study plants in the early 1940s, and facility operations have been described in detail elsewhere [17]. Styrene-butadiene rubber (SBR), a copolymer of 1,3-butadiene and styrene, was the main type of synthetic rubber produced initially at the plants. The main SBR production areas were polymerization, coagulation and finishing, and the plants also had tank farm, laboratory, maintenance, warehouse and utilities support operations. Monomer exposure potential varied by work area, type of job and time period. Exposure levels declined over time due to changes in production, work practices and engineering controls [16].

Work histories and butadiene and styrene exposure estimates were available for cohort members through the end of 1991. Of 4,079 workers still working at the end of 1991, 46% were exposed to monomers, but their last-known jobs entailed relatively low exposure to butadiene (median, 1.1 ppm) and styrene (0.4 ppm). We treated all workers active at the end of 1991 as unexposed thereafter. Exposure estimation entailed identifying for each plant-specific work area/job combination its component tasks that involved butadiene or styrene exposure and documenting historical changes in those tasks; calculating plant-, work area/job- and time-specific average 8-hour time-weighted average concentration in parts per million (ppm) for each monomer; compiling these estimates into job-exposure matrices; and linking the monomer-specific job-exposure matrices with each employee's work history to obtain estimates of ppm-years of butadiene and styrene exposure as of each day of follow-up [16].

2.2 Outcomes

Vital status was determined through 2009 for 99% of the cohort using information from the Social Security Administration, Pension Benefits Inc. and the National Death Index (NDI)

for US workers and from the national Canadian Mortality Data Base (CMDB) for Canadian workers [7]. Outcomes of interest were deaths from cancers of the bladder, lung, esophagus, pancreas and kidney and from all NMRD, COPD and pneumonia. For each outcome, events included any decedent with the condition as the underlying or a contributing cause of death. Data on underlying and contributing causes of death came from death certificates and International Classification of Diseases (ICD) codes from the NDI or from the CMDB. Complete information on all underlying and contributing causes of death was available for all US decedents with a death certificate or NDI record and for all female Canadian decedents. Information on all underlying and contributing causes of death also was available for male Canadian decedents who died in or after 1992. However, for male Canadian decedents who died before 1992 (N=1,267), contributing causes of death were obtained only for cancers; thus, information on NMRD as a contributing cause of death was unavailable for those decedents. For most of the cancers, the diagnosis was present as the underlying cause of death, and the proportion of cases identified by underlying cause of death information was 96% for esophageal cancer, 90% for pancreatic cancer, 93% for lung cancer in both women and men, 78% for bladder cancer and 86% for kidney cancer. For all NMRD and subtypes, more than 50% of cases were identified only as a contributing cause of death.

2.3 Statistical analysis

Follow-up began for male workers on their date of accruing one year of employment or on the earliest date when complete plant records were available, whichever was later, and for female workers on their hire date or on the earliest date when complete plant records were available, whichever was later [7]. For all workers, follow-up ended on the earliest of their death date, their loss-to-follow-up date or 31 December 2009.

Analyses of the relation between monomer exposure and a specific outcome used multivariable Cox regression to estimate hazard ratios and exposure-response trends within the cohort of workers. These "internal" Cox regression analyses provided maximum partial likelihood estimates of disease-specific hazard ratios, interpreted as rate ratios (RRs), and 95% confidence intervals (CIs) for each quartile of ppm-years of monomer exposure compared to no exposure, with quartiles specified according to the exposure distribution of cases with each outcome. Further Cox regression analyses estimated beta coefficients (β) and 95% CIs for trends in exposure-response using butadiene or styrene ppm-years as continuous variables. When a statistically significant trend was detected consistently, we also calculated RRs per 100-ppm-years for butadiene and per 50 ppm-years for styrene. We analyzed exposure-response trends using unlagged ppm-years, as well as ppm-years lagged by 10 or 20 years.

For bladder cancer, we used restricted cubic spline (RCS) Cox regression models to further describe monomer exposure-response curves and to explore the possibility of nonlinear associations [18]. RCS models were fitted to all exposure data and to "trimmed" exposure data (see below), with five knots corresponding to the 5, 27.5, 50, 72.5, and 95 percentile boundaries among the exposed. In addition, we analyzed butadiene/bladder cancer exposure-response separately in the following two strata of styrene exposure: lower styrene exposure, defined as below the median value of 21 ppm-years among bladder cancer decedents; and higher styrene exposure, defined as exposure at or above the median value. We also analyzed styrene/bladder cancer exposure-response, stratified by lower (below the median value, 87 ppm-years) versus higher (≥87 ppm-years) butadiene exposure. We did not perform RCS or stratified analyses for other outcomes because initial exposure-response models yielded null results.

All analyses used age as of each person-day of follow-up ("age at observation") as the

time scale and treated butadiene and styrene ppm-years as time-dependent: i.e., the data for each worker included his or her ppm-years of exposure to each monomer as of each person-day of follow-up. In our main analyses, exposure-response trends were assessed using all person-day records, and all models included as covariates age at hire, calendar year of hire, sex (except when analyzing men and women separately), race, plant and payroll status (ever or never hourly). Age at hire and year of hire were entered as continuous variables.

Preliminary Cox regression models included terms for monomer exposure-sex interaction and detected interaction in models of esophageal cancer, lung cancer and all NMRD. Therefore, we analyzed data on men and women separately for lung cancer, all NMRD, COPD and pneumonia and restricted analyses of esophageal cancer to men, as there were only four cases among women and no case among monomer-exposed women.

We conducted several sensitivity analyses for all outcomes. First, we excluded person-day records having zero cumulative exposure, in order to eliminate the possibility that any observed exposure-response trend was due to differences in uncontrolled factors between unexposed and exposed person-time [19]. Second, to investigate the influence of data at extreme exposure values, an issue reported [20] in other occupational cohort studies, we analyzed exposure-response trends using "trimmed" data that excluded all unexposed person-time and all person-time with ppm-years values above the 95^{th} percentile of the exposure distribution of outcome-specific decedents. Third, for each outcome we analyzed "reduced" models that contained fewer covariates. The latter analyses produced for each outcome a series of models containing all possible combinations of covariates and selected, as the best reduced model, the model with the fewest covariates and with a beta coefficient within 5% of that estimated in the corresponding full model containing all covariates. The reduced models did not identify any

additional statistically significant results and are not mentioned further.

We performed several additional sensitivity analyses for bladder cancer only. Over 20% of bladder cancer cases were identified using contributing cause of death data. Accordingly, one sensitivity analysis evaluated the impact of the possibly greater mis-specification of outcome events and event dates for bladder cancer cases identified using contributing, as opposed to underlying, causes of death. This analysis included as outcome events only those bladder cancers identified from underlying cause of death data. To determine if the inclusion of age at hire and year of hire as continuous variables (linear terms) in Cox regression models had any impact on our results, we constructed categorical variables (age at hire: <20, 20-29, 30-39, 40-49, ≥50 years; year of hire: <1950, 1950-1959, 1960-1969, 1970-1979, ≥1980) and adjusted for those variables, in addition to the covariates sex, race, plant and ever hourly status. Additional models included age at hire and calendar year of observation, instead of year of hire, as categorical variables, as well as the other covariates. Because there was no bladder cancer death before 1960, we also performed an analysis with the same covariates, but restricting the data to person-time occurring in or after 1960. To assess the impact of classifying workers active at the end of 1991 as unexposed to monomers thereafter, we conducted a sensitivity analysis that withdrew those employees from follow-up on December 31, 1991.

We used the SAS® version 9.4 Cox proportional hazard model procedure PHREG for the Cox regression analyses.

The Institutional Review Board of the University of Alabama at Birmingham reviewed and approved the study protocol.

3 RESULTS

The cohort of 21,087 workers included 16,579 men and 4,508 women (Table 1). Most

men (83%) had worked as hourly, whereas 72% of women had never been hourly. The median plant hire year was 1959, and workers had a median of 8.3 years of employment at the end of 1991; men had worked longer than women (median: men, 11.8 years; women, 1.7 years). As of the end of follow-up, the median time since hire was 40 years, the median age was 69 years, and 46% of the cohort was deceased.

Overall, proportions of employees ever exposed to butadiene and styrene were, respectively, 66% and 73% and were higher for men (butadiene, 77%; styrene, 84%) than for women (butadiene, 26%; styrene, 31%) (Table 2). The distributions of cumulative exposure to monomers were right-skewed (Figure 1), with median and mean values among all employees of 48 and 187, respectively, for butadiene ppm-years and of 11 and 38, respectively, for styrene ppm-years. Among all exposed workers, median ppm values, calculated for each worker as their cumulative ppm-years, divided by their years of exposure, were 8.8 ppm for butadiene and 1.6 ppm for styrene and were approximately the same for exposed men and exposed women.

