1,3-Butadiene, Styrene and Lymphohematopoietic 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 lymphohematopoietic 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% confidence intervals (CIs) by quartile of cumulative exposure to butadiene or styrene, measured in parts per million-years (ppm-years), and exposure-response trends for all leukemia, lymphoid leukemia, myeloid leukemia, acute myeloid leukemia, non-Hodgkin lymphoma, multiple myeloma and all B-cell malignancies.

Results – Among 21,087 workers, adjusted RRs for butadiene and all leukemia (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 leukemia (p=0.014) and for lymphoid leukemia (52 deaths, p=0.007). Styrene exposure-response trends for all leukemia and lymphoid leukemia were less consistent than those for butadiene. Cumulative exposures to butadiene and styrene were not associated consistently with myeloid leukemias or the B-cell malignancies, non-Hodgkin lymphoma and multiple myeloma.

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

Key words: Leukemia, rubber, occupational health.

INTRODUCTION

Synthetic rubber polymer manufacturing began in the United States (US) 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 polymerization, 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 Program[4] and other agencies have classified butadiene as a human carcinogen causing lymphohematopoietic cancer (LHC), especially leukemia. 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 leukemia, non-Hodgkin 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% confidence intervals (CIs); results pertaining to

B-cell malignancies; results for acute myeloid leukemia (AML), reported to be associated with styrene exposure[5]; results for each monomer and leukemia, 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 one year and 4,861 women employed for at least one day before 1 January 1992. Turnover among male employees in the first year of employment at the plants was large. The one-year duration of employment criterion was imposed on the large male cohort to maximize 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 4,079 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-, work area/job- 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- 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 leukemia, 84% of multiple myeloma cases and confirmed the diagnoses of 100% leukemia 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 analyze 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 (e.g., Spearman rank correlation coefficient = 0.89 for butadiene ppm-years and HITs).

Outcomes

Outcomes were all leukemia, lymphoid leukemia, myeloid leukemia, AML, NHL, multiple myeloma and all B-cell malignancies, including lymphoid leukemia, 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 leukemia. 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 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.[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 hazard ratios 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 hazard ratios, interpreted as rate ratios (RRs), and 95% 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 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 leukemia, 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 leukemia, we analyzed 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 leukemia decedents; and higher styrene exposure, defined as exposure at or above the median value. We also analyzed styrene exposure-response, stratified by lower (below the median value, 121 ppm-years) versus higher ($\geq$ 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 leukemia decedents (for analyses of all leukemias, lymphoid leukemia, myeloid leukemia 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 leukemia in analyses that excluded exposures above the 95th percentile[11] or categorized 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: (a) a monomer exposure parameter estimate within 5% of that obtained in the corresponding full model and (b) the fewest covariates.

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

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

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 leukemia, 52 for lymphoid leukemia, 67 for myeloid leukemia, 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 leukemia and lymphoid leukemia decedents. Supplemental Table S1 shows decedents with each outcome, cross-classified by quartiles of butadiene and styrene ppm-years.

All leukemia

For butadiene, RCS analyses (Figure 1a and 1b and Supplemental Figure S1a) indicated that the adjusted RR for all leukemia increased in an approximately linear fashion at exposures below about 1,000 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: $\beta=2.55\text{x}10^{-4}$, 95%

CI=(0.52 to 4.57)x10^{-4}, trend p=0.014) (excluding unexposed: β=2.50x10^{-4}, 95% CI=(0.27 to 4.73)x10^{-4}, trend p=0.028). Trimming to restrict data to ppm-years >0 and ≤95th percentile (1,144 ppm-years) of all leukemia decedents yielded a somewhat stronger exposure-response trend for butadiene (β=9.94x10^{-4}, 95% CI=(1.88 to 18.00)x10^{-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 (1,156.83 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 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 2a and 2b and Supplemental Figure S2a) 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 versus higher exposure to the other monomer, found that the butadiene exposure-response association was evident only in the category of higher styrene exposure (β=2.89x10^{-4}, 95% CI=(0.41 to 5.36)x10^{-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 leukemia (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: β=3.81x10^{-4}, 95%

CI=(1.05 to 6.58)x10^{-4}, trend p=0.007; excluding unexposed: β=4.78x10^{-4}, 95% CI=(1.34 to 8.23)x10^{-4}, trend p=0.007). For all myeloid leukemia 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 leukemia (β=15.40x10^{-4}, 95% CI=(4.19 to 26.53)x10^{-4}, trend p=0.007) but not for all myeloid leukemia or AML.

