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1,3-Butadiene and leukemia among synthetic rubber industry workers: Exposure–response relationships

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Available online 13 October 2006

Abstract

Previous research updated the mortality experience of North American synthetic rubber industry workers during the period 1944–1998, determined if leukemia and other cancers were associated with several employment factors and carried out Poisson regression analysis to examine exposure–response associations between estimated exposure to 1,3-butadiene (BD) or other chemicals and cancer. The present study used Cox regression procedures to examine further the exposure–response relationship between several unlagged and lagged, continuous, time-dependent BD exposure indices (BD parts per million (ppm)-years, the total number of exposures to BD concentrations >100 ppm ("peaks") and average intensity of BD) and leukemia, lymphoid neoplasms and myeloid neoplasms. All three BD exposure indices were associated positively with leukemia. Using continuous, untransformed BD ppm-years the regression coefficient (β) from an analysis that controlled only for age was 2.9×10^{-4} ($p < 0.01$); the regression coefficient adjusted for all covariates (age, year of birth, race, plant, years since hire and dimethyldithiocarbamate) was similar in magnitude ($\beta = 3.0 \times 10^{-4}$, $p = 0.04$). Lagging exposure had minimal impact on the results for leukemia for any of the three BD exposure indices. In models that controlled only for age, lymphoid neoplasms were associated with BD ppm-years and myeloid neoplasms, with BD peaks, but neither trend was statistically significant after adjusting for multiple covariates. The present results support the presence of a causal relationship between high cumulative exposure and high intensity of exposure to BD and leukemia.
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Keywords: 1,3-Butadiene; Leukemia; Lymphoid neoplasms; Myeloid neoplasms; Synthetic rubber industry

1. Introduction

We recently described an updated retrospective follow-up study of North American synthetic rubber industry workers [1,2]. The study examined mortality from leukemia and other cancers during the period 1944–1998 by duration of employment, time since hire, work area and estimated exposure to the monomers 1,3-butadiene (BD) and styrene and the polymerization shortstopping agent dimethyldithiocarbamate (DMDTC). The International Agency for Research on Cancer has classified BD as a probable human carcinogen (group 2A) [3] and styrene as possibly carcinogenic to humans (group 2B) [4]. DMDTC is an immune system depressant [5,6]. The updated study found that subgroups of workers with long duration of employment, many years since hire in the industry and history of employment in certain work areas had an excess of mortality from leukemia [1]. Cumulative exposure to BD

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was associated positively with all leukemia, but controlling for styrene and DMDTC attenuated this association [2]. The latter results were based on Poisson regression analyses in which BD and covariates were categorical variables. The present study used Cox proportional hazards models to examine further the exposure–response relationship between several indices of exposure to BD and leukemia and to estimate the exposure–response relationship between BD and all lymphoid neoplasms or all myeloid neoplasms.

2. Methods

In previous publications, we described plant operations and the methods used to identify subjects, to develop work histories and exposure estimates, and to determine vital status for the follow-up period of 1944–1998 [1,2,7]. Subjects included in the present study were 16,579 men classified as having worked, before 1 January 1992, for at least one year at any of six synthetic rubber plants, located in Texas (two plants), Louisiana (two plants), Kentucky (one plant) and Canada (one plant).

As described in detail elsewhere [8,9], we developed quantitative estimates of each subject's exposure to butadiene, styrene and DMDTC by identifying at each plant a series of work area/job groups, each of which was homogeneous with respect to its component tasks and exposure potential; identifying for each plant-specific work area/job group its component tasks that entailed exposure and documenting historical changes in those tasks; calculating plant-, work area/job group- and time-specific average exposure indices (8 h time-weighted average concentration) and compiling these into job-exposure matrices (JEMs); and linking the time- and work area/job group-specific exposure estimates in the JEMs with each subject's work history to obtain cumulative exposure estimates. The BD exposure indices analyzed for this paper were: (a) cumulative exposure to BD in parts per million (ppm)-years; (b) cumulative number of exposures to >100 ppm BD, referred to as peaks; (c) average intensity (ppm) of exposure to BD.

We used linkages with several national databases to determine subjects' vital status as of the end of 1998 [1]. Vital status ascertainment was about 97% complete. Cause of death information came from death certificates, the US National Death Index (NDI Plus) and the Canadian Mortality Data Base. We sought medical records for all subjects whose death certificate mentioned leukemia or any other cancer of the lymphatic and hematopoietic tissues. In total, we identified 81 decedents with leukemia.

Of the 16,579 subjects in updated study, 488 subjects were excluded from the Cox regression analyses of leukemia because they dropped out of follow-up at ages younger than the youngest leukemia decedent (age 33 years). Thus, results of leukemia analyses were based on 16,091 subjects and 485,732 person-years of observation.