Among monomer-exposed workers, median values of ppm-years at the end of follow-up were higher for men than for women, for ever-hourly compared to never-hourly employees, for black compared to white employees and for employees hired before the 1960 compared to those hired in or after 1960 (Table 2). Median butadiene and styrene ppm-years also varied by plant.

The total numbers of decedents with a cancer outcome event were 90 for bladder cancer, 915 for lung cancer (782 in men, 133 in women), 67 for esophageal cancer (men only), 155 for pancreatic cancer and 71 for kidney cancer. There were 1,740 events for all NMRD (1,428 in men, 312 in women), 759 for COPD (628 in men, 131 in women) and 624 for pneumonia (511 in men, 113 in women). Butadiene and styrene ppm-years were strongly correlated among decedents with outcome events (data not displayed in a table). The relevant Spearman correlation

coefficients ranged from 0.74 for male lung cancer decedents to 0.96 for female lung cancer decedents.

3.1 Bladder cancer

For butadiene, RCS curves (Figure 2a, 2b) appeared to be somewhat irregular, although departure from linearity was uncertain due to statistical imprecision. The adjusted RR for bladder cancer increased in a linear fashion until about 50 ppm-years, followed by a decrease in risk until about 181 ppm-years; then, the RR increased linearly until the upper limit of exposure. Patterns were similar for trimmed data (figure not displayed). Analyses by quartile of butadiene ppm-years yielded adjusted RRs of 1.18 (0.59 to 2.35) for quartile 1 (>0-<32.37 ppm-years), 1.69 (0.82 to 3.47) for quartile 2 (32.37-<86.87 ppm-years), 1.19 (0.57 to 2.47) for quartile 3 (86.87-<328.79 ppm-years) and 2.13 (1.03 to 4.41) quartile 4 (328.79-7,899.68 ppm-years) (Table 3). In the main analysis of the butadiene exposure-response trend, which included unexposed person-time, the RR per 100 ppm-years was 1.04 (95% CI=1.02 to 1.06). The exposure-response trend was statistically significant and positive with or without inclusion of unexposed person-time (including unexposed: $\beta=3.84\text{x}10^{-4}$, 95% CI=(1.55 to 6.12) $\text{x}10^{-4}$, trend p=0.001; excluding unexposed: $\beta=3.50\text{x}10^{-4}$, 95% CI=(1.05 to 5.95) $\text{x}10^{-4}$, trend p=0.005). Use of trimmed data restricting ppm-years to >0 and $\leq 95^{th}$ percentile (1,294 ppm-years) yielded a β for trend that was not statistically significant ($\beta=4.72\text{x}10^{-4}$, 95% CI=(–4.36 to 13.79) $\text{x}10^{-4}$, trend p=0.308).

For styrene, RCS curves (Figure 2c, 2d) indicated that the adjusted RR for bladder cancer increased in a linear fashion until about 11 ppm-years, followed by a decrease in risk until about 38 ppm-years; then, the RR increased linearly until the upper limit of exposure. Patterns were similar for trimmed data (figure not displayed). Analyses by quartile of styrene ppm-years yielded adjusted RRs of 1.07 (0.51 to 2.23), 1.18 (0.56 to 2.49), 1.16 (0.54 to 2.48) and 1.64

(0.76 to 3.54) in quartiles 1 (>0-<5.45 ppm-years), 2 (5.45-<21.37 ppm-years), 3 (21.37-<60.26 ppm-years) and 4 (60.26-1,273.99 ppm-years), respectively (Table 3). None of the quartile-specific RRs was statistically significant. In the main analysis of the styrene exposure-response trend, however, the RR per 50 ppm-years was 1.11 (95% CI=1.03 to 1.19). The exposure-response trend was statistically significant and positive, with or without inclusion of unexposed person-time (including unexposed: $\beta=2.03x10^{-3}$, 95% CI=(0.66 to 3.40) $x10^{-3}$, trend p=0.004; excluding unexposed: $\beta=1.90x10^{-3}$, 95% CI=(0.05 to 3.31) $x10^{-3}$, trend p=0.008). Use of trimmed data restricting ppm-years to >0 and $\leq 95^{th}$ percentile (275 ppm-years) yielded a β for trend that was not statistically significant ($\beta=3.31x10^{-3}$, 95% CI=(–1.09 to 7.71) $x10^{-3}$, trend p=0.141).

Analyses of each monomer, stratified by lower versus higher exposure to the other monomer, found that the butadiene exposure-response association was statistically significant only in the category of higher styrene exposure ($\beta=4.30x10^{-4}$, 95% CI=(1.53 to 7.07) $x10^{-4}$, trend p=0.002) (Table 3). Similarly, the styrene exposure-response association was statistically significant only in the category of higher butadiene exposure ($\beta=1.67x10^{-3}$, 95% CI=(0.09 to 3.25) $x10^{-3}$, trend p=0.039).

All sensitivity analyses for bladder cancer yielded statistically significant results for butadiene and styrene that were close to those of the main analysis that included all person-time and both underlying and contributing cause of death cases and that modeled age at hire and year of hire as continuous variables. For butadiene, the sensitivity analysis β coefficients varied from $3.37x10^{-4}$ when cases were restricted to those identified from underlying cause of death data only, to $3.84x10^{-4}$ when either continuous or categorical forms of calendar year of observation were included as covariates. For styrene, the sensitivity analysis β coefficients varied from

$1.76x10^{-4}$ when cases were restricted to those identified from underlying cause of death data only, to $2.03x10^{-4}$ when the continuous variable, year of observation, was included as a covariate.

3.2 Lung cancer

For lung cancer among men, the RR in each monomer exposure quartile was at or below the null, and none of the trend tests was statistically significant for butadiene or styrene (Table 4). Among women, the lung cancer RR was above the null value of 1.0 in each quartile of butadiene exposure, but there was no evidence of positive exposure-response (p-values of 0.971, 0.272 and 0.439, with and without inclusion of the unexposed person-time and with data trimmed to exposed ppm-years $\leq 95^{th}$ percentile, respectively). Results were similar for styrene ppm-years.

3.3 Esophageal, pancreatic and kidney cancers

The RRs for esophageal and pancreatic cancers were elevated in some quartiles of both butadiene and styrene ppm-years (Table 5). However, all of the elevated RRs were statistically imprecise, and there was no evidence of positive exposure-response. Monomer exposure was not associated with kidney cancer.

3.4 NMRD, COPD and pneumonia

Among men, neither monomer was associated with all NMRD (Table 6). For butadiene and COPD, the RR was slightly above 1.0, but not statistically significant, in each quartile of exposure. The exposure-response trend was statistically significant and positive in analyses that included all person-time ($\beta=1.42x10^{-4}$, 95% CI=(0.16 to 2.66) $x10^{-4}$, trend p=0.027) but not in analyses that excluded unexposed person-time (p=0.095) or that were restricted to exposed ppm-years $\leq 95^{th}$ percentile (p=0.746). Similar results were noted for styrene ppm-years and COPD in

men. No association was apparent for either monomer and pneumonia.

Among women (Table 7), monomer exposure was not associated with all NMRD. The number of deaths among monomer-exposed women was small for COPD (22 decedents exposed to butadiene, 30 exposed to styrene) and pneumonia (26 exposed to butadiene, 34 exposed to styrene); all results for these outcomes were statistically imprecise, and no association with monomer exposure was apparent.

3.5 Lagged monomer exposure

Analyses of lagged cumulative exposure (Table 8) found that for bladder cancer, trends were statistically significant for butadiene or styrene exposure lagged 10 or 20 years. For COPD in men, a statistically significant trend was noted for butadiene and styrene exposure lagged 10 years and butadiene exposure lagged 20 years. No trends were detected for lagged butadiene or styrene exposure and the other outcomes.

4 DISCUSSION

This paper provides information on exposure-response relationships between butadiene and styrene monomers and selected diseases in a large cohort of synthetic rubber polymer workers. Among the cancers analyzed, a consistent positive exposure-response relationship was evident only for bladder cancer. Among men, but not women, RRs for COPD were above 1.0 across quartiles of monomer exposure; however, exposure-response was not evident for COPD in the monomer-exposed component of the male cohort. All NMRD and pneumonia were not associated with cumulative exposure levels.

4.1 Bladder cancer

The highest quartile of butadiene cumulative exposure was associated with a statistically significant twofold increase in the risk of bladder cancer, compared to the unexposed. The

butadiene-bladder cancer exposure-response trend was positive, statistically significant and confirmed in most sensitivity analyses. Results for styrene and bladder cancer also indicated a positive exposure-response trend, although no quartile-specific RR was statistically significant. The exposure-response relationship for each monomer was statistically significant only within the higher exposure stratum of the other monomer. Therefore, separation of the effects of the two monomers was not possible.