For styrene, analyses by quartile of ppm-years yielded results similar to those for butadiene ppm-years for lymphoid leukemia, all myeloid leukemia 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 leukemia, 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 (1,083 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 leukemia and lymphoid leukemia, butadiene exposure-response beta coefficients were similar regardless of the exposure lag applied. For all leukemia, trends were not statistically significant

for styrene exposure lagged 10 or 20 years. For lymphoid leukemia, 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 percent of reduced models yielded exposure parameter estimates that were within 5% of those in full models, and all were within 10% (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.

Leukemia

Internal Cox regression analyses of all leukemia found a statistically significant exposure-response trend for butadiene but not for styrene. Analyses of major subtypes of leukemia indicated that for lymphoid leukemia 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 leukemia 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 leukemias and lymphoid leukemia, the butadiene trends were three to four times stronger when data were restricted to ppm-years >0 and $\leq 95^{th}$ percentile (1,144 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 leukemias or other outcomes, 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 leukemia, 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 leukemia that were null or weakly positive.[25-28]

With regard to styrene, increased risks of LHC, particularly leukemia 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 leukemia 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 leukemia.[31-33] However, studies of several other cohorts of reinforced plastics workers found little evidence of an association between styrene and overall leukemia.[34-37]

With regard to exposure to butadiene or styrene and cell-type specific leukemias, 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 leukemia.

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 leukemia.[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 leukemias 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 to 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 leukemia and supports the classification of butadiene as a human carcinogen. Results supported an association between butadiene and lymphoid leukemia, but not myeloid leukemia. Evidence of an independent causal association between styrene and leukemia 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 leukemia, including NHL and multiple myeloma.

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Institution and Ethics approval and informed consent: The Institutional Review Board of the University of Alabama at Birmingham reviewed and approved the study protocol.

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Disclaimer: None

1. 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 leukemia 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 lymphohematopoietic cancer, especially leukemia, and classified styrene as probably carcinogenic to humans.

2. What are the new findings?

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

3. 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.

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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 (4,508)	1,190 (26)	>0.00-1980	8.0 (1.6-45)	76 (184)	1,416 (31)	>0.00-380	1.8 (0.3-11)	19 (48)
Plant, location								
1, Kentucky (1,563)	1,144 (73)	>0.00-1499	75 (15-245)	195 (280)	1,171 (75)	0.01-477	20 (5.8-48)	38 (53)
2, Louisiana (2,463)	1,815 (74)	0.05-4185	72 (20-230)	251 (502)	1,782 (72)	>0.00-1469	16 (4.6-57)	71 (169)
3, Louisiana (2,849)	1,524 (53)	0.01-9264	73 (15-320)	483 (1267)	2,092 (73)	>0.00-1618	13 (3.7-48)	65 (178)
4, Texas (2,929)	1,690 (58)	>0.00-2114	38 (10-134)	132 (239)	2,227 (76)	>0.00-516	5.9 (1.7-22)	21 (40)
5, Ontario (7,044)	4,936 (70)	>0.00-5141	43 (8.3-143)	139 (282)	4,846 (69)	>0.00-442	12 (2.4-36)	33 (54)
6, Texas (4,239)	2,895 (68)	0.02-1575	32 (8.6-120)	102 (174)	3,304 (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 (5,978)	2,128 (36)	>0.00-916	7.4 (1.7-23)	24 (59)	2,016 (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 (2,413)	1,731 (72)	0.01-9264	105 (18-368)	526 (1236)	2,125 (88)	0.01-1618	24 (5.5-87)	105 (225)
Hire year								
1943-1949 (5,404)	3,600 (67)	>0.00-9264	77 (20-253)	257 (650)	3,938 (73)	0.01-1618	13 (3.8-48)	50 (125)
1950-1959 (5,613)	4,005 (71)	>0.00-9063	97 (30-266)	260 (617)	4,279 (76)	0.02-1462	25 (6.4-56)	55 (117)
1960-1969 (4,333)	2,871 (66)	>0.00-7102	42 (11-130)	134 (334)	3,065 (71)	>0.00-1105	13 (3.3-34)	30 (63)
>=1970 (5,737)	3,528 (62)	>0.00-4516	12 (3.0-41)	75 (287)	4,140 (72)	>0.00-697	3.8 (0.9-13)	16 (51)
All decedents (9,665)	6,914 (72)	>0.00-9264	79 (21-245)	245 (607)	7,481 (77)	>0.00-1618	17 (4.4-49)	50 (119)
All leukemia (132)	103 (78)	1.92-7741	121 (34-364)	367 (873)	109 (83)	1.09-1203	27 (8.4-61)	62 (158)
Lymphoid leukemia (52)	39 (75)	1.92-7741	225 (45-425)	542 (1303)	42 (81)	1.65-1203	29 (8.6-69)	90 (243)
Myeloid leukemia (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)