We used Cox regression, with age as the time variable: (a) to describe the BD-leukemia exposure–response relationship using penalized smoothing splines; (b) to obtain an estimate of the rate ratio (RR) and the 95% confidence interval (CI) for leukemia in each decile of BD exposure, compared to the unexposed; (c) to estimate the slope of the exposure–response trend using continuous BD variables [10]. The measure of association in these analyses was the hazard ratio, which can be interpreted as a RR. All exposure variables, as well as age and time since hire, were time-dependent. The models provided maximum partial likelihood estimates of the RR of leukemia across the exposure range experienced by subjects in the study. In this paper, we present the results of two sets of models. One set estimated of the association between a BD exposure variable and the outcome of interest, adjusting only for age. The second set estimated the association between a BD exposure variable and the outcome of interest, adjusting for age, as well as other potential confounders (see below).

We used penalized spline regression to smooth splines with equally spaced "knots" [10,11]. This procedure reduces assumptions about the form of the BD exposure–response curve and, in particular, accommodates different exposure–response slopes at "local" levels throughout the exposure range, with the segments of the exposure range demarcated by knots. We used S-Plus software to fit the smoothing splines. The procedure uses Akaike's information criteria (AIC) to select the "best" amount of smoothing (degrees of freedom (d.f.) and number of knots). AIC is a measure of goodness of model fit based on the deviance with a penalty for over-fitting measured by the d.f. The procedure specified 4 d.f. and 10 knots both for BD ppm-years and for BD peaks and specified 9 d.f. and 23 knots for BD ppm. Visual inspection of the graphical results of the penalized smoothing spline regressions allowed us to evaluate informally the adequacy of the Cox regression models that estimated a single regression coefficient (slope of the BD-leukemia exposure–response relationship) using continuous BD variables. Penalized spline regressions indicated that the exposure–response pattern for a particular BD variable in models that adjusted only for age was similar to the pattern in models that adjusted for multiple covariates, and we present only the former.

We further examined the trend in exposure–response relationships using: (a) deciles of each of the three BD variables; (b) continuous, untransformed BD variables; (c) natural logarithm (ln)-transformed and square-root transformed continuous BD variables. Each of these approaches has certain advantages. Analyses of continuous exposure variables do not require an arbitrary specification of exposure categories. Compared to analyses that use continuous exposure variables, analyses using deciles (or other quantiles) of BD exposure avoid assumptions about the functional form of a continuous exposure–response relationship and may reduce the influence of data at extreme exposure values and, in particular, may reduce the impact of misclassification that some investigators have suggested might selectively affect the upper range of exposure estimates [12,13]. Analyses using ln- or square root-transformed continuous BD variables also may reduce the influence of data at extreme exposure values.

Cutpoints for exposure deciles were based on the distribution of the 71 exposed leukemia decedents. To estimate the trend across deciles of BD, we assigned to each observation in a particular decile the mean value of BD exposure, determined from all observations in the decile [14]. We refer to the resulting variable as "mean-scored BD deciles." Our decision to use deciles instead of a smaller number of exposure categories such as quintiles was based on concern that it could be inappropriate to assume a constant effect within an exposure category if the category is "wide." Grouping by deciles of exposure could result in a better approximation of the exposure–response relationship, despite the fact that the exposure category-specific RR estimates would be less statistically stable than those obtained from an analysis that used fewer exposure categories. For BD ppm-years, we examined the impact on the magnitude of the exposure–response trend of using five or 20 mean-scored exposure categories, rather than deciles of exposure.

We compared the estimated partial likelihood among the different Cox regressions, using the convention that the model with the smallest value of (-2 log likelihood) has the best statistical fit. We evaluated the proportional hazards assumption for all the final Cox models by including an age–exposure interaction term in a model. Both untransformed and ln-transformed age were used in the construction of an interaction terms. None of the age–exposure interaction terms was statistically significant.

Potential confounders included categorical forms of DMDTC mg-years/cm (0, >0–<185.3, 185.3–<739.4, 739.4–<1610.3, 1610.3+), race (non-white, other), plant [1,3,4,6–8], years since hire (<20, 20–29, 30+ years) and year of birth (<1909, 1909–1915, 1916–1922, 1923–1932, 1933+). Plant was a surrogate for unmeasured workforce characteristics that may have varied by geographic region, and we included year of birth in order to adjust for a possible birth cohort effect. DMDTC mg-years/cm and years since hire were time-dependent variables. Categories of year of birth were quintiles determined from the distribution of all 81 leukemia decedents. Categories of DMDTC were no exposure and quartiles, determined from the distribution 64 leukemia decedents exposed to DMDTC. We also adjusted for DMDTC as a continuous variable in some models. Because there was no monotonic relationship between DMDTC and leukemia, the continuous variable did not have any impact on the regression coefficients for BD exposure variables, while the categorical DMDTC variable decreased BD regression coefficients by more than 20% in most models.