Earlier investigations [1,21] of the cohort evaluated in the present study did not find an excess of bladder cancer deaths, possibly because of their shorter follow-up times. Studies of other cohorts of butadiene-exposed workers have not reported an association with bladder cancer [22,23,24]. With regard to styrene and bladder cancer, an older European international mortality study of reinforced plastics workers exposed to styrene but not to butadiene found no association with bladder cancer mortality [25]. Several mortality studies of updated cohorts of reinforced plastics workers reported nonsignificant increases in bladder cancer deaths among workers compared to general populations [10,11,12,26]. A further investigation [27] of the cohort of boatbuilders studied by Ruder et al. [12] and by Bertke et al. [26] analyzed cancer mortality among workers in relation to improved exposure estimates. These internal analyses indicated a statistically significant exposure–response association using trimmed data. The cohort of boatbuilders had a median value of styrene ppm-years that was somewhat lower (5.7 ppm-years) than that in our cohort (11 ppm-years) and a mean value (about 31 ppm-years) that was similar to that in our cohort (38 ppm-years). In contrast, a large investigation of Danish reinforced plastics workers found no association between several measures of styrene exposure and bladder cancer incidence [28]. The null results of the Danish study and the imprecise findings for bladder cancer among the other studies of reinforced plastics industry workers do not support the hypothesis that

styrene alone is a bladder carcinogen.

Workers in some rubber products manufacturing plants have an increased risk of bladder cancer, presumably due to their exposure to aromatic amines [29]. To our knowledge, such exposure did not occur in the synthetic rubber polymer industry. Cigarette smoking is an established cause of bladder cancer [15]. The association that we observed could be due to uncontrolled confounding by smoking, but we do not have data on workers' smoking habits to support or refute this possibility. Our null results for butadiene and styrene exposures and lung cancer (in men) and for COPD and the other smoking-related cancers among monomer-exposed workers, discussed below, do not support confounding by smoking as an explanation for the positive exposure-response relationship seen for bladder cancer. Other risk factors for bladder cancer that were not controlled in our study include employment in several industries, medical conditions such as bladder irritation and infection and use of hair dyes and certain medications [2,30]. It is not known if any of these factors were associated with butadiene or styrene exposure in our cohort and thus could have confounded the observed monomer exposure-response trends.

4.2 Other cancers

The present study found no association between butadiene and styrene exposures and lung cancer among male workers. Compared to unexposed female workers, monomer-exposed women had elevated rates of lung cancer, but a monomer exposure-response trend was not evident in any analysis. These results are consistent with those from earlier studies of the same cohort [31,32]. The lack of a positive exposure-response trend does not support a causal interpretation. The interpretation of the elevated standardized mortality ratio (SMR) for lung cancer in the same cohort of women [7] and the elevated rates across quartile of exposure in the present study remains uncertain. While confounding by smoking may account in part for the

elevated SMR among women [31], our null results for all NMRD and COPD among women do not support the possibility that smoking explains the elevated rate of lung cancer seen in each monomer exposure quartile.

Other studies of butadiene-exposed workers, none of which included women, have not reported an association with lung cancer [22,23,24]. One study of male and female styrene-exposed workers in the British reinforced plastics industry found significantly elevated mortality from lung cancer, and the magnitude of risk rose across increasing exposure categories [11]. Other studies of styrene-exposed workers have reported elevated lung cancer SMRs but have not found any consistent evidence of a causal association between styrene and lung cancer [10,12,26,28,33]. A systematic review and meta-analysis of 14 independent studies concluded that the evidence of an association between occupational exposure and lung cancer was inconsistent [34]. Experimental studies have shown that styrene exposure causes lung tumors in several strains of mice, but not in rats [35]. The positive toxicological findings for lung tumors in mice have been interpreted as being specific to mice and as having low relevance to humans [35-37].

We found elevated but statistically non-significant RRs for esophageal and pancreatic cancers in some quartiles of monomer exposure. However, there was no evidence of exposure-response between styrene or butadiene and mortality from esophageal, pancreatic or kidney cancers. Thus, our results do not strengthen the currently limited evidence for an association between occupational styrene exposure and these cancers [6]. The systematic review and meta-analysis of Collins and Delzell also found little evidence that styrene monomer causes esophageal, pancreatic or kidney cancers [34].

4.3 NMRD, COPD and pneumonia

We observed no evidence of exposure-response between monomer exposure and all NMRD or pneumonia among men or women in the present study. Results for COPD among men indicated a slightly increased rate in each quartile of exposure compared to the unexposed and a statistically significant, positive exposure-response trend in analyses using all person-time but not in analyses restricted to the exposed person-time. This pattern of results suggests that chance or a difference in a confounding factor, such as smoking, between the unexposed and exposed person-time is a more likely explanation of the results rather than a causal relationship between monomer exposure and COPD in men. However, the lack of a similar pattern of results for lung cancer in men does not support confounding by smoking as the explanation. Among women, COPD RRs were largely below or close to the null, and there was no evidence of an exposure-response trend in any analysis.

Nett et al. [13] suggested that occupational exposure to styrene is a potential risk factor for NMRD and COPD. Several cohort studies of reinforced plastics industry workers have reported increased mortality from NMRD, but exposure-response analyses were either not done or produced null results, and none of the studies adjusted for potential confounding by tobacco use [10,11,12]. With regard to butadiene, epidemiologic evidence from independent studies is sparse and largely null [22,23,24]. Overall, there is no consistent external support for an association between styrene or butadiene and all NMRD, COPD or pneumonia.

4.4 Strengths and limitations

The cohort is the largest butadiene-exposed group studied to date. The long follow-up period of this study made it optimal for detecting relationships between monomer exposure and the diseases of interest. The use of quantitative estimates of cumulative exposure and the use of sensitivity analyses to aid interpretation of results are additional strengths. Limitations included

the lack of information on lifestyle factors, including tobacco use, and on employment in other industries. The study's ability to evaluate the effects of monomer exposure in women was hindered by the small size of this component of the cohort; also, most of the female cohort had worked in the industry for under five years and had no or low cumulative exposure. Other potential limitations were possible misclassification of employees by monomer exposure and by cause of death. The present study used mortality, rather than disease incidence, data to identify the outcomes of interest. The mortality end point is not optimal for cancers associated with relatively long survival, including bladder cancer, or for NMRD and its subtypes, which also may be associated with long survival. Our internal analyses included cancer and NMRD cases identified from multiple sources rather than from underlying cause of death data only and, thus, minimized, but did not eliminate, this limitation. Also, our lagged exposure analyses may have minimized any monomer exposure misclassification stemming from the inclusion of exposure occurring after disease incidence. Butadiene and styrene exposures were highly correlated; thus, statistical analyses could not definitively separate the effects of the two monomers. Finally, the cumulative styrene exposures of this synthetic rubber industry cohort were relatively low, with highest median levels of <50 ppm-years among case decedents including bladder cancer, when compared to the styrene exposures of reinforced plastics industry workers, many of whom in the past may have been exposed to average concentrations about 30 ppm to more than 100 ppm [6].

5 Conclusions

This study identified a positive exposure-response relationship between monomer exposure and bladder cancer. The independent effects of butadiene and styrene could not be determined because exposures to the two monomers were highly correlated. The reason for the elevated risk of lung cancer among monomer-exposed women remains unknown. Results

suggesting that this association is not causal include the lack of an exposure-response trend among women and the finding that monomers were not associated with lung cancer among men. An association between monomers and COPD in men, seen in some analyses, is probably non-causal. Butadiene and styrene exposures were not consistently associated with the other outcomes analyzed.

