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1,3-Butadiene, styrene and lymphohaematopoietic cancers among North American synthetic rubber polymer workers: exposure–response analyses

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ABSTRACT

Objective To evaluate exposure–response between 1,3-butadiene, styrene and lymphohaematopoietic cancers in an updated cohort of workers at six North American plants that made synthetic rubber polymers.

Methods Employees were followed from 1943 through 2009 to determine mortality outcomes. Cox regression analyses estimated rate ratios (RRs) and 95% CIs by quartile of cumulative exposure to butadiene or styrene, measured in parts per million-years (ppm-years), and exposure–response trends for all leukaemia, lymphoid leukaemia, myeloid leukaemia, acute myeloid leukaemia, non-Hodgkin's lymphoma (NHL), multiple myeloma and all B-cell malignancies.

Results Among 21 087 workers, adjusted RRs for butadiene and all leukaemia (132 deaths) rose with increasing exposure, with an RR of 2.53 (95% CI 1.37 to 4.67) in the highest exposure quartile (≥363.64 ppm-years), and the exposure–response trend was statistically significant for all leukaemia (p=0.014) and for lymphoid leukaemia (52 deaths, p=0.007). Styrene exposure–response trends for all leukaemia and lymphoid leukaemia were less consistent than those for butadiene. Cumulative exposures to butadiene and styrene were not associated consistently with myeloid leukaemias or the B-cell malignancies, NHL and multiple myeloma.

Conclusions We confirmed a positive exposure–response relationship between butadiene and all leukaemia among workers, most of whom had coexposure to styrene. Results supported an association between butadiene and lymphoid leukaemia, but not myeloid leukaemia, and provided little evidence of any association of butadiene or styrene exposures with major subtypes of B-cell malignancies other than lymphoid leukaemia, including NHL and multiple myeloma.

Key messages

What is already known about this subject?

► Workers in the synthetic rubber industry are exposed to butadiene and styrene. Our previous research on the largest cohort of synthetic rubber industry workers indicated that male workers had an excess of leukaemia that was likely to have been due to butadiene or butadiene plus styrene and other chemicals. The International Agency for Research on Cancer (IARC) and other agencies have classified butadiene as a human carcinogen causing lymphohaematopoietic cancer, especially leukaemia, and classified styrene as probably carcinogenic to humans.

What are the new findings?

► The study confirmed a positive exposure–response relationship between butadiene and all leukaemia among workers with coexposure to styrene, supporting the IARC classification of butadiene as a known human carcinogen. Results supported an association between butadiene and lymphoid leukaemia, but not myeloid leukaemia. There was less support for an independent causal association between styrene and leukaemia.

How might this impact on policy or clinical practice in the foreseeable future?

► In 2019, The US Environmental Protection Agency included butadiene in its list of 20 substances designated as high-priority for risk re-evaluation. Thus, butadiene will move through the process required by Toxic Substances Control Act (TSCA) to evaluate any unreasonable risk it may present to human health or the environment. The results will inform the management of this chemical under TSCA.

INTRODUCTION

Synthetic rubber polymer manufacturing began in the USA and Canada in the early 1940s. Operations at the plants included in the present study have been described in detail previously.[1] Styrene-butadiene rubber (SBR), a copolymer of 1,3-butadiene and styrene, initially was the main type of synthetic rubber produced. At all of the plants, SBR production areas included polymerisation, coagulation and finishing, with tank farm, laboratory, maintenance, warehouse and utilities support operations. Workers at the plants were exposed potentially to butadiene and styrene monomers and other chemicals. Monomer exposure potential varied by work area, type of job and time period. Exposure levels were relatively high in the 1940s and 1950s and declined thereafter due to changes in production, work practices and engineering controls. The International Agency for Research on Cancer (IARC),[2 3] the US National Toxicology Programme[4]

and other agencies have classified butadiene as a human carcinogen causing lymphohaematopoietic cancer (LHC), especially leukaemia. In 2019, The US Environmental Protection Agency listed butadiene as a high-priority for risk evaluation.[5] IARC has classified styrene as probably carcinogenic to humans (Group 2A), based on limited evidence of carcinogenicity in humans and sufficient evidence in experimental animals.[6]

This paper describes internal analyses of the exposure–response relation between cumulative exposure to butadiene and styrene and mortality from LHCs in the largest cohort of synthetic rubber polymer workers, adding to two previous papers that presented preliminary exposure–response analyses of all leukaemia, non-Hodgkin's lymphoma (NHL) and multiple myeloma.[7 8] New aspects of this paper include analyses by quartile of cumulative exposure to monomers for women and men combined, with beta coefficients (β) for the slope of the exposure–response curve and corresponding 95% CIs; results pertaining to B-cell malignancies; results for acute myeloid leukaemia (AML), reported to be associated with styrene exposure[5]; results for each monomer and leukaemia, stratified by exposure to the other monomer 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.

METHODS

Overview of study design and cohort data

Sathiakumar *et al*[8] 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 update included 17 924 men employed for at least 1 year and 4861 women employed for at least 1 day before 1 January 1992. Turnover among male employees in the first year of employment at the plants was large. The 1 year duration of employment criterion was imposed on the large male cohort to maximise informativeness. A similar restriction was deemed unnecessary for the smaller female cohort.

Quantitative butadiene and styrene monomer exposure estimates previously were developed for six of the eight plants by investigators who were blinded to disease outcomes.[9] All analyses were restricted to 21 087 employees who had worked only at these six plants.

Work histories and monomer exposure estimates were available through the end of 1991. We did not obtain post-1991 job histories for 4079 workers who were actively employed at the end of 1991. In their last 1991 job, 46% were exposed to monomers, but their exposures were relatively low (median values, 1.1 parts per million (ppm) for butadiene and 0.4 ppm for styrene). Exposure estimation entailed identifying for each plant-specific work area/job combination its component tasks and documenting historical changes in those tasks; calculating plant-specific, work area/job-specific and time-specific average exposure indices (8-hour time-weighted average concentration in ppm) and compiling these into job-exposure matrices; and linking the time-specific and work area/job-specific exposure estimates in the job-exposure matrices with each employee's work history to obtain cumulative exposure estimates as of each day of follow-up.

Updated vital status information through 2009 was available for 99% of the cohort.[8] Data on underlying and contributing causes of death came from death certificates, the US National Death Index and the Canadian Mortality Data Base of Statistics Canada. In a prior update, we attempted to obtain medical records of men whose death certificate mentioned any type of LHC.[10] Medical records were retrieved for 86% of leukaemia, 84% of NHL and 81% of multiple myeloma cases and confirmed the diagnoses of 100% of leukaemia and multiple myeloma and 96% of NHL cases with records. We did not obtain any additional medical records for the current update. Causes of death were determined without knowledge of monomer exposure status.

Monomer exposure variables

No new exposure estimates were developed for the present analysis. Exposure variables were time-dependent butadiene and styrene cumulative ppm-years. Analyses evaluated unlagged cumulative ppm-years and cumulative ppm-years lagged by 10 or 20 years to allow for potential latency. We did not analyse other exposure variables previously studied,[11] including number of high-intensity tasks (HITs), average ppm and ppm-years below and above a threshold, all of which were highly correlated with ppm-years (eg, Spearman rank correlation coefficient=0.86 for butadiene ppm-years and HITs).