We did not adjust for exposure to styrene. Epidemiologic research has not provided consistent evidence that this agent causes leukemia in humans [4]. In our study, styrene (treated as a continuous variable) was moderately to strongly correlated with BD ppm-years (Pearson correlation coefficient, $r = 0.85$, $p < 0.01$) and BD average intensity ($r = 0.53$, $p < 0.01$) and weakly correlated with BD peaks ($r = 0.015$, $p < 0.01$). Controlling for styrene, in addition to other covariates, increased the strength of the association between leukemia and BD ppm-years and had little impact on results for other BD variables.

To account for the possibility that exposure occurring relatively close in time to death from leukemia did not contribute to the causation of leukemia, some analyses used lagged BD exposure variables, with lag periods of 5, 10, 15 or 20 years. In these analyses, models adjusting for multiple covariates included, in addition to age as the time variable, year of birth, lagged DMDTC, race and plant.

We used similar Cox regression procedures to evaluate the exposure–response relationship between continuous, untransformed BD exposure variables and lymphoid neoplasms or myeloid neoplasms. Lymphoid neoplasms ($N = 120$) included lymphoid leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma and multiple myeloma. Myeloid neoplasms ($N = 56$) included myeloid and monocytic leukemia, myelofibrosis, myelodysplasia, myeloproliferative disorders and polycythemia vera.

3. Results

On average, the leukemia cases were similar to other subjects with regard to race, age at the close of

Table 1
Characteristics of leukemia decedents and of other subjects included in Cox regression analyses

Characteristics	Number (%) or mean (S.D.)	
	Leukemia decedents	Other subjects
Number of subjects	81 (100.0)	16,010 (100.0)
Race, *N*		
White or unknown race	69 (85)	14,016 (88)
Non-white	12 (15)	1,994 (12)
Year of birth, mean	1920 (14.0)	1930 (17.2)
Year of hire, mean	1952 (9.7)	1960 (13.2)
Age[a], mean	63.5 (12.7)	61.3 (13.4)
Years since hire[a], mean	29.5 (10.9)	30.3 (12.3)
Plant, *N*		
1	10 (12.4)	1,347 (8.4)
3	7 (8.6)	1,906 (11.9)
4	7 (8.6)	1,990 (12.4)
6	15 (18.5)	2,217 (13.9)
7	22 (27.2)	5,264 (32.9)
8	20 (24.7)	3,286 (20.5)
BD ppm-years[a]		
Mean	396.8 (960.5)	199.4 (539.4)
Median	184.7	55.2
BD peaks[a]		
Mean	2601.1 (4625.1)	1465.9 (3209.1)
Median	965.4	401.8
BD average intensity[a] (ppm)		
Mean	35.5 (71.4)	24.0 (54.8)
Median	15.0	8.9

[a] At end of follow-up. Values reported for BD variables were calculated on the basis of exposed subjects (71 leukemias for BD ppm-years, BD peaks and BD average intensity; 12,404 others for BD ppm-years and BD average intensity; 11,234 others for BD peaks).

follow-up and years since hire but were born earlier and hired earlier than other subjects (Table 1). Mean and median values of all BD exposure variables at the end of follow-up were higher for cases than for others.

The three BD exposure variables were correlated, but in general correlations were weaker for continuous than for categorical variables. For example, the Pearson correlation coefficients for continuous BD variables were 0.30 for BD ppm-years and BD peaks, 0.60 for BD ppm-years and BD average intensity and 0.08 for BD peaks and BD average intensity. In contrast, correlation coefficients for categorical (deciles) BD variables were 0.80 for BD ppm-years and BD peaks, 0.74 for BD ppm-years and BD average intensity and 0.54 for BD peaks and BD average intensity.

3.1. Penalized spline regressions

Spline regression indicated that the In hazard ratio for leukemia increased in a fairly linear fashion in the exposure range below the 95th percentile of exposure for each of the three BD variables: that is, up to about 1123 for BD ppm-years (Fig. 1, panel 1-a), to about 7859 for BD peaks (Fig. 1, panel 1-c) and to about 80 ppm for BD average intensity (not displayed). Above these exposure levels, data were sparse (there were only four leukemia decedents), and exposure–response trends were erratic.

Most subsequent Cox regression analyses used the all data, regardless of the exposure level. However, we performed a limited set of analyses of continuous forms of the exposure variables that were restricted to data below the 95th percentile cutpoints mentioned above, i.e., <1123 BD ppm-years, <7859 BD peaks or <80 BD ppm. In Fig. 1, panels 1-b and d display the penalized splines for the restricted data, for BD ppm-years and for BD peaks, respectively.