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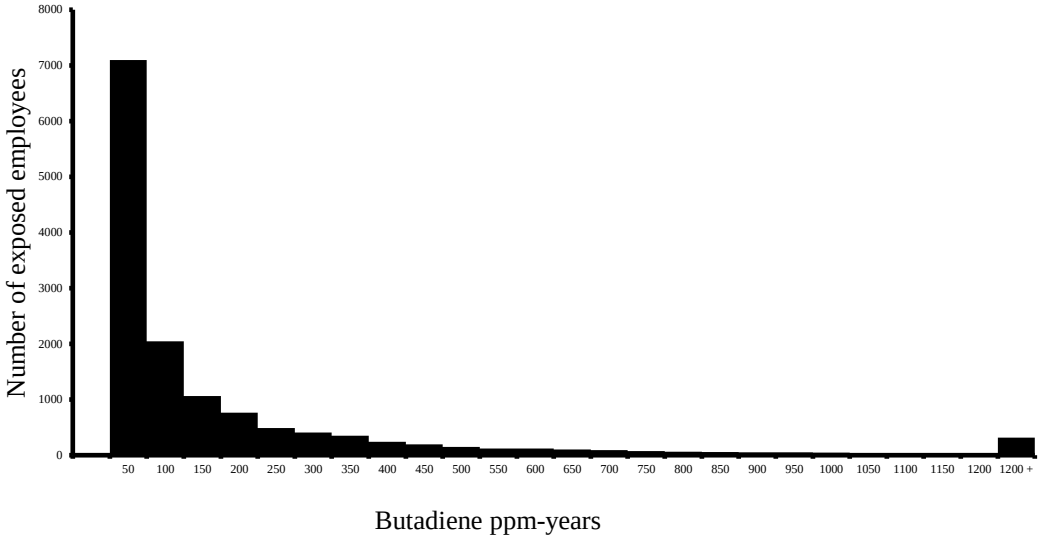


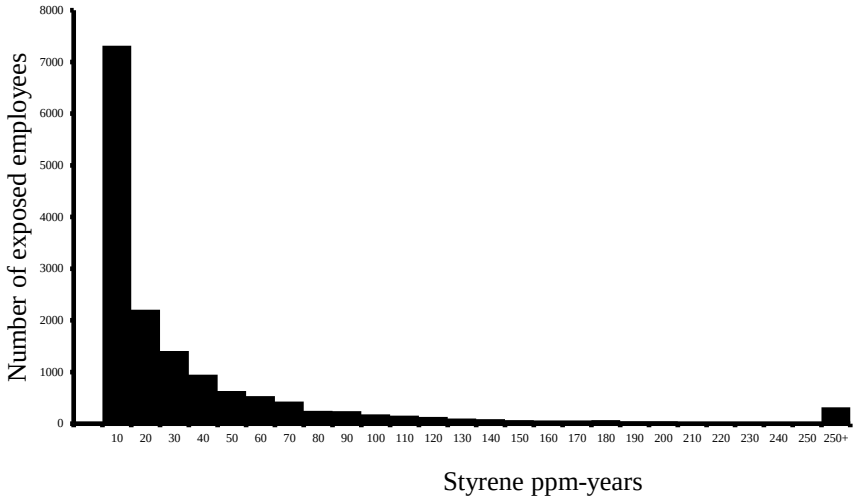
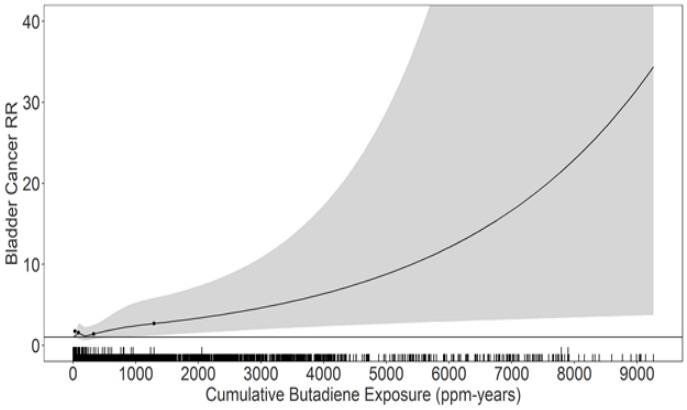
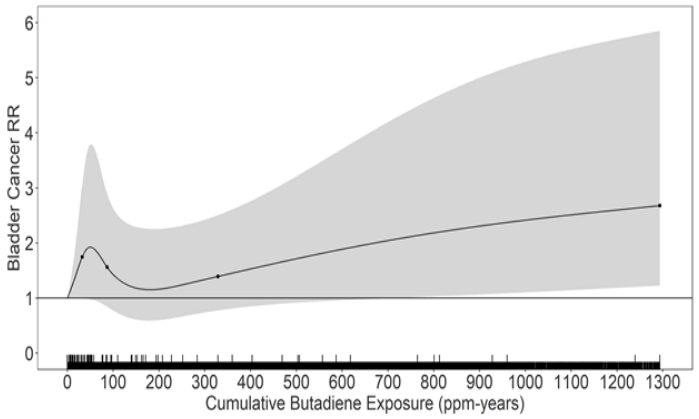


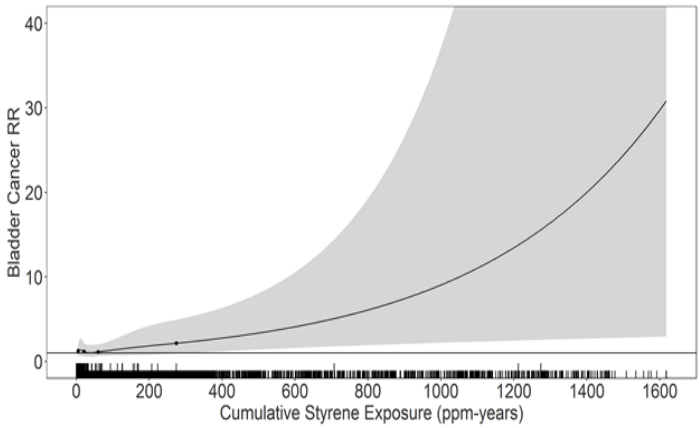
Figure 1. Distribution of exposed employees by butadiene and styrene ppm-years



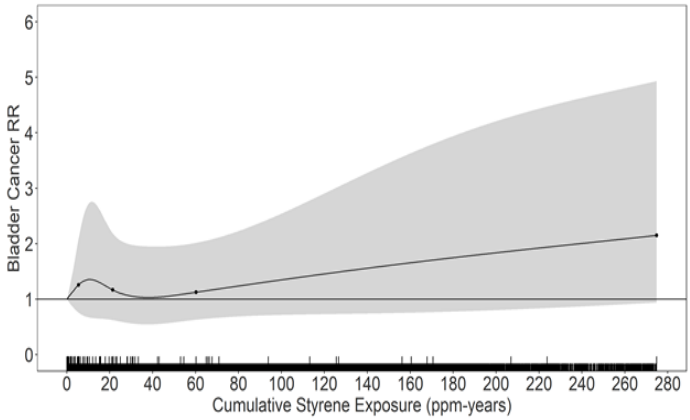
2a. Butadiene, all ppm-years (with Y-axis limit)



2b. Butadiene, up to 1,294 ppm-years



2c. Styrene, all ppm-years (with Y-axis limit)



2d. Styrene, up to 275 ppm-years

Figure 2. Restricted cubic splines for butadiene ppm-years and bladder cancer (2a and 2b) and styrene ppm-years and bladder cancer (2c and 2d). Panels 2a and 2c display curves for butadiene and styrene, respectively, over the entire range of exposure, while panels 2b and 2d focus on the part of the curves just below the 95th percentile of exposure values for butadiene (at 1,294 ppm-years) and styrene (at 275 ppm-years), respectively. Data rugs just above the X-axis of each figure depict the frequency of all observations (lower rug) and bladder cancers (upper rug) at corresponding monomer exposure values. Circles indicate cutpoints for quartiles 2, 3 and 4 and for the 95th percentile.

Table 1
Characteristics of workers at six synthetic rubber polymer plants

Characteristic[a]	All workers	Men	Women
Employees, N (%)	21,087 (100)	16,579 (100)	4,508 (100)
Person-years of follow-up	804,718	614,806	189,911
Plant, location, follow-up start year, N (%)			
1, Kentucky, 1960, 1960	1,563 (7)	1,391 (8)	172 (4)
2, Louisiana, 1944, 1943	2,463 (12)	1,988 (12)	475 (11)
3, Louisiana, 1944, 1943	2,849 (14)	2,084 (13)	765 (17)
4, Texas, 1944, 1943	2,929 (14)	2,328 (14)	601 (13)
5, Ontario, 1950, 1950	7,044 (33)	5,356 (32)	1,688 (37)
6, Texas, 1944, 1943	4,239 (20)	3,432 (21)	807 (18)
Race, N (%)			
White/unknown	18,674 (89)	14,486 (87)	4,188 (93)
Black/other	2,413 (11)	2,093 (13)	320 (7)
Payroll status, N (%)			
Ever hourly	15,109 (72)	13,830 (83)	1,279 (28)
Never hourly	5,978 (28)	2,749 (17)	3,229 (72)
Year of hire, median (IQR)	1959 (1949-1971)	1958 (1949-1970)	1960 (1947-1974)
Years worked as of the end of 1991, median (IQR)	8.3 (2.3-22)	11.8 (3.4-24)	1.7 (0.4-5.9)
Years since hire, median (IQR)	40.0 (30-49)	39.3 (30-48)	43.5 (32-53)
Age at end of follow-up, median (IQR)	69 (59-78)	69 (59-77)	69 (59-79)
Vital status, N (%)			
Alive	11,180 (53)	8,228 (50)	2,952 (65)
Deceased	9,665 (46)	8,214 (50)	1,451 (32)
Unknown	242 (1)	137 (<1)	105 (2)

[a]Abbreviations: N, number of subjects; IQR, interquartile range.