*Abbreviations: AML, acute myeloid leukemia; NHL, non-Hodgkin lymphoma.

†Included lymphoid leukemia, non-Hodgkin lymphoma and multiple myeloma.

‡Number of exposed employees (% of total number in each group).

Table 2 Exposure-response analyses of butadiene or styrene ppm-years and leukemia: number (N) of cases, adjusted rate ratio (RR) with 95% confidence interval (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‡	$2.55x10^{-4}$ [(0.52 to 4.57) $x10^{-4}$], p=0.014, AIC=2384, N=132			$1.04x10^{-3}$ [(−0.26 to 2.33) $x10^{-3}$], p=0.116, AIC=2386, N=132		
Exposed person-time: β [95% CI], trend p-value, AIC, N	$2.50x10^{-4}$ [(0.27 to 4.73) $x10^{-4}$], p=0.028, AIC=1786, N=103			$0.84x10^{-3}$ [(−0.51 to 2.20) $x10^{-3}$], p=0.220, AIC=1912, N=109		
Exposed person-time ≤95th percentile§: β [95% CI], trend p-value, AIC, N	$9.94x10^{-4}$ [(1.88 to 18.00) $x10^{-4}$], p=0.016, AIC=1673, N=97			$4.05x10^{-3}$ [(−1.19 to 9.30) $x10^{-3}$], p=0.130, AIC=1795, N=103		
Stratified¶:						
Styrene <27.00 ppm-years	$1.34x10^{-4}$ [(−20.94 to 23.61) $x10^{-4}$], p=0.907, AIC=1340, N=77					
Styrene ≥27.00 ppm-years	$2.86x10^{-4}$ [(0.38 to 5.34) $x10^{-4}$], p=0.024, AIC=870, N=55					
Butadiene <121.28 ppm-years				$-7.26x10^{-4}$ [(−120.19 to 105.67) $x10^{-4}$], p=0.900, AIC=1415, N=80		
Butadiene ≥121.28 ppm-years				$4.17x10^{-4}$ [(−12.45 to 20.78) $x10^{-4}$], 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 of butadiene within the stratum ≥27.00 styrene ppm-years, the data were restricted to men due to the lack of events among women; for the model of styrene within the stratum ≥121.28 butadiene ppm-years, the data were restricted to ever-hourly men due to the lack of events among female and never hourly workers.

†Quartile (Q) cutpoints were at the following values of ppm-years:

- butadiene: Q2, 34.00; Q3, 121.28; Q4, 363.64, maximum=7,741.41
- styrene: Q2, 5.76; Q3, 27.00; Q4, 60.53, maximum=1,203.21.

‡AIC, Akaike information criterion; N, number of cases included in the model.

§95th percentile was at 1,144 ppm-years for butadiene and 171 ppm-years for styrene.

¶Models used all person-time.