3.2. RRs for butadiene and leukemia by decile of exposure

The relationship between BD and leukemia was irregular across deciles of all three BD variables (Table 2). After controlling for age, year of birth, race, DMDTC, years since hire and plant, BD peaks was the only exposure variable for which some of the decile-specific RRs were statistically significant.

3.3. Exposure–response in models using continuous BD variables and all data

Models using continuous exposure variables indicated that for BD ppm-years, the exposure–response trend for leukemia was positive and statistically significant in all but two of the eight models evaluated (Table 3). In analyses that used continuous, untransformed BD ppm-years, the regression coefficient (β) adjusted only for age was 2.9×10^{-4} (S.E. $= 1.0 \times 10^{-4}$, $p < 0.01$); the regression coefficient adjusted for all covariates was 3.0×10^{-4} (S.E. $= 1.4 \times 10^{-4}$, $p = 0.04$).

Compared to the regression coefficient obtained when using the continuous form of BD ppm-years, the regression coefficient for the mean-scored decile form of BD ppm-years was about twice as high (adjusted only for age, $\beta = 7.5 \times 10^{-4}$); adjusted for all covariates, $\beta = 5.8 \times 10^{-4}$). Use of mean-scored quintiles yielded an exposure–response association (adjusted only for age, $\beta = 8.4 \times 10^{-4}$, $p < 0.01$); adjusted for all covari-
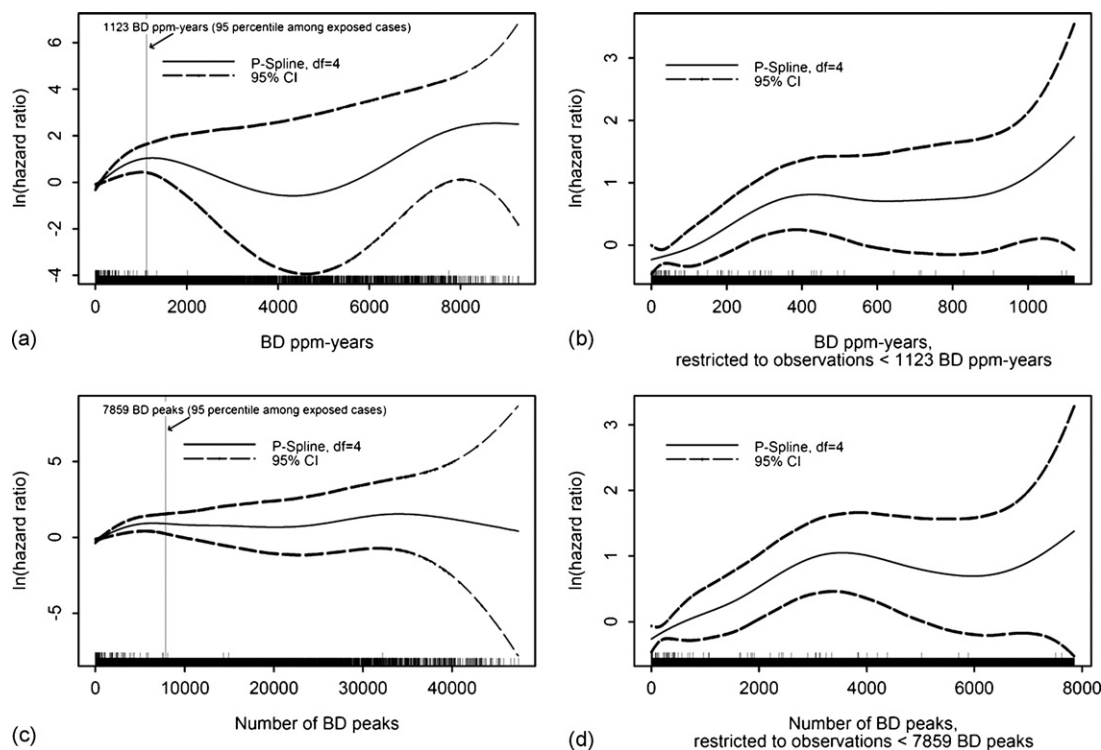
Fig. 1. Penalized splines for BD ppm-years and leukemia (a and b) and for BD peaks and leukemia (c and d). Rugs just above the *x*-axis of each figure depict the frequency of observations (lower rug) and leukemias (upper rug) at corresponding BD variable values.

ates ($\beta = 6.1 \times 10^{-4}$, $p = 0.04$) similar to that observed when we used mean-scored deciles, whereas use of 20 exposure categories resulted in a somewhat weaker relationship (adjusted only for age, $\beta = 4.9 \times 10^{-4}$, $p < 0.01$); adjusted for all covariates ($\beta = 3.8 \times 10^{-4}$, $p = 0.07$).