Outcomes

Outcomes were all leukaemia, lymphoid leukaemia, myeloid leukaemia, AML, NHL, multiple myeloma and all B-cell malignancies, including lymphoid leukaemia, NHL and multiple myeloma.[12] The B-cell malignancy cases may have included a few T-cell neoplasms, which are thought to comprise 10%–15% of NHL and lymphoid leukaemia. For each LHC category, events included any decedent with the condition as the underlying or a contributing cause of death or with a medical record indicating that the condition was present.

Statistical analysis

Follow-up began for male workers on their date of accruing 1 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.[8] 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 LHC mortality used multivariable Cox regression methods to estimate LHC HRs and exposure–response trends within the cohort of workers, without reference to an external comparison population. These 'internal' Cox regression analyses provided maximum partial likelihood estimates of disease-specific HRs, interpreted as rate ratios (RRs) and 95% CIs for each quartile of ppm-years of monomer exposure compared with no exposure, with quartiles specified according to the exposure distribution of cases with each form of LHC. Additional Cox regression analyses estimated beta coefficients (β) and 95% CIs for trends in exposure–response using butadiene or styrene ppm-years. For all leukaemia, we further described the exposure–response curve with restricted cubic spline (RCS) Cox regression models, fitted to all exposure data and to the trimmed data, with five knots corresponding to the 5, 27.5, 50, 72.5 and 95 percentile boundaries among the exposed. Also, for all leukaemia, we analysed butadiene exposure–response separately in the following two strata of styrene exposure: lower styrene exposure, defined as below the median value of 27 styrene ppm-years among leukaemia decedents; and higher styrene exposure, defined as exposure at or above the median value. We also analysed styrene exposure–response, stratified by lower (below the median value,

121 ppm-years) versus higher (≥121 ppm-years) butadiene exposure.

All analyses used age as of each person-day of follow-up as the time scale and treated monomer ppm-years as time-dependent. Our main analyses assessed exposure–response trends using all person-day records, and models included as covariates, age at hire, calendar year of hire, sex, race, plant and payroll status (ever hourly paid or always salaried). Salaried employees mainly held supervisory or managerial positions, while hourly employees typically worked directly and regularly with manufacturing operations and had higher potential exposure to monomers. Payroll status also was associated with socioeconomic factors.

We conducted several series of sensitivity analyses. One of these 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.[13]

To investigate the influence of data at extreme exposure values, additional sensitivity analyses estimated exposure–response trends using 'trimmed' data that excluded all unexposed person-time and all person-time with ppm-years values above the 95th percentile of the exposure distribution of leukaemia decedents (for analyses of all leukaemias, lymphoid leukaemia, myeloid leukaemia and AML) or of B-cell malignancy decedents (for analyses of NHL, multiple myeloma and all B-cell malignancies). Several considerations prompted these analyses. Cohort studies in other industry settings have reported that exposure–response curves tend to diminish at higher exposure levels.[14] Two of our earlier studies of male synthetic rubber polymer workers found stronger exposure–response trends for butadiene and leukaemia in analyses that excluded exposures above the 95th percentile[11] or categorised butadiene into deciles.[7] Both of the latter procedures can reduce the impact of exposure outliers. In addition, an investigation at the largest study plant, performed to validate our butadiene exposure estimates, found greater misclassification for jobs entailing higher exposures than for jobs with lower exposures.[15]

Additional sensitivity analyses used 'reduced' models that contained fewer covariates. The goal of the reduced models was to preserve the control of confounding, while providing more precise results. Thus, we examined models containing all possible subsets of covariates and selected a reduced model on the basis of having: (1) a monomer exposure parameter estimate within 5% of that obtained in the corresponding full model and (2) the fewest covariates.

Table 1 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				Styrene ppm-years			
	N (%)*	Range	Median (IQR)	Mean (SD)	N (%)	Range	Median (IQR)	Mean (SD)
Total cohort (21 087)	14 004 (66)	>0.00–9264	48 (11–167)	187 (517)	15 422 (73)	>0.00–1618	11 (2.8–36)	38 (98)
Sex								
Male (16 579)	12 814 (77)	>0.00–9264	54 (13–178)	197 (537)	14 006 (84)	>0.00–1618	13 (3.4–38)	40 (101)
Female (4508)	1190 (26)	>0.00–1980	8.0 (1.6–45)	76 (184)	1416 (31)	>0.00–380	1.8 (0.3–11)	19 (48)
Plant, location								
Kentucky (1563)	1144 (73)	>0.00–1499	75 (15–245)	195 (280)	1171 (75)	0.01–477	20 (5.8–48)	38 (53)
Louisiana (2463)	1815 (74)	0.05–4185	72 (20–230)	251 (502)	1782 (72)	>0.00–1469	16 (4.6–57)	71 (169)
Louisiana (2849)	1524 (53)	0.01–9264	73 (15–320)	483 (1267)	2092 (73)	>0.00–1618	13 (3.7–48)	65 (178)
Texas (2929)	1690 (58)	>0.00–2114	38 (10–134)	132 (239)	2227 (76)	>0.00–516	5.9 (1.7–22)	21 (40)
Ontario (7044)	4936 (70)	>0.00–5141	43 (8.3–143)	139 (282)	4846 (69)	>0.00–442	12 (2.4–36)	33 (54)
Texas (4239)	2895 (68)	0.02–1575	32 (8.6–120)	102 (174)	3304 (78)	>0.00–368	10 (2.5–29)	23 (35)
Ever hourly								
Yes (15 109)	11 876 (79)	>0.00–9264	65 (16–203)	216 (556)	13 406 (89)	>0.00–1618	14 (3.6–42)	43 (104)
No (5978)	2128 (36)	>0.00–916	7.4 (1.7–23)	24 (59)	2016 (34)	>0.00–310	2.5 (0.5–8.1)	7.8 (16)
Race								
White (18 674)	12 273 (66)	>0.00–5141	44 (10–149)	139 (268)	13 297 (71)	>0.00–681	10 (2.5–32)	27 (46)
Black (2413)	1731 (72)	0.01–9264	105 (18–368)	526 (1236)	2125 (88)	0.01–1618	24 (5.5–87)	105 (225)
Hire year								
1943–1949 (5404)	3600 (67)	>0.00–9264	77 (20–253)	257 (650)	3938 (73)	0.01–1618	13 (3.8–48)	50 (125)
1950–1959 (5613)	4005 (71)	>0.00–9063	97 (30–266)	260 (617)	4279 (76)	0.02–1462	25 (6.4–56)	55 (117)
1960–1969 (4333)	2871 (66)	>0.00–7102	42 (11–130)	134 (334)	3065 (71)	>0.00–1105	13 (3.3–34)	30 (63)
≥1970 (5737)	3528 (62)	>0.00–4516	12 (3.0–41)	75 (287)	4140 (72)	>0.00–697	3.8 (0.9–13)	16 (51)
All decedents (9665)	6914 (72)	>0.00–9264	79 (21–245)	245 (607)	7481 (77)	>0.00–1618	17 (4.4–49)	50 (119)
All leukaemia (132)	103 (78)	1.92–7741	121 (34–364)	367 (873)	109 (83)	1.09–1203	27 (8.4–61)	62 (158)
Lymphoid leukaemia (52)	39 (75)	1.92–7741	225 (45–425)	542 (1303)	42 (81)	1.65–1203	29 (8.6–69)	90 (243)
Myeloid leukaemia (67)	53 (79)	5.03–2010	70 (26–230)	238 (425)	56 (84)	1.09–341	21 (5.4–49)	39 (57)
AML†(41)	32 (78)	5.03–2010	62 (20–188)	158 (351)	35 (85)	1.09–341	20 (5.2–36)	31 (58)
B-cell malignancy‡ (213)	148 (69)	>0.00–7741	125 (29–373)	334 (756)	163 (77)	0.09–1203	21 (4.6–62)	64 (157)
NHL† (110)	76 (69)	>0.00–1496	121 (19–335)	234 (302)	86 (78)	0.09–231	24 (6.0–60)	41 (49)
Multiple myeloma (60)	40 (67)	>0.00–2398	111 (34–395)	314 (527)	43 (72)	0.21–840	15 (2.8–78)	82 (177)

*Number of exposed employees (% of total number in each group).
† AML, acute myeloid leukemia; NHL, non-Hodgkin's lymphoma.
‡Included lymphoid leukaemia, non-Hodgkin's lymphoma and multiple myeloma.
†AML, acute myeloid leukaemia; NHL, non-Hodgkin's lymphoma.