Table 2
Cumulative exposure to monomers as of the end of follow-up in the overall six-plant cohort and in cohort subgroups

Group (total number in group)	Butadiene ppm-years N (%)[a]	Butadiene ppm-years Median (IQR)[b]	Styrene ppm-years N (%)	Styrene ppm-years Median (IQR)
Total cohort (21,087)	14,004 (66)	48 (11-167)	15,422 (73)	11 (2.8-36)
Sex				
Male (16,579)	12,814 (77)	54 (13-178)	14,006 (84)	13 (3.4-38)
Female (4,508)	1,190 (26)	8.0 (1.6-45)	1,416 (31)	1.8 (0.3-11)
		p[c]=<0.0001		p=<0.0001
Plant, location				
1, Kentucky (1,563)	1,144 (73)	75 (15-245)	1,171 (75)	20 (5.8-48)
2, Louisiana (2,463)	1,815 (74)	72 (20-230)	1,782 (72)	16 (4.6-57)
3, Louisiana (2,849)	1,524 (53)	73 (15-320)	2,092 (73)	13 (3.7-48)
4, Texas (2,929)	1,690 (58)	38 (10-134)	2,227 (76)	5.9 (1.7-22)
5, Ontario (7,044)	4,936 (70)	43 (8.3-143)	4,846 (69)	12 (2.4-36)
6, Texas (4,239)	2,895 (68)	32 (8.6-120)	3,304 (78)	10 (2.5-29)
		p=<0.0001		p=<0.0001
Ever hourly				
Yes (15,109)	11,876 (79)	65 (16-203)	13,406 (89)	14 (3.6-42)
No (5,978)	2,128 (36)	7.4 (1.7-23)	2,016 (34)	2.5 (0.5-8.1)
		p=<0.0001		p=<0.0001
Race				
White (18,674)	12,273 (66)	44 (10-149)	13,297 (71)	10 (2.5-32)
Black (2,413)	1,731 (72)	105 (18-368)	2,125 (88)	24 (5.5-87)
		p=<0.0001		p=<0.0001
Hire year				
1943-1949 (5,404)	3,600 (67)	77 (20-253)	3,938 (73)	13 (3.8-48)
1950-1959 (5,613)	4,005 (71)	97 (30-266)	4,279 (76)	25 (6.4-56)
1960-1969 (4,333)	2,871 (66)	42 (11-130)	3,065 (71)	13 (3.3-34)
≥1970 (5,737)	3,528 (62)	12 (3.0-41)	4,140 (72)	3.8 (0.9-13)
		p=<0.0001		p=<0.0001

[a]Number of exposed employees (% of total number in each group).
[b]IQR, interquartile range.
[c]All p-values are from the Kruskal-Wallis test for differences in median values.

Table 3

Exposure-response analyses of butadiene or styrene ppm-years and bladder cancer: number (N) of cases, adjusted rate ratio (RR) with 95% confidence interval (CI) by exposure quartile, RR with 95% CI per 100 ppm-years (for butadiene) or 50 ppm-years (for styrene), beta-coefficient (β) with 95% CI and trend p-value

	Butadiene			Styrene		
Model[a]	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**
Quartile[b]						
Unexposed	17	1.0	ref	15	1.0	ref
1	18	1.18	0.59 to 2.35	18	1.07	0.51 to 2.23
2	18	1.69	0.82 to 3.47	19	1.18	0.56 to 2.49
3	18	1.19	0.57 to 2.47	19	1.16	0.54 to 2.48
4	19	2.13	1.03 to 4.41	19	1.64	0.76 to 3.54
Trend[c]						
All person-time	RR=1.04 (1.02 to 1.06), $\beta=3.84\times10^{-4}$ [(1.55 to 6.12) $\times10^{-4}$], p=0.001, N=90			RR=1.11 (1.03 to 1.19), $\beta=2.03\times10^{-3}$ [(0.66 to 3.40) $\times10^{-3}$], p=0.004, N=90		
Exposed person-time	RR=1.04 (1.01 to 1.06), $\beta=3.50\times10^{-4}$ [(1.05 to 5.95) $\times10^{-4}$], p=0.005, N= 73			RR=1.10 (1.03 to 1.18), $\beta=1.90\times10^{-3}$ [(0.50 to 3.31) $\times10^{-3}$], p=0.008, N=75		
Exposed person-time ≤95th percentile[d]	RR=1.05 (0.96 to 1.15), $\beta=4.72\times10^{-4}$ [(−4.36 to 13.79) $\times10^{-4}$], p=0.308, N=69			RR=1.18 (0.95 to 1.47), $\beta=3.31\times10^{-3}$ [(−1.09 to 7.71) $\times10^{-3}$], p=0.141, N=72		
Stratified[e] trend[c]						
Styrene <21 ppm-years	RR=1.06 (0.87 to 1.28), $\beta=5.56\times10^{-4}$ [(−13.78 to 24.90) $\times10^{-4}$], p=0.573, N=52					
Styrene ≥21 ppm-years	RR= 1.04 (1.02 to 1.07), $\beta=4.30\times10^{-4}$ [(1.53 to 7.07) $\times10^{-4}$], p=0.002, N=38					
Butadiene <87 ppm-years				RR=0.97 (0.50 to 1.89), $\beta=-0.53\times10^{-3}$ [(−13.81 to 12.75) $\times10^{-3}$], p=0.938, N=53		
Butadiene ≥87 ppm-years				RR=1.09 (1.00 to 1.18), $\beta=1.67\times10^{-3}$ [(0.09 to 3.25) $\times10^{-3}$], p=0.039, N=37		

[a]All models used attained age as of each day of follow-up as the time scale. Except where indicated, covariates were age at hire, year of hire, race, sex, plant and ever hourly status.

[b]Quartile (Q) cutpoints were at the following values of ppm-years:

- butadiene: Q2, 32.37; Q3, 86.87; Q4, 328.79, maximum=7899.68
- styrene: Q2, 5.45; Q3, 21.37; Q4, 60.26, maximum=1273.99.

[c]Trend results are displayed as: RR (95% CI) per 100 ppm-years for butadiene or per 50 ppm-years for styrene; β [95% CI], trend p-value and N cases.

[d]95th percentile was at 1,294 ppm-years for butadiene and 275 ppm-years for styrene.

[e]Models used all person-time. Analyses within lower monomer exposure strata were restricted to Whites due to lack of an event in Blacks/other.

Table 4

Butadiene ppm-years, styrene ppm-years and lung cancers: number (N) of cases, adjusted rate ratio (RR) with 95% confidence interval (CI) by exposure quartile, beta-coefficient (β) with 95% confidence interval (CI) and trend p-values

Butadiene ppm-years, model[a]	**Lung cancer (men)**			**Lung cancer (women)**		
	N	**RR**	**95% CI**	**N**	**RR**	**95% CI**
Quartile						
Unexposed	164	1.0	ref	77	1.0	ref
1	154	0.94	0.75 to 1.17	14	2.47	1.37 to 4.43
2	155	1.01	0.81 to 1.27	14	1.94	1.08 to 3.47
3	154	0.90	0.72 to 1.13	14	1.90	1.03 to 3.51
4	155	0.86	0.68 to 1.09	14	1.48	0.76 to 2.90
Trend[b]						
All person-time	$\beta=3.14\text{x}10^{-6}$ [(−124.31 to 130.59) $\text{x}10^{-6}$], p=0.962, N=782			$\beta=-0.03\text{x}10^{-3}$ [(−1.48 to 1.43) $\text{x}10^{-3}$], p=0.971, N=133		
Exposed person-time	$\beta=32.40\text{x}10^{-6}$ [(−97.10 to 161.93) $\text{x}10^{-6}$], p=0.624, N=618			$\beta=-1.01\text{x}10^{-3}$ [(−2.81 to 0.79) $\text{x}10^{-3}$], p=0.272, N=56		
Exposed person-time ≤95th percentile[c]	$\beta=-288.70\text{x}10^{-6}$ [(−746.18 to 168.71) $\text{x}10^{-6}$], p=0.216, N=587			$\beta=-1.24\text{x}10^{-3}$ [(−4.36 to 1.89) $\text{x}10^{-3}$], p=0.439, N=53		
Styrene ppm-years, model[a]	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**
Quartile						
Unexposed	105	1.0	ref	76	1.0	ref
1	169	1.07	0.83 to 1.37	14	1.49	0.81 to 2.76
2	169	1.10	0.86 to 1.41	14	1.23	0.67 to 2.26
3	169	0.91	0.71 to 1.18	14	2.31	1.22 to 4.36
4	170	0.89	0.68 to 1.15	15	1.65	0.84 to 3.25
Trend						
All person-time	$\beta=1.23\text{x}10^{-5}$ [(−65.93 to 68.39) $\text{x}10^{-5}$], p=0.971, N=782			$\beta=-0.38\text{x}10^{-3}$ [(−5.16 to 4.39) $\text{x}10^{-3}$], p=0.875, N=133		
Exposed person-time	$\beta=1.57\text{x}10^{-5}$ [(−66.27 to 69.41) $\text{x}10^{-5}$], p=0.964, N=677			$\beta=-2.10\text{x}10^{-3}$ [(−7.46 to 3.26) $\text{x}10^{-3}$], p=0.442, N=57		
Exposed person-time ≤95th percentile of ppm-years[d]	$\beta=-131.00\text{x}10^{-5}$ [(−374.78 to 113.76) $\text{x}10^{-5}$], p=0.295, N=644			$\beta=-1.06\text{x}10^{-3}$ [(−11.78 to 9.66) $\text{x}10^{-3}$], p=0.846, N=54		