The exposure–response trend for BD peaks and leukemia was positive and statistically significant in all eight models (Table 3). The exposure–response relationship was slightly stronger for the mean-scored categorical form of BD peaks than for continuous, untransformed BD peaks.

BD average intensity also was associated with leukemia mortality. Adjustment for multiple covariates reduced the magnitude of the exposure–response relationship by 10–48% in all but one model, and after adjustment for multiple covariates, the association was statistically significant only in the model using the square root-transformation of BD ppm.

The statistical fit tended to be poorer for the continuous, untransformed BD variables than for the mean-scored deciles or the ln- or square root-transformed variables. However, results did not suggest a substantially better statistical fit for any of the alternatives.

3.4. Exposure–response in models using continuous BD variables and restricted data

When we restricted the analysis to the lower 95% of the exposure range of all subjects, the exposure–response relationship, estimated using continuous, untransformed BD variables, was larger than the relationship estimated using the full data for all three BD variables. Compared to regression coefficients obtained from the full exposure data, coefficients based on the restricted data and adjusted for multiple covariates, were 4.4 times higher for BD ppm-years ($\beta = 13.1 \times 10^{-4}$, S.E. $= 4.7 \times 10^{-4}$, $p < 0.01$), 3.7 times higher for BD peaks ($\beta = 20.7 \times 10^{-5}$, S.E. $= 6.0 \times 10^{-5}$, $p < 0.01$) and 1.6 times higher for BD ppm ($\beta = 11.3 \times 10^{-3}$, S.E. $= 6.3 \times 10^{-3}$, $p = 0.07$) in analyses of continuous, untransformed exposure variables. For the ln-transformed BD variables, regression coefficients for the restricted data were similar to those for the full data. For the square root-transformed BD variables, regression coefficients for the restricted data were 1.5–1.6 times higher than those for the full data for each of the three exposure variables.

Table 2
Mean value of butadiene (BD) exposure, number (N) of leukemias, estimated rate ratio (RR) and 95% confidence interval (CI) by decile of exposure, for data included in Cox regressions

BD variable and diecile range of values	Mean exposure	N	RR[a] (95% CI)	RR[b] (95% CI)
BD ppm-years				
0	0	10	1.0	1.0
>0–<12.1	4.82	7	1.13 (0.43, 2.98)	0.98 (0.37, 2.61)
12.1–<22.9	17.20	7	2.12 (0.81, 5.56)	1.67 (0.62, 4.50)
22.9–<38.8	30.52	7	2.03 (0.77, 5.34)	1.45 (0.53, 3.97)
38.8–<78.1	56.88	7	1.22 (0.47, 3.22)	0.83 (0.30, 2.32)
78.1–<184.6	124.02	7	0.94 (0.36, 2.46)	0.61 (0.21, 1.73)
184.6–<251.1	215.34	7	2.96 (1.13, 7.79)	1.77 (0.60, 5.24)
251.1–<318.5	282.31	7	4.00 (1.52, 10.51)	2.47 (0.82, 7.44)
318.5–<450.9	374.93	7	3.37 (1.28, 8.86)	1.96 (0.65, 5.87)
450.9–<829.6	606.37	7	2.94 (1.12, 7.73)	1.86 (0.62, 5.55)
829.6+	1852.59	8	3.84 (1.51, 9.76)	2.56 (0.85, 7.66)
ln likelihood test, d.f., p-value			23.19, 10, 0.01	14.41, 10, 0.16
BD number of peaks				
0	0	10	1.0	1.0
>0–<22.8	8.43	8	3.65 (1.44, 9.26)	2.74 (1.04, 7.23)
22.8–<241.9	111.44	7	1.25 (0.47, 3.28)	0.89 (0.32, 2.46)
241.9–<295.1	267.73	7	8.92 (3.39, 23.43)	6.08 (2.16, 17.09)
295.1–<434.9	365.19	7	3.99 (1.52, 10.47)	2.75 (0.98, 7.74)
434.9–<985.4	668.28	7	1.60 (0.60, 4.15)	1.09 (0.38, 3.09)
985.4–<1878.9	1385.44	7	2.32 (0.88, 6.09)	1.54 (0.53, 4.45)
1878.9–<2901.2	2350.77	7	3.74 (1.42, 9.82)	2.71 (0.92, 8.03)
2901.2–<3837.8	3334.46	7	6.92 (2.63, 18.19)	5.05 (1.70, 15.04)
3837.8–<5715.5	4699.74	7	5.77 (2.19, 15.18)	4.11 (1.38, 12.22)
5717.5+	11269.31	7	4.26 (1.62, 11.21)	3.26 (1.07, 9.93)
ln likelihood test, d.f., p-value			39.46, 10, <0.01	28.26, 10, <0.01
BD average intensity (ppm)				
0	0	10	1.0	1.0
>0–<4.8	2.34	7	0.72 (0.28, 1.90)	0.55 (0.20, 1.50)
4.8–<6.5	5.73	7	1.83 (0.70, 4.82)	1.47 (0.54, 4.03)
6.5–<8.2	7.22	7	3.42 (1.35, 8.66)	2.27 (0.85, 6.04)
8.2–<11.0	9.71	8	2.64 (1.00, 6.93)	1.69 (0.60, 4.79)
11.0–<15.0	12.93	7	1.37 (0.50, 3.78)	0.81 (0.27, 2.41)
15.0–<21.5	17.66	7	2.23 (0.88, 5.65)	1.32 (0.48, 3.65)
21.5–<28.4	25.19	7	2.81 (1.07, 7.39)	1.96 (0.70, 5.51)
28.4–<42.3	35.55	7	2.20 (0.84, 5.77)	1.46 (0.52, 4.13)
42.3–<51.6	46.57	7	3.93 (1.50, 10.32)	2.46 (0.86, 7.04)
51.6+	145.51	7	2.35 (0.90, 6.19)	1.43 (0.48, 4.24)
ln likelihood test, d.f., p-value			21.83, 10, 0.02	14.10, 10, 0.17