Preliminary models evaluated possible differences in monomer exposure-LHC associations between women and men. Those analyses found no statistically significant sex-monomer exposure interaction and are not described further.

We used the SAS V.9.4 Cox proportional hazard model procedure Proportional Hazards REGression (PHREG) for the Cox regression analyses. We used the Akaike information criterion (AIC) to compare the statistical fit of reduced versus full models.[16]

RESULTS

Of the 21 087 workers in the cohort, 14 004 (66%) were classified as ever exposed to butadiene, and 15 422 (73%) were ever exposed to styrene (table 1). Cumulative exposure to monomers was right-skewed: overall, exposed workers had median and mean values of 48 and 187, respectively, for butadiene ppm-years and of 11 and 38, respectively, for styrene ppm-years. Monomer exposure was higher among men than among women and also varied by plant, payroll status, race and period of hire. The cohort had a median of 8.3 years of employment at the end of 1991. At the end of the follow-up, the median time since hire was 40 years, the median age was 69 years, and 46% of the cohort was deceased.

Total numbers of decedents with an outcome event were 132 for all leukaemia, 52 for lymphoid leukaemia, 67 for myeloid leukaemia, 41 for AML, 110 for NHL, 60 for multiple myeloma and 213 for B-cell malignancy. Butadiene and styrene ppm-years were strongly correlated, with Spearman correlation coefficients ranging from 0.81 for NHL decedents to 0.87 for all leukaemia and lymphoid leukaemia decedents. Online supplemental table S1 shows decedents with each outcome, cross-classified by quartiles of butadiene and styrene ppm-years.

All leukaemia

For butadiene, RCS analyses (figure 1A,B and online supplemental figure S1A) indicated that the adjusted RR for all leukaemia increased in an approximately linear fashion at exposures below about 1000 ppm-years, with attenuation of the curve at higher exposures. Analyses by quartile of ppm-years also indicated that adjusted RRs rose with increasing exposure, with an RR of 2.53 (95% CI 1.37 to 4.67) in the highest exposure category (≥363.64 ppm-years) (table 2). Using untrimmed butadiene ppm-years, the exposure–response trend was statistically significant, regardless of the inclusion of unexposed person-time (including unexposed: $\beta=2.55\times10^{-4}$, (95% CI 0.52 to 4.57)$\times10^{-4}$, trend p=0.014) (excluding unexposed: $\beta=2.50\times10^{-4}$, (95% CI 0.27 to 4.73)$\times10^{-4}$, trend p=0.028). Trimming to restrict data to ppm-years >0 and ≤95th percentile (1144 ppm-years) of all leukaemia decedents yielded a somewhat stronger exposure–response trend for butadiene ($\beta=9.94\times10^{-4}$, (95% CI 1.88 to 18.00)$\times10^{-4}$, trend p=0.016). This result was consistent with RRs from the analysis by exposure quartile. For example, the beta coefficient obtained from the trimmed data, evaluated at the mean (1156.83 ppm-years) or median (725.08 ppm-years) value of exposure in quartile 4, yielded RRs of 3.16 and 2.06, respectively, as compared the RR of 2.53 from the

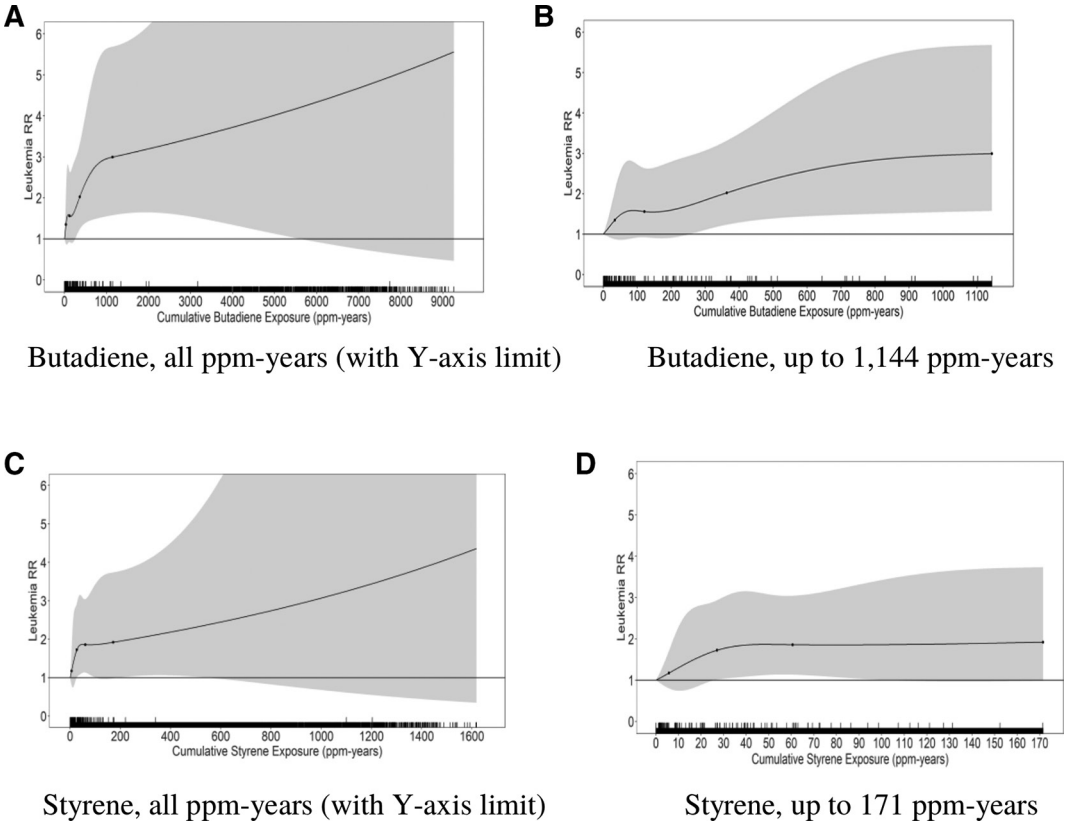

Figure 1 Restricted cubic splines for butadiene ppm-years and leukaemia (A and B) and styrene ppm-years and leukaemia (C and D). (A) and (C) display curves for butadiene and styrene, respectively, over the entire range of exposure, while (B) and (D) focus on the part of the curves just below the 95th percentile of exposure values for butadiene (at 1144 ppm-years) and styrene (at 171 ppm-years), respectively. All models used unrestricted ppm-years, without trimming. Rugs just above the X-axis of each figure depict the frequency of all observations (lower rug) and leukaemias (upper rug) at corresponding monomer exposure values. Circles indicate cutpoints for quartiles 2, 3 and 4 and for the 95th percentile.