[a]Models used attained age as of each day of follow-up as the time scale. Covariates were age at hire, year of hire, race, plant and ever hourly status. Monomer exposure quartile (Q) cutpoints (in ppm-years) were as follows:

- butadiene: men - Q2, 25.36; Q3, 81.18; Q4, 235.56, maximum=7026.58; women - Q2, 1.94; Q3, 12.09; Q4, 56.35, maximum=676.40
- styrene: men - Q2, 4.71; Q3, 16.19; Q4, 45.26, maximum=1283.93 (men); women - Q2, 0.67; Q3, 6.07; Q4, 22.37, maximum=246.90

[b]Trend results are displayed as: β [95% CI], trend p-value and N cases.

[c]95th percentile of butadiene lung cancer: 968 ppm-years for men and 529 ppm-years for women.

[d]95th percentile of styrene ppm-years: lung cancer: 169 ppm-years for men and 157 ppm-years for women.

Table 5

Butadiene ppm-years, styrene ppm-years and other cancers: number (N) of cases, adjusted rate ratio (RR) with 95% confidence interval (CI) by exposure quartile (Q), beta-coefficient (β) with 95% confidence interval (CI) and trend p-value

Butadiene ppm-years, model[a]	**Esophageal cancer (men)**			**Pancreatic cancer**			**Kidney cancer**		
	N	**RR**	**95% CI**	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**
Quartile									
Unexposed	9	1.0	ref	43	1.0	ref	19	1.0	ref
1	14	1.00	0.43 to 2.32	28	0.95	0.58 to 1.57	13	0.76	0.37 to 1.57
2	15	1.93	0.82 to 4.54	28	1.03	0.61 to 1.73	13	1.25	0.60 to 2.64
3	14	1.53	0.64 to 3.70	28	1.12	0.65 to 1.91	13	0.89	0.42 to 1.89
4	15	1.98	0.82 to 4.81	28	1.48	0.86 to 2.55	13	0.86	0.40 to 1.85
Trend[b]									
All person-time	$\beta=-0.81\times10^{-4}$ [(−7.05 to 5.42) $\times10^{-4}$], p=0.799, N=67			$\beta=1.30\times10^{-4}$ [(−1.05 to 3.64) $\times10^{-4}$], p=0.278, N=155			$\beta=-5.86\times10^{-4}$ [(−17.41 to 5.68) $\times10^{-4}$], p=0.320, N=71		
Exposed person-time	$\beta=-1.19\times10^{-4}$ [(−8.61 to 6.24) $\times10^{-4}$], p=0.754, N=58			$\beta=1.15\times10^{-4}$ [(−1.34 to 3.63) $\times10^{-4}$], p=0.366, N=112			$\beta=-6.39\times10^{-4}$ [(−18.51 to 5.72) $\times10^{-4}$], p=0.301, N=52		
Exposed person-time ≤95th percentile ppm-years[c]	$\beta=11.00\times10^{-4}$ [(−5.40 to 27.40) $\times10^{-4}$], p=0.189, N=55			$\beta=2.80\times10^{-4}$ [(−5.77 to 11.36) $\times10^{-4}$], p=0.523, N=106			$\beta=5.95\times10^{-4}$ [(−17.81 to 29.70) $\times10^{-4}$], p=0.624, N=49		
Styrene ppm-years, model[a]	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**
Quartile									
Unexposed	7	1.0	ref	31	1.0	ref	17	1.0	ref
1	15	1.11	0.44 to 2.77	31	1.31	0.76 to 2.25	13	0.65	0.30 to 1.39
2	15	1.50	0.59 to 3.80	31	1.57	0.89 to 2.77	14	0.76	0.36 to 1.62
3	15	1.77	0.69 to 4.58	31	0.86	0.48 to 1.54	13	0.63	0.29 to 1.39
4	15	1.70	0.65 to 4.49	31	1.75	0.96 to 3.19	14	0.68	0.31 to 1.52
Trend									
All person-time	$\beta=0.10\times10^{-4}$ [(−25.12 to 25.32) $\times10^{-4}$], p=0.994, N=67			$\beta=7.83\times10^{-4}$ [(−4.21 to 19.87) $\times10^{-4}$], p=0.202, N=155			$\beta=-1.03\times10^{-3}$ [(−5.67 to 3.60) $\times10^{-3}$], p=0.662, N=71		
Exposed person-time	$\beta=-3.23\times10^{-4}$ [(−30.77 to 24.30) $\times10^{-4}$], p =0.818, N=60			$\beta=7.40\times10^{-4}$ [(−5.40 to 20.21) $\times10^{-4}$], p=0.257, N=124			$\beta=-0.53\times10^{-3}$ [(−4.78 to 3.72) $\times10^{-3}$], p=0.807, N=54		

Exposed person-time ≤95th percentile ppm-years[d]	$\beta=26.50x10^{-4}$ [(−46.42 to 99.50) $x10^{-4}$], p=0.476, N=57	$\beta=23.40x10^{-4}$ [(−22.90 to 69.77) $x10^{-4}$], p=0.322, N=117	$\beta=1.45x10^{-3}$ [(−8.38 to 11.29) $x10^{-3}$], p=0.772, N=51

[a]Models used attained age as of each day of follow-up as the time scale. Covariates were age at hire, year of hire, race, sex (except for esophageal cancer, restricted to men), plant and ever hourly status. Monomer exposure quartile (Q) cutpoints (in ppm-years) were as follows:

- butadiene: esophageal cancer - Q2, 41.73; Q3, 99.59; Q4, 284.63, maximum=1209.26; pancreatic cancer - Q2, 26.42; Q3, 98.51; Q4, 309.87, maximum=7266.03; kidney cancer - Q2, 28.06; Q3, 67.79; Q4, 198.09, maximum=876.87
- styrene: esophageal cancer - Q2, 7.48; Q3, 24.29; Q4, 54.85, maximum=477.16; pancreatic cancer - Q2, 4.12; Q3, 12.99; Q4, 61.00, maximum=1163.93; kidney cancer - Q2, 4.45; Q3, 15.45; Q4, 41.96, maximum=235.40.

[b]Trend results are displayed as: β [95% CI], trend p-value and N cases.

[c]95th percentile of butadiene ppm-years: 698 ppm-years for esophageal cancer (men only), 1,148 ppm-years for pancreatic cancer and 518 ppm-years for kidney cancer.

[d]95th percentile of styrene ppm-years: 163 ppm-years for esophageal cancer (men only), 193 ppm-years for pancreatic cancer and 140 ppm-years for kidney cancer.