[a] Rate ratio, controlling only for age.
[b] Rate ratio, controlling for age, year of birth, race, DMDTC, years since hire and plant.

3.5. BD ppm-years and BD peaks

We carried out two additional analyses to attempt to determine if an association between BD ppm-years and leukemia remained after (1) adjusting for BD peaks or (2) restricting the data to observations having values of BD peaks below the median of BD peaks among leukemia decedents (i.e., <965.4 peaks). For the first of these analyses, the Cox regression model that included both BD ppm-years (continuous, untransformed) and BD peaks (continuous, untransformed) indicated that the regression coefficient for both variables was lower than in the corresponding model that included only one of the BD variables. Results were statistically significant for both BD ppm-years ($\beta = 2.5 \times 10^{-4}$, $p = 0.03$) and BD peaks ($\beta = 5.1 \times 10^{-5}$, $p = 0.01$) in the model that controlled only for age. Results were not statistically significant, but regression coefficients were similar to those above, for BD ppm-years ($\beta = 2.5 \times 10^{-4}$, $p = 0.11$) and BD peaks ($\beta = 4.7 \times 10^{-5}$, $p = 0.06$) in models that adjusted for

Table 3
Beta coefficient (β), standard error (S.E.), Wald p-value, and 95% confidence interval (CI) of β for the relation between butadiene (BD) exposure and leukemia, for selected exposure variables and models