Table 2 Exposure-response analyses of butadiene or styrene ppm-years and leukaemia: number (N) of cases, adjusted rate ratio (RR) with 95% CI by exposure quartile, beta-coefficient (β) with 95% CI and trend p value

	Butadiene			Styrene		
Model*	**N**	**RR**	**95% CI**	**N**	**RR**	**95% CI**
Quartile†						
Unexposed	29	1.0	ref	23	1.0	ref
1	26	1.04	0.60 to 1.83	27	1.12	0.61 to 2.07
2	26	1.37	0.76 to 2.46	27	1.12	0.59 to 2.11
3	25	1.60	0.87 to 2.94	28	1.79	0.93 to 3.45
4	26	2.53	1.37 to 4.67	27	1.96	1.00 to 3.82
Trend						
All person-time: β(95% CI), trend p value, AIC, N‡	$2.55\times10^{-4}((0.52 \text{ to } 4.57)\times10^{-4})$, p=0.014, AIC=2384, N=132			$1.04\times10^{-3}((-0.26 \text{ to } 2.33)\times10^{-3})$, p=0.116, AIC=2386, N=132		
Exposed person-time: β(95% CI), trend p value, AIC, N	$2.50\times10^{-4}((0.27 \text{ to } 4.73)\times10^{-4})$, p=0.028, AIC=1786, N=103			$0.84\times10^{-3}((-0.51 \text{ to } 2.20)\times10^{-3})$, p=0.220, AIC=1912, N=109		
Exposed person-time ≤95th percentile§: β(95% CI), trend p value, AIC, N	$9.94\times10^{-4}((1.88 \text{ to } 18.00)\times10^{-4})$, p=0.016, AIC=1673, N=97			$4.05\times10^{-3}((-1.19 \text{ to } 9.30)\times10^{-3})$, p=0.130, AIC=1795, N=103		
Stratified¶						
Styrene <27.00 ppm-years	$1.34\times10^{-4}((-20.94 \text{ to } 23.61)\times10^{-4})$, p=0.907, AIC=1340, N=77					
Styrene ≥27.00 ppm-years	$2.86\times10^{-4}((0.38 \text{ to } 5.34)\times10^{-4})$, p=0.024, AIC=870, N=55					
Butadiene <121.28 ppm-years				$-7.26\times10^{-4}((-120.19 \text{ to } 105.67)\times10^{-4})$, p=0.900, AIC=1415, N=80		
Butadiene ≥121.28 ppm-years				$4.17\times10^{-4}((-12.45 \text{ to } 20.78)\times10^{-4})$, p=0.623, AIC=803, N=52		

*All 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, plant and ever hourly status, except as follows: for the model ofbutadiene within the stratum ≥27.00 styrene ppm-years, sex was not included due to the lack of events among women; for the model of styrene within the stratum ≥121.28 butadiene ppm-years, sex and ever-hourly were not included due to the lack of events among women and never hourly workers.
†Quartile (Q) cutpoints were at the following values of ppm-years: (1) butadiene: Q2, 34.00; Q3, 121.28; Q4, 363.64, maximum=7741.41; (2) styrene: Q2, 5.76; Q3, 27.00; Q4, 60.53, maximum=1203.21.
‡AIC, Akaike information criterion; N, number of cases included in the model.
§95th percentile was at 1144 ppm-years for butadiene and 171 ppm-years for styrene.
¶Models used all person-time.

analysis by quartile. In contrast, the beta coefficient from the analysis of untrimmed butadiene data, evaluated at the same mean and median ppm-years, yielded RRs of 1.34 and 1.20, respectively.

For styrene, RCS results (figure 1C,D and online supplemental figure S1B) indicated a positive exposure–response curve, with attenuation at higher exposures. Other analyses (table 2) yielded results similar to those for butadiene ppm-years, but those results were not statistically significant.

Analyses of each monomer, stratified by lower vs higher exposure to the other monomer, found that the butadiene exposure–response association was evident only in the category of higher styrene exposure ($\beta=2.89\times10^{-4}$, (95% CI 0.41 to 5.36)$\times10^{-4}$, trend p=0.022) (table 2). Styrene exposure–response was not observed in either category of butadiene exposure.

Lymphoid and myeloid leukemia

For lymphoid leukaemia (table 3), the pattern of RRs by quartile of butadiene ppm-years was irregular, with RRs of 2.61 (95% CI 1.02 to 6.67) and 1.95 (95% CI 0.76 to 5.03) in the third (213.43–<376.31 ppm-years) and fourth (≥376.31 ppm-years) quartiles, respectively; exposure–response trends were statistically significant (including unexposed: $\beta=3.81\times10^{-4}$, (95% CI 1.05 to 6.58)$\times10^{-4}$, trend p=0.007; excluding unexposed: $\beta=4.78\times10^{-4}$, (95% CI 1.34 to 8.23)$\times10^{-4}$, trend p=0.007). For all myeloid leukaemia and AML, the RR for each butadiene exposure quartile was elevated but statistically imprecise, and none of the exposure–response trends was significant. Analysis of trimmed exposure data yielded a statistically significant exposure–response trend for butadiene and lymphoid leukaemia ($\beta=15.40\times10^{-4}$, (95% CI 4.19 to 26.53)$\times10^{-4}$, trend p=0.007) but not for all myeloid leukaemia or AML.

For styrene, analyses by quartile of ppm-years yielded results similar to those for butadiene ppm-years for lymphoid leukaemia, all myeloid leukaemia and AML (table 3), but the only statistically significant RR was that for AML in the third exposure quartile. The only statistically significant exposure–response trend was that for lymphoid leukaemia, with the inclusion of the unexposed (trend p=0.046).

NHL, multiple myeloma and B-cell malignancy

For butadiene and NHL (table 3), no exposure–response was detected in analyses of exposure quartile or trends using untrimmed butadiene ppm-years. However, trimming to restrict data to ppm-years >0 and ≤95th percentile (1083 ppm-years) yielded a trend p value of 0.002. No statistically significant butadiene exposure–response was found for multiple myeloma. For butadiene and all B-cell malignancies combined, the trend was statistically significant (p=0.002) only in analyses of trimmed exposure data. Styrene did not appear to be associated with NHL, multiple myeloma or all B-cell malignancy.

Other results

Analyses that lagged cumulative exposure by 10 or 20 years (table 4) found that for all leukaemia and lymphoid leukaemia, butadiene exposure–response beta coefficients were similar regardless of the exposure lag applied. For all leukaemia, trends were not statistically significant for styrene exposure lagged 10 or 20 years. For lymphoid leukaemia, only the trend for styrene lagged 10 years approached statistical significance. No trends were detected for lagged butadiene or styrene exposure and other LHCs.