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

Model*, Form of LHC	**Butadiene**			**Styrene**		
Lymphoid leukemia						
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‡	$3.81x10^{-4}$ [(1.05 to 6.58) $x10^{-4}$], p=0.007, AIC=933, N=52			$1.63x10^{-3}$ [(0.03 to 3.23) $x10^{-3}$], p=0.046, AIC=936, N=52		
Exposed person-time: β [95% CI], trend p-value, AIC, N	$4.78x10^{-4}$ [(1.34 to 8.23) $x10^{-4}$], p=0.007, AIC=664, N=39§			$1.24x10^{-3}$ [(−0.43 to 2.91) $x10^{-3}$], p=0.146, AIC=727, N=42§		
Exposed person-time ≤95th percentile: β [95% CI], trend p-value, AIC, N	$15.40x10^{-4}$ [(4.19 to 26.53) $x10^{-4}$], p=0.007, AIC=625, N=37§			$3.33x10^{-3}$ [(−4.81 to 11.47) $x10^{-3}$], p=0.422, AIC=689, N=40§		
Myeloid leukemia						
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	$1.09x10^{-4}$ [(−3.01 to 5.18) $x10^{-4}$], p=0.602, AIC=1235, N=67			$-2.36x10^{-4}$ [(−32.20 to 27.48) $x10^{-4}$], p=0.877, AIC=1235, N= 67		
Exposed person-time: β [95% CI], trend p-value, AIC, N	$0.63x10^{-4}$ [(−3.89 to 5.15) $x10^{-4}$], p=0.784, AIC=941, N=53¶			$-3.77x10^{-4}$ [(−35.71 to 28.17) $x10^{-4}$], p=0.817, AIC=1006, N=56		
Exposed person-time ≤95th percentile: β [95% CI], trend p-value, AIC, N	$-0.16x10^{-4}$ [(−14.68 to 14.37) $x10^{-4}$], p=0.983, AIC=880, N=50¶			$29.50x10^{-4}$ [(−49.06 to 108.13) $x10^{-4}$], p=0.461, AIC=963, N=54		
Acute myeloid leukemia						
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	$-1.08x10^{-4}$ [(−9.12 to 6.97) $x10^{-4}$], p=0.793, AIC=746, N=41			$-6.23x10^{-4}$ [(−51.03 to 38.56) $x10^{-4}$], p=0.785, AIC= 746, N=41		
Exposed person-time: β [95% CI], trend p-value, AIC, N	$-2.27x10^{-4}$ [(−12.25 to 7.70) $x10^{-4}$], p=0.655, AIC=561, N=32¶			$-1.13x10^{-3}$ [(−6.48 to 4.22) $x10^{-3}$], p=0.679, AIC=623, N=35		

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

Model*, Form of LHC	**Butadiene**			**Styrene**		
Exposed person-time ≤95th percentile: β [95% CI], trend p-value, AIC, N	$-1.34x10^{-3}$ [(−3.93 to 1.25) $x10^{-3}$], p=0.310, AIC=540, N=31¶			$-3.02x10^{-3}$ [(−15.36 to 9.32) $x10^{-3}$], p=0.631, AIC=602, N=34		
Non-Hodgkin 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	$0.26x10^{-4}$ [(−3.73 to 4.25) $x10^{-4}$], p=0.898, AIC= 1976, N=110			$-0.23x10^{-3}$ [(−2.62 to 2.17) $x10^{-3}$], p=0.854, AIC=1976, N=110		
Exposed person-time: β [95% CI], trend p-value, AIC, N	$1.55x10^{-4}$ [(−2.49 to 5.58) $x10^{-4}$], p=0.452, AIC=1317, N=76			$-0.15x10^{-3}$ [(−2.56 to 2.26) $x10^{-3}$], p=0.900, AIC=1506, N=86		
Exposed person-time ≤95th percentile: β [95% CI], trend p-value, AIC, N	$14.80x10^{-4}$ [(5.68 to 23.99) $x10^{-4}$], p=0.002, AIC=1286, N=75			$4.20\ x10^{-3}$ [(−0.73 to 9.13) $x10^{-3}$], 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	$-0.82x10^{-4}$ [(−5.08 to 3.45) $x10^{-4}$], p=0.707, AIC=1056, N=60			$0.15x10^{-3}$ [(−1.55 to 1.85) $x10^{-3}$], p=0.858, AIC=1056, N=60		
Exposed person-time: β [95% CI], trend p-value, AIC, N	$-0.36x10^{-4}$ [(−4.86 to 4.14) $x10^{-4}$], p=0.876, AIC=669, N=40			$0.31x10^{-3}$ [(−1.44 to 2.05) $x10^{-3}$], p=0.731, AIC=730, N=43		
Exposed person-time ≤95th percentile: β [95% CI], trend p-value, AIC, N	$5.83x10^{-4}$ [(−7.64 to 19.30) $x10^{-4}$], p=0.396, AIC=634, N=38			$-1.61x10^{-3}$ [(−9.61 to 6.38) $x10^{-3}$], 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	$1.15x10^{-4}$ [(−0.75 to 3.05) $x10^{-4}$], p=0.237, AIC=3785, N=213			$5.65x10^{-4}$ [(−4.74 to 16.03) $x10^{-4}$], p=0.287, AIC=3785, N=213		