BD exposure variable and model[a]	β (S.E.)	p-Value	95% CI	$-2\ln$ likelihood
BD ppm-years, mean-scored deciles				
$RR = e^{\beta x}$				
Model 1	7.5×10^{-4} (2.2×10^{-4})	<0.01	$3.1 \times 10^{-4}, 11.8 \times 10^{-4}$	1379.99
Model 2	5.8×10^{-4} (2.7×10^{-4})	0.03	$0.5 \times 10^{-4}, 11.1 \times 10^{-4}$	1347.25
BD ppm-years, continuous				
$RR = e^{\beta x}$				
Model 1	2.9×10^{-4} (1.0×10^{-4})	<0.01	$0.9 \times 10^{-4}, 4.9 \times 10^{-4}$	1384.12
Model 2	3.0×10^{-4} (1.4×10^{-4})	0.04	$0.1 \times 10^{-4}, 5.8 \times 10^{-4}$	1348.12
$RR = e^{\beta \ln(x+0.0027)}$				
Model 1	9.3×10^{-2} (3.2×10^{-2})	<0.01	$3.1 \times 10^{-2}, 15.6 \times 10^{-2}$	1378.77
Model 2	4.7×10^{-2} (3.7×10^{-2})	0.21	$-2.7 \times 10^{-2}, 12.0 \times 10^{-2}$	1349.67
$RR = e^{\beta \sqrt{x}}$				
Model 1	2.8×10^{-2} (0.7×10^{-2})	<0.01	$1.3 \times 10^{-2}, 4.2 \times 10^{-2}$	1378.19
Model 2	2.5×10^{-2} (1.1×10^{-2})	0.02	$0.4 \times 10^{-2}, 4.6 \times 10^{-2}$	1346.64
BD peaks, mean-scored deciles				
$RR = e^{\beta x}$				
Model 1	9.5×10^{-5} (3.1×10^{-5})	<0.01	$3.5 \times 10^{-5}, 15.6 \times 10^{-5}$	1381.31
Model 2	7.5×10^{-5} (3.7×10^{-5})	0.04	$0.3 \times 10^{-5}, 14.7 \times 10^{-5}$	1347.66
BD peaks, continuous				
$RR = e^{\beta x}$				
Model 1	5.9×10^{-5} (1.9×10^{-5})	<0.01	$2.2 \times 10^{-5}, 9.7 \times 10^{-5}$	1382.82
Model 2	5.6×10^{-5} (2.4×10^{-5})	0.02	$0.8 \times 10^{-5}, 10.4 \times 10^{-5}$	1347.37
$RR = e^{\beta \ln(x+0.0027)}$				
Model 1	9.8×10^{-2} (2.6×10^{-2})	<0.01	$4.7 \times 10^{-2}, 14.9 \times 10^{-2}$	1370.84
Model 2	7.3×10^{-2} (3.1×10^{-2})	0.02	$1.2 \times 10^{-2}, 13.5 \times 10^{-2}$	1345.33
$RR = e^{\beta \sqrt{x}}$				
Model 1	1.2×10^{-2} (0.3×10^{-2})	<0.01	$0.6 \times 10^{-2}, 1.8 \times 10^{-2}$	1375.24
Model 2	1.1×10^{-2} (0.4×10^{-2})	<0.01	$0.4 \times 10^{-2}, 1.9 \times 10^{-2}$	1344.05
BD average intensity (ppm), mean-scored deciles				
$RR = e^{\beta x}$				
Model 1	6.6×10^{-3} (3.1×10^{-3})	0.05	$0.7 \times 10^{-3}, 12.6 \times 10^{-3}$	1385.84
Model 2	3.8×10^{-3} (3.7×10^{-3})	0.40	$-3.5 \times 10^{-3}, 11.0 \times 10^{-3}$	1350.63
BD average intensity (ppm), continuous				
$RR = e^{\beta x}$				
Model 1	3.4×10^{-3} (1.5×10^{-3})	0.02	$0.5 \times 10^{-3}, 6.3 \times 10^{-3}$	1385.22
Model 2	3.6×10^{-3} (2.1×10^{-3})	0.09	$-0.5 \times 10^{-3}, 7.7 \times 10^{-3}$	1348.67
$RR = e^{\beta \ln(x+0.0027)}$				
Model 1	11.4×10^{-2} (4.0×10^{-2})	<0.01	$3.6 \times 10^{-2}, 19.1 \times 10^{-2}$	1379.10
Model 2	6.1×10^{-2} (4.5×10^{-2})	0.17	$-2.6 \times 10^{-2}, 14.9 \times 10^{-2}$	1349.29
$RR = e^{\beta \sqrt{x}}$				
Model 1	8.4×10^{-2} (2.6×10^{-2})	<0.01	$3.2 \times 10^{-2}, 13.5 \times 10^{-2}$	1380.80
Model 2	7.4×10^{-2} (3.7×10^{-2})	0.05	$0.1 \times 10^{-2}, 14.7 \times 10^{-2}$	1347.57

[a] Model 1 controlled only for age; model 2 controlled for age, year of birth, race, DMDTC, years since hire and plant.

multiple covariates. We repeated the analysis, including in the model the continuous, untransformed form or the mean-scored decile form of BD ppm-years and deciles (categorical) of BD peaks. Regression coefficients for BD ppm-years (controlling only for age, $\beta = 2.1 \times 10^{-4}$, $p = 0.11$; controlling for all covariables, $\beta = 2.4 \times 10^{-4}$, $p = 0.13$) were about the same as those estimated with BD peaks included in the models as a continuous variable.

Analyses that restricted the data to observations having values of BD peaks below the median included 46 leukemias. In the restricted data, mean and median values of BD ppm-years at the end of follow-up were 168.1 and 37.9 ppm-years for leukemia decedents compared to 75.8 and 14.4 ppm-years for others. These analyses yielded regression coefficients for BD ppm-years that were not statistically significant but were slightly larger (controlling only for age, $\beta = 4.4 \times 10^{-4}$, $p = 0.19$; controlling for all covariates, $\beta = 4.4 \times 10^{-4}$, $p = 0.40$) than in the full data (controlling only for age, $\beta = 2.9 \times 10^{-4}$, $p = 0.03$; controlling for all covariates, $\beta = 3.0 \times 10^{-4}$, $p = 0.19$).

3.6. Lagged exposure

Lagging exposure had the greatest impact on the relationship between BD average intensity and leukemia, with a lag period of at least 10 years strengthening both the magnitude and the statistical significance of the association (Table 4). There was no clear effect of lagging on the relationship between BD ppm-years or BD peaks and leukemia.

3.7. Lymphoid and myeloid neoplasms

In models that controlled only for age, lymphoid neoplasms were associated with BD ppm-years and myeloid neoplasms, with BD peaks (Table 5). Neither of these exposure–response relationships was statistically significant after adjusting for multiple covariates.