Seventy-eight per cent of reduced models yielded exposure parameter estimates that were within 5% of those in full models,

Table 3 Exposure-response analyses of butadiene or styrene ppm-years and other lymphohaematopoietic cancers (LHCs): number (N) of cases, adjusted rate ratio (RR) with 95% CI by exposure quartile, beta-coefficient (β) with 95% CI and trend p value

Model*, form of LHC	Butadiene			Styrene		
Lymphoid leukaemia						
Quartile†	N	RR	95% CI	N	RR	95% CI
Unexposed	13	1.0	ref	10	1.0	ref
1	9	0.72	0.29 to 1.78	10	0.75	0.29 to 1.98
2	10	0.85	0.34 to 2.14	11	1.25	0.47 to 3.33
3	10	2.61	1.02 to 6.67	10	1.14	0.41 to 3.16
4	10	1.95	0.76 to 5.03	11	1.78	0.64 to 4.91
Trend						
All person-time: β(95% CI), trend p value, AIC, N‡	3.81×10^{-4}((1.05 to $6.58)\times10^{-4}$), p=0.007, AIC=933, N=52			1.63×10^{-3}((0.03 to $3.23)\times10^{-3}$), p=0.046, AIC=936, N=52		
Exposed person-time: β(95% CI), trend p value, AIC, N	4.78×10^{-4}((1.34 to $8.23)\times10^{-4}$), p=0.007, AIC=664, N=39§			1.24×10^{-3}((-0.43 to $2.91)\times10^{-3}$), p=0.146, AIC=727, N=42§		
Exposed person-time ≤95th percentile: β(95% CI), trend p value, AIC, N	15.40×10^{-4}((4.19 to $26.53)\times10^{-4}$), p=0.007, AIC=625, N=37§			3.33×10^{-3}((-4.81 to $11.47)\times10^{-3}$), p=0.422, AIC=689, N=40§		
Myeloid leukaemia						
Quartile	N	RR	95% CI	N	RR	95% CI
Unexposed	14	1.0	ref	11	1.0	ref
1	13	1.16	0.53 to 2.56	14	1.27	0.54 to 2.98
2	14	1.96	0.88 to 4.38	14	1.37	0.56 to 3.31
3	13	1.47	0.64 to 3.40	14	1.85	0.74 to 4.60
4	13	1.72	0.73 to 4.07	14	1.81	0.71 to 4.64
Trend						
All person-time: β(95% CI), trend p value, AIC, N	1.09×10^{-4}((-3.01 to $5.18)\times10^{-4}$), p=0.602, AIC=1235, N=67			-2.36×10^{-4}((-32.20 to $27.48)\times10^{-4}$), p=0.877, AIC=1235, N=67		
Exposed person-time: β(95% CI), trend p value, AIC, N	0.63×10^{-4}((-3.89 to $5.15)\times10^{-4}$), p=0.784, AIC=941, N=53¶			-3.77×10^{-4}((-35.71 to $28.17)\times10^{-4}$), p=0.817, AIC=1006, N=56		
Exposed person-time ≤95th percentile: β(95% CI), trend p value, AIC, N	-0.16×10^{-4}((-14.68 to $14.37)\times10^{-4}$), p=0.983, AIC=880, N=50¶			29.50×10^{-4}((-49.06 to $108.13)\times10^{-4}$), p=0.461, AIC=963, N=54		
Acute myeloid leukaemia						
Quartile	N	RR	95% CI	N	RR	95% CI
Unexposed	9	1.0	ref	6	1.0	ref
1	8	1.28	0.47 to 3.48	8	1.55	0.49 to 4.91
2	8	2.04	0.73 to 5.70	9	2.26	0.70 to 7.31
3	8	1.85	0.64 to 5.36	9	4.61	1.37 to 15.56
4	8	1.90	0.63 to 5.73	9	2.42	0.69 to 8.54
Trend						
All person-time: β(95% CI), trend p value, AIC, N	-1.08×10^{-4}((-9.12 to $6.97)\times10^{-4}$), p=0.793, AIC=746, N=41			-6.23×10^{-4}((-51.03 to $38.56)\times10^{-4}$), p=0.785, AIC=746, N=41		
Exposed person-time: β(95% CI), trend p value, AIC, N	-2.27×10^{-4}((-12.25 to $7.70)\times10^{-4}$), p=0.655, AIC=561, N=32¶			-1.13×10^{-3}((-6.48 to $4.22)\times10^{-3}$), p=0.679, AIC=623, N=35		
Exposed person-time ≤95th percentile: β(95% CI), trend p value, AIC, N	-1.34×10^{-3}((-3.93 to $1.25)\times10^{-3}$), p=0.310, AIC=540, N=31¶			-3.02×10^{-3}((-15.36 to $9.32)\times10^{-3}$), p=0.631, AIC=602, N=34		
Non-Hodgkin's lymphoma						
Quartile	N	RR	95% CI	N	RR	95% CI
Unexposed	34	1.0	ref	24	1.0	ref
1	19	0.90	0.50 to 1.61	21	0.81	0.42 to 1.55
2	19	0.57	0.31 to 1.04	22	1.02	0.53 to 1.98
3	19	0.94	0.50 to 1.75	21	1.11	0.56 to 2.21
4	19	1.33	0.71 to 2.49	22	1.55	0.77 to 3.09
Trend						
All person-time: β(95% CI), trend p value, AIC, N	0.26×10^{-4}((-3.73 to $4.25)\times10^{-4}$), p=0.898, AIC=1976, N=110			-0.23×10^{-3}((-2.62 to $2.17)\times10^{-3}$), p=0.854, AIC=1976, N=110		
Exposed person-time: β(95% CI), trend p value, AIC, N	1.55×10^{-4}((-2.49 to $5.58)\times10^{-4}$), p=0.452, AIC=1317, N=76			-0.15×10^{-3}((-2.56 to $2.26)\times10^{-3}$), p=0.900, AIC=1506, N=86		

continued

Table 3 continued

Model*, form of LHC	Butadiene			Styrene		
Exposed person-time ≤95th percentile: β(95% CI), trend p value, AIC, N	$14.80\times10^{-4}((5.68 \text{ to } 23.99)\times10^{-4})$, p=0.002, AIC=1286, N=75			$4.20\times10^{-3}((-0.73 \text{ to } 9.13)\times10^{-3})$, p=0.095, AIC=1462, N=84		
Multiple myeloma						
Quartile	N	RR	95% CI	N	RR	95% CI
Unexposed	20	1.0	ref	17	1.0	ref
1	10	0.61	0.27 to 1.35	10	0.96	0.42 to 2.20
2	10	0.74	0.32 to 1.71	11	0.61	0.26 to 1.40
3	10	0.69	0.29 to 1.60	11	0.44	0.19 to 1.04
4	10	1.01	0.43 to 2.42	11	0.84	0.34 to 2.08
Trend						
All person-time: β(95% CI), trend p value, AIC, N	$-0.82\times10^{-4}((-5.08 \text{ to } 3.45)\times10^{-4})$, p=0.707, AIC=1056, N=60			$0.15\times10^{-3}((-1.55 \text{ to } 1.85)\times10^{-3})$, p=0.858, AIC=1056, N=60		
Exposed person-time: β(95% CI), trend p value, AIC, N	$-0.36\times10^{-4}((-4.86 \text{ to } 4.14)\times10^{-4})$, p=0.876, AIC=669, N=40			$0.31\times10^{-3}((-1.44 \text{ to } 2.05)\times10^{-3})$, p=0.731, AIC=730, N=43		
Exposed person-time ≤95th percentile: β(95% CI), trend p value, AIC, N	$5.83\times10^{-4}((-7.64 \text{ to } 19.30)\times10^{-4})$, p=0.396, AIC=634, N=38			$-1.61\times10^{-3}((-9.61 \text{ to } 6.38)\times10^{-3})$, p=0.692, AIC=644, N=38		
B-cell malignancy						
Quartile	N	RR	95% CI	N	RR	95% CI
Unexposed	65	1.0	ref	50	1.0	ref
1	37	0.75	0.49 to 1.15	41	0.89	0.57 to 1.40
2	37	0.70	0.45 to 1.08	40	0.83	0.52 to 1.32
3	37	0.94	0.60 to 1.49	41	0.85	0.53 to 1.38
4	37	1.39	0.88 to 2.20	41	1.18	0.72 to 1.93
Trend						
All person-time: β(95% CI), trend p value, AIC, N	$1.15\times10^{-4}((-0.75 \text{ to } 3.05)\times10^{-4})$, p=0.237, AIC=3785, N=213			$5.65\times10^{-4}((-4.74 \text{ to } 16.03)\times10^{-4})$, p=0.287, AIC=3785, N=213		
Exposed person-time: β(95% CI), trend p value, AIC, N	$1.95\times10^{-4}((-0.11 \text{ to } 4.02)\times10^{-4})$, p=0.064, AIC=2517, N=148			$5.51\times10^{-4}((-5.19 \text{ to } 16.20)\times10^{-4})$, p=0.313, AIC=2809, N=163		
Exposed person-time ≤95th percentile: β(95% CI), trend p value, AIC, N	$11.00\times10^{-4}((4.23 \text{ to } 17.82)\times10^{-4})$, p=0.002, AIC=2380, N=141			$17.00\times10^{-4}((-21.05 \text{ to } 55.06)\times10^{-4})$, p=0.381, AIC=2639, N=154		