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

Model*, Form of LHC	**Butadiene**	**Styrene**
Exposed person-time: β [95% CI], trend p-value, AIC, N	$1.95x10^{-4}$ [(−0.11 to 4.02) $x10^{-4}$], p=0.064, AIC=2517, N=148	$5.51x10^{-4}$ [(−5.19 to 16.20) $x10^{-4}$], p=0.313, AIC=2809, N=163
Exposed person-time ≤95th percentile: β [95% CI], trend p-value, AIC, N	$11.00x10^{-4}$ [(4.23 to 17.82) $x10^{-4}$], p=0.002, AIC=2380, N=141	$17.00x10^{-4}$[(−21.05 to 55.06) $x10^{-4}$], 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 1,144 and 171 ppm-years for butadiene and styrene, respectively, for leukemias and above 1,083 and 213 ppm-years for butadiene and styrene, respectively, for non-Hodgkin lymphoma, multiple myeloma and B-cell malignancy.

†Quartile (Q) cutpoints were at the following values of ppm-years:

Lymphoid leukemia –

- butadiene: Q2, 44.73; Q3, 213.43; Q4, 376.31, maximum=7,741.41
- styrene: Q2, 8.52; Q3, 27.21; Q4, 69.29, maximum=1,203.21

Myeloid leukemia –

- butadiene: Q2, 25.20; Q3, 70.05; Q4, 230.08, maximum=–2,009.71
- styrene: Q2, 5.21; Q3, 20.71; Q4, 48.25, maximum=340.52

Acute myeloid leukemia –

- butadiene: Q2, 19.14; Q3, 59.19; Q4, 185.63, maximum=2,009.71
- styrene: Q2, 5.21; Q3, 19.73; Q4, 34, maximum=340.52

Non-Hodgkin lymphoma –

- butadiene: Q2, 17.94; Q3, 117.22; Q4, 334.83, maximum=1,495.51
- styrene: Q2, 5.97; Q3, 23.61; Q4, 59.67, maximum=231.34

Multiple myeloma –

- butadiene: Q2, 31.42; Q3, 107.78; Q4, 386.04, maximum=2,397.73
- styrene: Q2, 2.80; Q3, 14.67; Q4, 77.99, maximum=839.61

B-cell malignancy –

- butadiene: Q2, 27.04; Q3, 124.38; Q4, 370.89, maximum=7,741.41
- styrene: Q2, 4.63; Q3, 20.74; Q4, 61.70, maximum=1,203.21.

‡ 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.

Table 4 Adjusted* beta-coefficient (β) with 95% confidence interval (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 lymphohematopoietic cancers (LHC)

Monomer, Form of LHC, Lag period (years)	**β**	**95% CI**	**Trend p-value**	**AIC**
I. Butadiene				
All leukemia				
0	$2.55\text{x}10^{-4}$	(0.52 to 4.57) $\text{x}10^{-4}$	0.014	2384
10	$2.58\text{x}10^{-4}$	(0.38 to 4.78) $\text{x}10^{-4}$	0.022	2337
20	$2.63\text{x}10^{-4}$	(−0.05 to 5.31) $\text{x}10^{-4}$	0.055	2120
Lymphoid leukemia				
0	$3.81\text{x}10^{-4}$	(1.05 to 6.58) $\text{x}10^{-4}$	0.007	933
10	$3.73\text{x}10^{-4}$	(0.78 to 6.68) $\text{x}10^{-4}$	0.013	933
20	$3.00\text{x}10^{-4}$	(−0.70 to 6.69) $\text{x}10^{-4}$	0.112	868
Myeloid leukemia				
0	$1.09\text{x}10^{-4}$	(−3.01 to 5.18) $\text{x}10^{-4}$	0.602	1235
10	$1.16\text{x}10^{-4}$	(−3.33 to 5.66) $\text{x}10^{-4}$	0.612	1189
20	$2.11\text{x}10^{-4}$	(−2.90 to 7.11) $\text{x}10^{-4}$	0.410	1054
Acute myeloid leukemia				
0	$-1.08\text{x}10^{-4}$	(−9.12 to 6.97) $\text{x}10^{-4}$	0.793	746
10	$-0.72\text{x}10^{-4}$	(−8.54 to 7.10) $\text{x}10^{-4}$	0.857	724
20	$-0.14\text{x}10^{-4}$	(−8.85 to 8.57) $\text{x}10^{-4}$	0.975	641
Non-Hodgkin lymphoma				
0	$0.26\text{x}10^{-4}$	(−3.73 to 4.25) $\text{x}10^{-4}$	0.898	1976
10	$1.10\text{x}10^{-5}$	(−43.61 to 45.80) $\text{x}10^{-5}$	0.962	1973
20	$-6.18\text{x}10^{-5}$	(−67.04 to 54.67) $\text{x}10^{-5}$	0.842	1876
Multiple myeloma				
0	$-0.82\text{x}10^{-4}$	(−5.08 to 3.45) $\text{x}10^{-4}$	0.707	1056
10	$-7.54\text{x}10^{-5}$	(−52.81 to 37.74) $\text{x}10^{-5}$	0.744	1054
20	$-9.77\text{x}10^{-5}$	(−64.26 to 44.73) $\text{x}10^{-5}$	0.725	955
B-cell malignancy				
0	$1.15\text{x}10^{-4}$	(−0.75 to 3.05) $\text{x}10^{-4}$	0.237	3785
10	$1.13\text{x}10^{-4}$	(−0.95 to 3.21) $\text{x}10^{-4}$	0.287	3779
20	$0.73\text{x}10^{-4}$	(−1.95 to 3.40) $\text{x}10^{-4}$	0.595	3517
II. Styrene				
Leukemia				
0	$1.04\text{x}10^{-3}$	(−0.26 to 2.33) $\text{x}10^{-3}$	0.116	2386
10	$1.03\text{x}10^{-3}$	(−0.38 to 2.45) $\text{x}10^{-3}$	0.153	2339
20	$0.96\text{x}10^{-3}$	(−0.82 to 2.74) $\text{x}10^{-3}$	0.289	2122