Table 6

Butadiene ppm-years, styrene ppm-years and non-malignant respiratory disease among men: number (N) of cases, adjusted rate ratio (RR) with 95% confidence interval (CI) by exposure quartile (Q), beta-coefficient (β) with 95% confidence interval (CI) and trend p-value

Butadiene ppm-years, model[a]	**Non-malignant respiratory disease**			**COPD**			**Pneumonia**		
	N	**RR**	**95% CI**	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**
Quartile									
Unexposed	288	1.0	ref	113	1.0	ref	103	1.0	ref
1	285	1.00	0.85 to 1.18	128	1.14	0.88 to 1.47	102	1.10	0.83 to 1.45
2	285	1.06	0.90 to 1.25	129	1.13	0.88 to 1.47	102	1.10	0.83 to 1.45
3	285	1.06	0.89 to 1.25	129	1.17	0.90 to 1.51	102	1.11	0.84 to 1.47
4	285	1.05	0.88 to 1.24	129	1.18	0.91 to 1.54	102	1.02	0.77 to 1.36
Trend[b]									
All person-time	$\beta=0.38x10^{-4}$ [(−0.50 to 1.25) $x10^{-4}$], p=0.398, N=1428			$\beta=1.42x10^{-4}$ [(0.16 to 2.66) $x10^{-4}$], p=0.027, N=628			$\beta=0.68x10^{-4}$ [(−0.67 to 2.04) $x10^{-4}$], p=0.323, N=511		
Exposed person-time	$\beta=0.41x10^{-4}$ [(−0.50 to 1.33) $x10^{-4}$], p=0.378, N=1140			$\beta=1.12x10^{-4}$ [(−0.19 to 2.43) $x10^{-4}$], p=0.095, N=515			$\beta=0.70x10^{-4}$ [(−0.75 to 2.14) $x10^{-4}$], p=0.343, N=408		
Exposed person-time ≤95th percentile ppm-years[c]	$\beta=0.88x10^{-4}$ [(−2.29 to 4.05) $x10^{-4}$], p=0.588, N=1083			$\beta=0.81x10^{-4}$ [(−4.08 to 5.70) $x10^{-4}$], p=0.746, N=489			$\beta=-1.73x10^{-4}$ [(−7.06 to 3.61) $x10^{-4}$], p=0.526, N=387		
Styrene ppm-years, model[a]	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**
Quartile									
Unexposed	198	1.0	ref	83	1.0	ref	74	1.0	ref
1	307	0.98	0.82 to 1.18	136	1.05	0.79 to 1.39	109	1.07	0.79 to 1.44
2	308	1.04	0.86 to 1.24	136	1.15	0.87 to 1.52	109	1.11	0.82 to 1.50
3	307	1.02	0.85 to 1.23	136	1.01	0.76 to 1.34	109	0.93	0.69 to 1.27
4	308	1.05	0.86 to 1.27	137	1.09	0.82 to 1.46	110	1.00	0.73 to 1.37
Trend									
All person-time	$\beta=1.05x10^{-4}$ [(−3.72 to 5.82) $x10^{-4}$], p=0.666, N=1428			$\beta=7.00x10^{-4}$ [(0.29 to 13.71) $x10^{-4}$], p=0.041, N=628			$\beta=3.59x10^{-4}$ [(−3.53 to 10.72) $x10^{-4}$], p=0.323, N=511		
Exposed person-time	$\beta=0.77x10^{-4}$ [(−4.11 to 5.65) $x10^{-4}$], p=0.757, N=1230			$\beta=6.06x10^{-4}$ [(−0.79 to 12.91) $x10^{-4}$], p=0.083, N=545			$\beta=3.42x10^{-4}$ [(−3.92 to 10.75) $x10^{-4}$], p=0.361, N=437		
Exposed person-time ≤95th percentile ppm-years[d]	$\beta=6.78x10^{-4}$ [(−10.07 to 23.63) $x10^{-4}$], p=0.430, N=1168			$\beta=13.70x10^{-4}$ [(−11.69 to 39.05) $x10^{-4}$], p=0.291, N=517			$\beta=-13.80x10^{-4}$ [(−39.95 to 12.28) $x10^{-4}$], p=0.299, N=416		

[a]Models used attained age as of each day of follow-up as the time scale. Covariates were age at hire, year of hire, race, plant and ever hourly status. Monomer exposure quartile

(Q) cutpoints (in ppm-years) were as follows:

- butadiene: all non-malignant respiratory disease - Q2, 28.67; Q3, 94.39; Q4, 262.23, maximum=9263.97; COPD - Q2, 27.36; Q3, 94.57; Q4, 261.15, maximum=9263.97; pneumonia - Q2, 25.74; Q3, 88.44; Q4, 245.85, maximum=7724.27
- styrene: all non-malignant respiratory disease - Q2, 5.61; Q3, 20.70; Q4, 50.19, maximum=1618.29; COPD - Q2, 5.50; Q3, 19.16; Q4, 48.20, maximum=1618.29; pneumonia - Q2, 4.99; Q3, 16.94; Q4, 46.48, maximum=1369.02.

[b]Trend results are displayed as: β [95% CI], trend p-value and N cases.

[c]95th percentile of butadiene ppm-years: 943 ppm-years for all non-malignant respiratory disease, 915 ppm-years for COPD and 979 ppm-years for pneumonia.

[d]95th percentile of styrene ppm-years: 173 ppm-years for all non-malignant respiratory disease, 170 ppm-years for COPD and 209 ppm-years for pneumonia.

Table 7

Butadiene ppm-years, styrene ppm-years and non-malignant respiratory disease among women: number (N) of cases, adjusted rate ratio (RR) with 95% confidence interval (CI) by exposure quartile (Q), beta-coefficient (β) with 95% confidence interval (CI) and trend p-value

Butadiene ppm-years, model[a]	**Non-malignant respiratory disease**			**COPD**			**Pneumonia**		
	N	**RR**	**95% CI**	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**
Quartile									
Unexposed	242	1.0	ref	109	1.0	ref	87	1.0	ref
1	17	0.76	0.46 to 1.25	5	0.51	0.21 to 1.26	6	0.90	0.39 to 2.10
2	18	0.81	0.49 to 1.32	6	0.46	0.20 to 1.06	7	1.26	0.57 to 2.81
3	17	0.89	0.52 to 1.50	5	0.94	0.37 to 2.40	6	0.76	0.32 to 1.84
4	18	0.79	0.46 to 1.36	6	0.43	0.18 to 1.05	7	0.78	0.32 to 1.91
Trend[b]									
All person-time	$\beta=-2.98x10^{-4}$ [(−12.88 to 6.92) $x10^{-4}$], p=0.555, N=312			$\beta=-1.05x10^{-3}$ [(−3.25 to 1.15) $x10^{-3}$], p=0.349, N=131			$\beta=-0.53x10^{-3}$ [(−2.03 to 0.98) $x10^{-3}$], p=0.494, N=113		
Exposed person-time	$\beta=-2.44x10^{-4}$ [(−14.09 to 9.21) $x10^{-4}$], p=0.681, N=70[e]			$\beta=-0.27x10^{-3}$ [(−2.69 to 2.15) $x10^{-3}$], p=0.829, N=22[f]			$\beta=-0.43x10^{-3}$ [(−2.32 to 1.47) $x10^{-3}$], p=0.661, N=26[f]		
Exposed person-time ≤95th percentile ppm-years[c]	$\beta=11.60x10^{-4}$ [(−7.96 to 31.22) $x10^{-4}$], p=0.245, N=66[e]			$\beta=1.80x10^{-3}$ [(−3.58 to 7.18) $x10^{-3}$], p=0.512, N=20[f]			$\beta=0.47x10^{-3}$ [(−2.62 to 3.56) $x10^{-3}$], p=0.766, N=24[f]		
Styrene ppm-years, model[a]	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**
Quartile									
Unexposed	220	1.0	ref	101	1.0	ref	79	1.0	ref
1	23	0.94	0.59 to 1.49	7	0.51	0.23 to 1.14	8	1.12	0.52 to 2.45
2	23	1.45	0.92 to 2.28	8	1.03	0.49 to 2.20	9	1.48	0.70 to 3.13
3	23	0.66	0.42 to 1.05	7	0.35	0.16 to 0.79	8	0.97	0.45 to 2.11
4	23	0.86	0.52 to 1.42	8	0.52	0.23 to 1.18	9	0.92	0.40 to 2.10
Trend									
All person-time	$\beta=-1.19x10^{-3}$ [(−4.28 to 1.89) $x10^{-3}$], p=0.448, N=312			$\beta=-3.39x10^{-3}$ [(−9.85 to 3.07) $x10^{-3}$], p=0.304, N=131			$\beta=-1.79x10^{-3}$ [(−6.57 to 2.98) $x10^{-3}$], p=0.461, N=113		
Exposed person-time	$\beta=-1.30x10^{-3}$ [(−4.74 to 2.15) $x10^{-3}$], p=0.461, N=92			$\beta=-1.60x10^{-3}$ [(−8.40 to 5.20) $x10^{-3}$], p=0.645, N=30[f]			$\beta=-1.85x10^{-3}$ [(−7.20 to 3.50) $x10^{-3}$], p=0.497, N=34[f]		
Exposed person-time ≤95th percentile ppm-years[d]	$\beta=1.07x10^{-3}$ [(−5.57 to 7.70) $x10^{-3}$], p=0.752, N=87			$\beta=2.84x10^{-3}$ [(−11.65 to 17.33) $x10^{-3}$], p=0.701, N=28[f]			$\beta=0.28x10^{-3}$ [(−10.21 to 10.76) $x10^{-3}$], p=0.959, N=32[f]		

[a]Models used attained age as of each day of follow-up as the time scale. Covariates were age at hire, year of hire, race, plant and ever hourly status, except as noted. Monomer exposure quartile (Q) cutpoints (in ppm-years) were as follows:

- butadiene: all non-malignant respiratory disease - Q2, 4.14; Q3, 21.25; Q4, 97.71, maximum=1013.74; COPD - Q2, 3.46; Q3, 25.78; Q4, 56.35, maximum=676.40; pneumonia - Q2, 4.28; Q3, 14.55; Q4, 118.37, maximum=722.88
- styrene: all non-malignant respiratory disease - Q2, 0.70; Q3, 2.14; Q4, 26.99, maximum=322.18; COPD - Q2, 0.73; Q3, 1.98; Q4, 22.91, maximum=178.00; pneumonia - Q2, 0.67; Q3, 2.77; Q4, 23.73, maximum, 322.18.