*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, plant and ever hourly status. Models using exposed person-time ≤95th percentile trimmed data above 1144 and 171 ppm-years for butadiene and styrene, respectively, for leukaemias and above 1083 and 213 ppm-years for butadiene and styrene, respectively, for non-Hodgkin's lymphoma, multiple myeloma and B-cell malignancy.
†Quartile (Q) cutpoints were at the following values of ppm-years: lymphoid leukaemia—(1) butadiene: Q2, 44.73; Q3, 213.43; Q4, 376.31, maximum=7741.41; (2) styrene: Q2, 8.52; Q3, 27.21; Q4, 69.29, maximum=1203.21; myeloid leukaemia—(1) butadiene: Q2, 25.20; Q3, 70.05; Q4, 230.08, maximum=–2009.71; (2) styrene: Q2, 5.21; Q3, 20.71; Q4, 48.25, maximum=340.52; acute myeloid leukaemia—(1) butadiene: Q2, 19.14; Q3, 59.19; Q4, 185.63, maximum=2009.71; (2) styrene: Q2, 5.21; Q3, 19.73; Q4, 34, maximum=340.52; non-Hodgkin's lymphoma—(1) butadiene: Q2, 17.94; Q3, 117.22; Q4, 334.83, maximum=1495.51 (2) styrene: Q2, 5.97; Q3, 23.61; Q4, 59.67, maximum=231.34; multiple myeloma—(1) butadiene: Q2, 31.42; Q3, 107.78; Q4, 386.04, maximum=2397.73; (2) styrene: Q2, 2.80; Q3, 14.67; Q4, 77.99, maximum=839.61; B-cell malignancy—(1) butadiene: Q2, 27.04; Q3, 124.38; Q4, 370.89, maximum=7741.41; (2) styrene: Q2, 4.63; Q3, 20.74; Q4, 61.70, maximum=1203.21.
‡AIC, Akaike information criterion; N, number of cases included in each model.
§Restricted to ever hourly due to lack of events among never hourly.
¶Restricted to men due to lack of events among women.

and all were within 10% online supplemental tables S2–S5. Use of the reduced models did not identify any additional statistically significant results.

DISCUSSION

The present cohort comprises the largest butadiene-exposed group studied to date and includes the only large group of butadiene-exposed women. The update[8] on which the current analyses were based substantially augmented information from our previous studies of male[1 17] and female[18] synthetic rubber polymer workers.

Leukaemia

Internal Cox regression analyses of all leukaemia found a statistically significant exposure–response trend for butadiene but not for styrene. Analyses of major subtypes of leukaemia indicated that for lymphoid leukaemia a trend of increasing risk with increasing cumulative exposure to butadiene was present, with evidence of a similar pattern for styrene that, however, was not statistically significant in most analyses. For all myeloid leukaemia and AML a positive exposure–response trend was not evident for either monomer. Restricting data to exposed person-time did not substantively alter these results. For all leukaemias and lymphoid leukaemia, the butadiene trends were three to four times stronger when data were restricted to ppm-years >0 and ≤95th percentile (1144 ppm-years). Alternative explanations for this pattern include biological irrelevance of higher exposures, exposure misclassification, depletion of the pool of susceptible people and other possible reasons.[14] Lagging exposure had little effect on results for leukaemias or other outcomes,

Table 4 Adjusted* beta-coefficient (β) with 95% CI, trend p value, with Akaike information criterion (AIC), for the relation between butadiene or styrene ppm-years (including person-time with zero monomer exposure), lagged 0, 10 or 20 years, and lymphohaematopoietic cancers (LHC)

Monomer, Form of LHC, lag period (years)	β	95% CI	Trend p value	AIC
I. Butadiene				
All leukaemia				
0	2.55×10^{-4}	0.52 to 4.57×10^{-4}	0.014	2384
10	2.58×10^{-4}	0.38 to 4.78×10^{-4}	0.022	2337
20	2.63×10^{-4}	−0.05 to 5.31×10^{-4}	0.055	2120
Lymphoid leukaemia				
0	3.81×10^{-4}	1.05 to 6.58×10^{-4}	0.007	933
10	3.73×10^{-4}	0.78 to 6.68×10^{-4}	0.013	933
20	3.00×10^{-4}	−0.70 to 6.69×10^{-4}	0.112	868
Myeloid leukaemia				
0	1.09×10^{-4}	−3.01 to 5.18×10^{-4}	0.602	1235
10	1.16×10^{-4}	−3.33 to 5.66×10^{-4}	0.612	1189
20	2.11×10^{-4}	−2.90 to 7.11×10^{-4}	0.410	1054
Acute myeloid leukaemia				
0	-1.08×10^{-4}	−9.12 to 6.97×10^{-4}	0.793	746
10	-0.72×10^{-4}	−8.54 to 7.10×10^{-4}	0.857	724
20	-0.14×10^{-4}	−8.85 to 8.57×10^{-4}	0.975	641
Non-Hodgkin's lymphoma				
0	0.26×10^{-4}	−3.73 to 4.25×10^{-4}	0.898	1976
10	1.10×10^{-5}	−43.61 to 45.80×10^{-5}	0.962	1973
20	-6.18×10^{-5}	−67.04 to 54.67×10^{-5}	0.842	1876
Multiple myeloma				
0	-0.82×10^{-4}	−5.08 to 3.45×10^{-4}	0.707	1056
10	-7.54×10^{-5}	−52.81 to 37.74×10^{-5}	0.744	1054
20	-9.77×10^{-5}	−64.26 to 44.73×10^{-5}	0.725	955
B-cell malignancy				
0	1.15×10^{-4}	−0.75 to 3.05×10^{-4}	0.237	3785
10	1.13×10^{-4}	−0.95 to 3.21×10^{-4}	0.287	3779
20	0.73×10^{-4}	−1.95 to 3.40×10^{-4}	0.595	3517
II. Styrene				
Leukaemia				
0	1.04×10^{-3}	−0.26 to 2.33×10^{-3}	0.116	2386
10	1.03×10^{-3}	−0.38 to 2.45×10^{-3}	0.153	2339
20	0.96×10^{-3}	−0.82 to 2.74×10^{-3}	0.289	2122
Lymphoid leukaemia				
0	1.63×10^{-3}	0.03 to 3.23×10^{-3}	0.046	936
10	1.67×10^{-3}	−0.06 to 3.40×10^{-3}	0.058	934
20	1.43×10^{-3}	−0.74 to 3.60×10^{-3}	0.197	869
Myeloid leukaemia				
0	-2.36×10^{-4}	−32.20 to 27.48×10^{-4}	0.877	1235
10	-4.37×10^{-4}	−39.04 to 30.30×10^{-4}	0.805	1189
20	-3.53×10^{-4}	−46.45 to 39.40×10^{-4}	0.872	1054
Acute myeloid leukaemia				
0	-6.23×10^{-4}	−51.03 to 38.56×10^{-4}	0.785	746
10	-4.02×10^{-4}	−47.81 to 39.77×10^{-4}	0.857	724
20	-2.72×10^{-4}	−54.77 to 49.32×10^{-4}	0.918	641
Non-Hodgkin's lymphoma				
0	-0.23×10^{-3}	−2.62 to 2.17×10^{-3}	0.854	1976
10	-3.04×10^{-4}	−29.50 to 23.43×10^{-4}	0.822	1973
20	-7.57×10^{-4}	−42.45 to 27.30×10^{-4}	0.670	1876
Multiple myeloma				
0	0.15×10^{-3}	−1.55 to 1.85×10^{-3}	0.858	1056
10	1.04×10^{-4}	−17.61 to 19.70×10^{-4}	0.913	1054
20	-0.52×10^{-4}	−23.95 to 22.90×10^{-4}	0.965	955
B-cell malignancy				