Table 4 Adjusted* beta-coefficient (β) with 95% confidence interval (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 lymphohematopoietic cancers (LHC)

Monomer, Form of LHC, Lag period (years)	**β**	**95% CI**	**Trend p-value**	**AIC**
Lymphoid leukemia				
0	1.63×10^{-3}	$(0.03 \text{ to } 3.23) \times 10^{-3}$	0.046	936
10	1.67×10^{-3}	$(-0.06 \text{ to } 3.40) \times 10^{-3}$	0.058	934
20	1.43×10^{-3}	$(-0.74 \text{ to } 3.60) \times 10^{-3}$	0.197	869
Myeloid leukemia				
0	-2.36×10^{-4}	$(-32.20 \text{ to } 27.48) \times 10^{-4}$	0.877	1235
10	-4.37×10^{-4}	$(-39.04 \text{ to } 30.30) \times 10^{-4}$	0.805	1189
20	-3.53×10^{-4}	$(-46.45 \text{ to } 39.40) \times 10^{-4}$	0.872	1054
Acute myeloid leukemia				
0	-6.23×10^{-4}	$(-51.03 \text{ to } 38.56) \times 10^{-4}$	0.785	746
10	-4.02×10^{-4}	$(-47.81 \text{ to } 39.77) \times 10^{-4}$	0.857	724
20	-2.72×10^{-4}	$(-54.77 \text{ to } 49.32) \times 10^{-4}$	0.918	641
Non-Hodgkin lymphoma				
0	-0.23×10^{-3}	$(-2.62 \text{ to } 2.17) \times 10^{-3}$	0.854	1976
10	-3.04×10^{-4}	$(-29.50 \text{ to } 23.43) \times 10^{-4}$	0.822	1973
20	-7.57×10^{-4}	$(-42.45 \text{ to } 27.30) \times 10^{-4}$	0.670	1876
Multiple myeloma				
0	0.15×10^{-3}	$(-1.55 \text{ to } 1.85) \times 10^{-3}$	0.858	1056
10	1.04×10^{-4}	$(-17.61 \text{ to } 19.70) \times 10^{-4}$	0.913	1054
20	-0.52×10^{-4}	$(-23.95 \text{ to } 22.90) \times 10^{-4}$	0.965	955
B-cell malignancy				
0	5.65×10^{-4}	$(-4.74 \text{ to } 16.03) \times 10^{-4}$	0.287	3785
10	5.42×10^{-4}	$(-5.97 \text{ to } 16.81) \times 10^{-4}$	0.351	3779
20	3.36×10^{-4}	$(-11.18 \text{ to } 17.91) \times 10^{-4}$	0.651	3517