[b]Trend results are displayed as: β [95% CI], trend p-value and N cases.
[c]95th percentile of butadiene ppm-years: 576 ppm-years for all non-malignant respiratory disease, 440 ppm-years for COPD and 576 ppm-years for pneumonia.
[d]95th percentile of styrene ppm-years: 173 ppm-years for all non-malignant respiratory disease, 147 ppm-years for COPD and 173 ppm-years for pneumonia.
[e]Model excluded women at plant 1 due to lack of a case.
[f]Model excluded women at plant 1 and nonwhites due to lack of a case in those subgroups.

Table 8

Adjusted[a] beta-coefficient (β) with 95% confidence interval (CI) and trend p-value for the relation between butadiene or styrene ppm-years, lagged 10 or 20 years, and outcomes of interest

	ppm-years, lagged 10 years			ppm-years, lagged 20 years		
***Monomer*, Outcome[b]**	**β**	**95% CI**	**Trend p-value**	**β**	**95% CI**	**Trend p-value**
Butadiene						
Bladder cancer	$3.87x10^{-4}$	$(1.53 \text{ to } 6.21)x10^{-4}$	0.001	$4.22x10^{-4}$	$(1.64 \text{ to } 6.80)x10^{-4}$	0.001
Lung cancer, men	$-2.02x10^{-5}$	$(-16.64 \text{ to } 12.60)x10^{-5}$	0.786	$-4.54x10^{-5}$	$(-23.18 \text{ to } 14.11)x10^{-5}$	0.633
Lung cancer, women	$-1.61x10^{-5}$	$(-156.79 \text{ to } 153.56)x10^{-5}$	0.984	$-9.76x10^{-5}$	$(-200.35 \text{ to } 180.83)x10^{-5}$	0.920
Esophageal cancer[c]	$-1.37x10^{-4}$	$(-8.67 \text{ to } 5.94)x10^{-4}$	0.714	$-1.09x10^{-4}$	$(-9.54 \text{ to } 7.35)x10^{-4}$	0.800
Pancreatic cancer	$1.19x10^{-4}$	$(-1.37 \text{ to } 3.75)x10^{-4}$	0.363	$0.79x10^{-4}$	$(-2.60 \text{ to } 4.19)x10^{-4}$	0.647
Kidney cancer	$-5.97x10^{-4}$	$(-18.14 \text{ to } 6.19)x10^{-4}$	0.336	$-5.85x10^{-4}$	$(-19.89 \text{ to } 8.19)x10^{-4}$	0.414
NMRD, men	$0.36x10^{-4}$	$(-0.56 \text{ to } 1.27)x10^{-4}$	0.443	$0.13x10^{-4}$	$(-0.96 \text{ to } 1.22)x10^{-4}$	0.816
NMRD, women	$-0.52x10^{-3}$	$(-1.60 \text{ to } 0.56)x10^{-3}$	0.347	$-0.94x10^{-3}$	$(-2.28 \text{ to } 0.40)x10^{-3}$	0.169
COPD, men	$1.49x10^{-4}$	$(0.21 \text{ to } 2.78)x10^{-4}$	0.023	$1.65x10^{-4}$	$(0.20 \text{ to } 3.09)x10^{-4}$	0.026
COPD, women	$-1.29x10^{-3}$	$(-3.68 \text{ to } 1.10)x10^{-3}$	0.290	$-2.56x10^{-3}$	$(-6.07 \text{ to } 0.95)x10^{-3}$	0.153
Pneumonia, men	$0.51x10^{-4}$	$(-0.95 \text{ to } 1.97)x10^{-4}$	0.491	$0.24x10^{-4}$	$(-1.48 \text{ to } 1.96)\ x10^{-4}$	0.786
Pneumonia, women	$-1.01x10^{-3}$	$(-2.80 \text{ to } 0.77)x10^{-3}$	0.265	$-1.80x10^{-3}$	$(-4.29 \text{ to } 0.69)x10^{-3}$	0.157
Styrene						
Bladder cancer	$1.95x10^{-3}$	$(0.50 \text{ to } 3.41)x10^{-3}$	0.008	$2.19x10^{-3}$	$(0.50 \text{ to } 3.87)x10^{-3}$	0.011
Lung cancer, men	$-1.12x10^{-4}$	$(-8.78 \text{ to } 6.53)x10^{-4}$	0.774	$-2.47x10^{-4}$	$(-12.16 \text{ to } 7.22)x10^{-4}$	0.617

Table 8

Adjusted[a] beta-coefficient (β) with 95% confidence interval (CI) and trend p-value for the relation between butadiene or styrene ppm-years, lagged 10 or 20 years, and outcomes of interest

	ppm-years, lagged 10 years			ppm-years, lagged 20 years		
***Monomer*, Outcome[b]**	**β**	**95% CI**	**Trend p-value**	**β**	**95% CI**	**Trend p-value**
Lung cancer, women	$-1.92\text{x}10^{-4}$	$(-51.46 \text{ to } 47.63)\text{x}10^{-4}$	0.940	$-4.25\text{x}10^{-4}$	$(-62.44 \text{ to } 53.94)\text{x}10^{-4}$	0.886
Esophageal cancer[c]	$1.52\text{x}10^{-4}$	$(-25.11 \text{ to } 28.15)\text{x}10^{-4}$	0.911	$5.84\text{x}10^{-4}$	$(-24.00 \text{ to } 35.68)\text{x}10^{-4}$	0.701
Pancreatic cancer	$8.09\text{x}10^{-4}$	$(-4.68 \text{ to } 20.85)\text{x}10^{-4}$	0.214	$8.24\text{x}10^{-4}$	$(-7.06 \text{ to } 23.54)\text{x}10^{-4}$	0.291
Kidney cancer	$-1.06\text{x}10^{-3}$	$(-5.99 \text{ to } 3.87)\text{x}10^{-3}$	0.673	$-0.95\text{x}10^{-3}$	$(-7.08 \text{ to } 5.18)\text{x}10^{-3}$	0.761
NMRD, men	$1.00\text{x}10^{-4}$	$(-3.98 \text{ to } 5.97)\text{x}10^{-4}$	0.694	$0.19\text{x}10^{-4}$	$(-5.68 \text{ to } 6.05)\text{x}10^{-4}$	0.950
NMRD, women	$-1.59\text{x}10^{-3}$	$(-4.85 \text{ to } 1.67)\text{x}10^{-3}$	0.339	$-2.46\text{x}10^{-3}$	$(-6.28 \text{ to } 1.36)\text{x}10^{-3}$	0.207
COPD, men	$7.25\text{x}10^{-4}$	$(0.26 \text{ to } 14.24)\ \text{x}10^{-4}$	0.042	$8.08\text{x}10^{-4}$	$(-0.04 \text{ to } 16.21)\text{x}10^{-4}$	0.051
COPD, women	$-3.89\text{x}10^{-3}$	$(-10.75 \text{ to } 2.97)\text{x}10^{-3}$	0.267	$-6.65\text{x}10^{-3}$	$(-15.86 \text{ to } 2.55)\text{x}10^{-3}$	0.157
Pneumonia, men	$2.97\text{x}10^{-4}$	$(-4.58 \text{ to } 10.53)\text{x}10^{-4}$	0.441	$1.81\text{x}10^{-4}$	$(-7.09 \text{ to } 10.72)\text{x}10^{-4}$	0.690
Pneumonia, women	$-2.61\text{x}10^{-3}$	$(-7.89 \text{ to } 2.67)\text{x}10^{-3}$	0.333	$-3.88\text{x}10^{-3}$	$(-10.39 \text{ to } 2.63)\text{x}10^{-3}$	0.243

[a]Models used attained age as the time scale and included all person-time. Covariates were age at hire, year of hire, sex (for bladder, pancreatic and kidney cancers), race, plant and ever-hourly status.

[b]Abbreviations: NMRD, non-malignant respiratory disease; COPD, chronic obstructive pulmonary disease.

[c]Analyses were restricted to men, due to small number of events among women.