continued

Table 4 continued

Monomer, Form of LHC, lag period (years)	β	95% CI	Trend p value	AIC
0	5.65×10^{-4}	-4.74 to 16.03×10^{-4}	0.287	3785
10	5.42×10^{-4}	-5.97 to 16.81×10^{-4}	0.351	3779
20	3.36×10^{-4}	-11.18 to 17.91×10^{-4}	0.651	3517

as exposure diminished over calendar time,[9] more than 90% of the LHC cases died 20 years or more after hire, and no exposure was recorded after 1991.

With regard to butadiene and leukaemia, the results of the present study are consistent with those reported earlier by other investigators[19–22] and us[1 7 8 10 11 17 18 23 24] in supporting a positive association in the synthetic rubber polymer industry. In contrast, investigations of relatively small cohorts of butadiene monomer production workers, who were exposed to butadiene but not to styrene, have reported results for leukaemia that were null or weakly positive.[25–28]

With regard to styrene, increased risks of LHC, particularly leukaemia and lymphoma, have been reported among styrene-exposed workers in both synthetic rubber polymer and reinforced plastic industries.[6] Reinforced plastics industry workers were exposed to styrene concentrations at higher levels than were typically found in the synthetic rubber industry and were not exposed to butadiene. Positive exposure–response relationships between styrene exposure and leukaemia were reported in an older multinational European study of reinforced plastics workers[29] but not in a recent reanalysis of that study.[30] A study of mortality among workers in the reinforced plastics boatbuilding industry reported an association between several indices of exposure to styrene and leukaemia.[31–33] However, studies of several other cohorts of reinforced plastics workers found little evidence of an association between styrene and overall leukaemia.[34–37]

With regard to exposure to butadiene or styrene and cell-type specific leukaemias, data from other studies are limited.[6] Christensen *et al*[36] reported a positive exposure–response trend for a styrene cumulative exposure score and AML. Collins *et al*[35] found no statistically significant exposure–response trend among workers employed in the US reinforced plastics and composite industry.

NHL, multiple myeloma and B-cell malignancy

We found little evidence of any association between cumulative exposure to butadiene or styrene and NHL or multiple myeloma. These results are consistent with our previous analyses.[7 8] The positive exposure–response for butadiene and all B-cell malignancies combined, seen only in analyses using trimmed exposure data, may have reflected the association between butadiene and lymphoid leukaemia.

Several studies have assessed mortality from NHL or subtypes of NHL in three cohorts of butadiene monomer production workers exposed to butadiene but not to styrene.[25–28] The observed number of NHL deaths exceeded the expected number in each study, but all results were based on small numbers.

An investigation that included many of the subjects in our study reported a positive association between styrene and NHL.[21] The reanalysis of the European reinforced plastics cohort reported an association between mean level of exposure to styrene and NHL but found no association with cumulative exposure to styrene.[30] In contrast, updated studies of the reinforced plastics industry did not find a clear excess of NHL, overall or in subgroups with higher styrene exposure.[31 32 34–36 38]

Matanoski *et al*[21] reported that multiple myeloma was associated with butadiene in a study that included most of the subjects in our male cohort, in contrast to our analyses by cumulative exposure, which provided no support for an association with butadiene or styrene. Divine and Hartman[25] reported slightly more than expected deaths from multiple myeloma among butadiene production workers, but data on multiple myeloma were sparse and internally inconsistent.

Strengths and limitations

Study strengths included the long follow-up period, the use of objective procedures to classify workers according to monomer exposure and cause of death, the inclusion of female employees and the use of sensitivity analyses to facilitate interpretation of results. Potential misclassification of monomer exposure remains a concern. Previous investigations have validated the butadiene exposure estimates[15] and assessed the impact of exposure misclassification on the exposure–response relation between butadiene and leukaemia.[1 39] However, sensitivity analyses to assess the potential impact of monomer exposure uncertainties would strengthen the data if used for risk assessment.

Other limitations include lack of information on lifestyle factors and the use of mortality, rather than incidence, data to ascertain LHCs. Mortality data are not optimal for cancers with relatively long survival including certain leukaemias and B-cell malignancies. Although our results provided little support for the hypothesis that styrene causes LHC, the styrene concentrations experienced by this cohort were relatively low, as compared with the exposures of reinforced plastics industry workers.[35] We performed multiple comparisons, and it is possible that the observed associations occurred by chance.

CONCLUSIONS

This study confirmed a positive exposure–response relationship between butadiene and all leukaemia and supports the classification of butadiene as a human carcinogen. Results supported an association between butadiene and lymphoid leukaemia, but not myeloid leukaemia. Evidence of an independent causal association between styrene and leukaemia remained less convincing. The study found little evidence that butadiene or styrene exposures were associated with major subtypes of B-cell malignancy other than lymphoid leukaemia, including NHL and multiple myeloma.

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REFERENCES

1 Delzell E, Sathiakumar N, Graff J, *et al*. An updated study of mortality among North American synthetic rubber industry workers. *Res Rep Health Eff Inst* 2006;132:1–65.
2 International Agency for Research on Cancer (IARC). *1,3-Butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). IARC Monographs on the evaluation of carcinogenic risks to humans*, 2008: 97.
3 International Agency for Research on Cancer (IARC. *Chemical agents and related occupations. IARC Monographs on the evaluation of carcinogenic risks to humans*, 2012: 100F.
4 National Toxicology Program (NTP). *14Th report on carcinogens. research triangle Park, NC: U.S. department of health and human services, public health services*, 2016.
5 Environmental Protection Agency (EPA). High-Priority substance designations under the toxic substances control act (TSCA) and initiation of risk evaluation on High-Priority substances; notice of availability. Available: https://www.federalregister.gov/documents/2019/12/30/2019-28225/high-priority-substance-designations-under-the-toxic-substances-control-act-tsca-and-initiation-of [Accessed 16 Oct 2020].
6 International Agency for Research on Cancer (IARC). *Styrene, styrene-7,8-oxide, and quinoline. IARC Monographs on the evaluation of carcinogenic risks to humans*, 2019: 121.
7 Sathiakumar N, Brill I, Leader M, *et al*. 1,3-Butadiene, styrene and lymphohematopoietic cancer among male synthetic rubber industry workers--Preliminary exposure-response analyses. *Chem Biol Interact* 2015;241:40–9.
8 Sathiakumar N, Tipre M, Leader M, *et al*. Mortality among men and women in the North American synthetic rubber industry, 1943 to 2009. *J Occup Environ Med* 2019;61:887–97.
9 Macaluso M, Larson R, Lynch J, *et al*. Historical estimation of exposure to 1,3-butadiene, styrene, and dimethyldithiocarbamate among synthetic rubber workers. *J Occup Environ Hyg* 2004;1:371–90.
10 Graff JJ, Sathiakumar N, Macaluso M, *et al*. Chemical exposures in the synthetic rubber industry and lymphohematopoietic cancer mortality. *J Occup Environ Med* 2005;47:916–32.
11 Cheng H, Sathiakumar N, Graff J, *et al*. 1,3-Butadiene and leukemia among synthetic rubber industry workers: exposure-response relationships. *Chem Biol Interact* 2007;166:15–24.
12 Swerdlow SH, Campo E, Pileri SA, *et al*. The 2016 revision of the world Health organization classification of lymphoid neoplasms. *Blood* 2016;127:2375–90.
13 Greenland S. Analysis of polytomous exposures and outcomes. In: Rothman K, Greenland S, Lash T, eds. *Modern epidemiology*. Philadelphia, PA: Lippincott Williams & Wilkins, 2008: 303–27.
14 Stayner L, Steenland K, Dosemeci M, *et al*. Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. *Scand J Work Environ Health* 2003;29:317–24.
15 Sathiakumar N, Delzell E, Cheng H, *et al*. Validation of 1,3-butadiene exposure estimates for workers at a synthetic rubber plant. *Chem Biol Interact* 2007;166:29–43.
16 Portet S. A primer on model selection using the Akaike information criterion. *Infect Dis Model* 2020;5:111–28.
17 Sathiakumar N, Graff J, Macaluso M, *et al*. An updated study of mortality among North American synthetic rubber industry workers. *Occup Environ Med* 2005;62:822–9.
18 Sathiakumar N, Delzell E. A follow-up study of mortality among women in the North American synthetic rubber industry. *J Occup Environ Med* 2009;51:1314–25.
19 Santos-Burgoa C, Matanoski GM, Zeger S, *et al*. Lymphohematopoietic cancer in styrene-butadiene polymerization workers. *Am J Epidemiol* 1992;136:843–54.
20 Matanoski GM, Santos-Burgoa C, Schwartz L. Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry (1943-1982). *Environ Health Perspect* 1990;86:107–17.
21 Matanoski G, Elliott E, Tao X, *et al*. Lymphohematopoietic cancers and butadiene and styrene exposure in synthetic rubber manufacture. *Ann N Y Acad Sci* 1997;837:157–69.
22 Meinhardt TJ, Lemen RA, Crandall MS, *et al*. Environmental epidemiologic investigation of the styrene-butadiene rubber industry. mortality patterns with discussion of the hematopoietic and lymphatic malignancies. *Scand J Work Environ Health* 1982;8:250–9.
23 Delzell E, Macaluso M, Sathiakumar N, *et al*. Leukemia and exposure to 1,3-butadiene, styrene and dimethyldithiocarbamate among workers in the synthetic rubber industry. *Chem Biol Interact* 2001;135-136:515–34.
24 Sathiakumar N, Delzell E, Hovinga M, *et al*. Mortality from cancer and other causes of death among synthetic rubber workers. *Occup Environ Med* 1998;55:230–5.
25 Divine BJ, Hartman CM. A cohort mortality study among workers at a 1,3 butadiene facility. *Chem Biol Interact* 2001;135-136:535–53.
26 Tsai SP, Wendt JK, Ransdell JD. A mortality, morbidity, and hematology study of petrochemical employees potentially exposed to 1,3-butadiene monomer. *Chem Biol Interact* 2001;135-136:555–67.
27 Ward EM, Fajen JM, Ruder AM, *et al*. Mortality study of workers in 1,3-butadiene production units identified from a chemical workers cohort. *Environ Health Perspect* 1995;103:598–603.
28 Ward EM, Fajen JM, Ruder AM, *et al*. Mortality study of workers employed in 1,3-butadiene production units identified from a large chemical workers cohort. *Toxicology* 1996;113:157–68.
29 Kogevinas M, Ferro G, Saracci R. Cancer mortality in an international cohort of workers exposed to styrene. *IARC Sci Publ* 1993;127:289–300.
30 Loomis D, Guha N, Kogevinas M, *et al*. Cancer mortality in an international cohort of reinforced plastics workers exposed to styrene: a reanalysis. *Occup Environ Med* 2019;76:157–62.
31 Ruder AM, Meyers AR, Bertke SJ. Mortality among styrene-exposed workers in the reinforced plastic boatbuilding industry. *Occup Environ Med* 2016;73:97–102.
32 Bertke SJ, Yiin JH, Daniels RD. Cancer mortality update with an exposure response analysis among styrene-exposed workers in the reinforced plastics boatbuilding industry. *Am J Ind Med* 2018;61:566–71.
33 Daniels RD, Bertke SJ. Exposure-Response assessment of cancer mortality in styrene-exposed boatbuilders. *Occup Environ Med* 2020;77:706–12.
34 Coggon D, Ntani G, Harris EC, *et al*. Risk of cancer in workers exposed to styrene at eight British companies making glass-reinforced plastics. *Occup Environ Med* 2015;72:165–70.
35 Collins JJ, Bodner KM, Bus JS. Cancer mortality of workers exposed to styrene in the U.S. reinforced plastics and composite industry. *Epidemiology* 2013;24:195–203.
36 Christensen MS, Hansen J, Ramlau-Hansen CH, *et al*. Cancer incidence in workers exposed to styrene in the Danish-reinforced plastics industry, 1968-2012. *Epidemiology* 2017;28:300–10.
37 Collins JJ, Delzell E. A systematic review of epidemiologic studies of styrene and cancer. *Crit Rev Toxicol* 2018;48:443–70.
38 Christensen MS, Vestergaard JM, d'Amore F, *et al*. Styrene exposure and risk of lymphohematopoietic malignancies in 73,036 reinforced plastics workers. *Epidemiology* 2018;29:342–51.
39 Graff JJ, Sathiakumar N, Macaluso M, *et al*. The effect of uncertainty in exposure estimation on the exposure-response relation between 1,3-butadiene and leukemia. *Int J Environ Res Public Health* 2009;6:2436–55.