3.8. DMDTC

As noted earlier, DMDTC, when treated as a continuous variable, was not associated with leukemia in any of our models. RRs for DMDTC, adjusted for BD ppm-years and other covariates, were 2.44 (95% CI, 1.20–4.99), 2.87 (95% CI, 1.42–5.83), 4.45 (95% CI, 2.22–8.95) and 2.10 (95% CI, 1.01–4.36) for exposure quartiles one through four, respectively, compared to the unexposed. Lagging exposure to DMDTC did not change this pattern.

Table 4
Cox regression coefficient (and standard error, S.E.) and (95% confidence interval, CI) for the association between butadiene (BD) ppm-years, BD peaks and BD average intensity (all variables continuous) and leukemia with lag periods of 0, 5, 10, 15 or 20 years

Lag period	Model 1[a], β (S.E.) (95% CI)[b]	Model 2[c], β (S.E.) (95% CI)[b]
BD ppm-years		
0	2.9 (1.0) (0.9, 4.9)[d]	3.0 (1.4) (0.1, 5.8)[d]
5	3.2 (1.1) (1.1, 5.2)[d]	3.2 (1.5) (0.4, 6.1)[d]
10	3.3 (1.2) (1.0, 5.6)[d]	2.9 (1.6) (−0.4, 6.1)
15	3.7 (1.3) (1.0, 6.3)[d]	3.0 (1.9) (−0.7, 6.7)
20	4.2 (1.7) (0.9, 7.5)[d]	3.3 (2.4) (−1.3, 7.9)
BD peaks		
0	5.9 (1.9) (2.2, 9.7)[d]	5.6 (2.4) (0.8, 10.4)[d]
5	6.2 (2.0) (2.3, 10.1)[d]	5.7 (2.5) (0.9, 10.6)[d]
10	6.4 (2.2) (2.1, 10.7)[d]	4.9 (2.8) (−0.6, 10.4)
15	6.6 (2.5) (1.7, 11.4)[d]	4.9 (3.2) (−1.3, 11.1)
20	7.1 (3.9) (1.4, 12.7)[d]	5.3 (3.6) (−1.7, 12.4)
BD average intensity (ppm)		
0	3.4 (1.5) (0.5, 6.3)[d]	3.6 (2.1) (−0.5, 7.7)
5	3.6 (1.5) (0.8, 6.5)[d]	3.8 (2.1) (−0.2, 7.9)
10	4.0 (1.4) (1.2, 6.7)[d]	4.2 (2.1) (0.2, 8.2)[d]
15	4.4 (1.4) (1.8, 7.1)[d]	4.7 (2.0) (0.7, 8.6)[d]
20	4.5 (1.4) (1.7, 7.4)[d]	4.3 (2.0) (0.3, 8.3)[d]

[a] Model 1 controlled only for age.
[b] β, S.E. and CI are $\times 10^{-4}$ for BD ppm-years, $\times 10^{-5}$ for BD peaks, and $\times 10^{-3}$ for BD average intensity.
[c] Model 2 controlled for age, year of birth, race, DMDTC and plant.
[d] $p < 0.05$.

4. Discussion

The Cox regression techniques used in the present study have several advantages over previously reported analytic procedures [2]. Cox regression procedures permit estimation of the exposure–response relationship throughout the exposure range, they potentially provide optimal control of confounding by age, and they may be less affected than Poisson regression analyses by correlations among exposure variables.

The present analyses indicated a positive exposure–response relationship between all BD exposure variables and leukemia. Lagging exposure by 5, 10, 15 or 20 years did not have any major impact on the magnitude of the association. The positive associations between BD exposure indices and leukemia persisted, although with reduced statistical significance, after adjusting for DMDTC and other covariates. Because of statistical imprecision, we were not able to determine if there is any true association between BD ppm-years and leukemia among subjects who were exposed to a relatively low number of high-intensity BD peaks.

For all of the BD variables, most of the models using the mean-scored decile variable yielded larger regres-

Table 5
Beta coefficient (β), standard error (S.E.), *p*-value, 95% confidence interval (CI) and likelihood ratio test for the relation between butadiene (BD) exposure and lymphoid or myeloid neoplasms ($e\beta^x$), for selected exposure variables and models

BD exposure variable and model[a]	β (S.E.)[b]	*p*-value	95% CI[b]	$-2\ln$ likelihood
Lymphoid neoplasms				
BD ppm-years, continuous				
Model 1	2.3 (1.0)	0.02	0.4, 4.2	2045.05
Model 2	2.0 (1.2)	0.10	−0.4, 4.4	2030.70
BD peaks, continuous				
Model 1	2.5 (2.3)	0.28	−2.1, 7.0	2047.78
Model 2	2.4 (2.7)	0.36	−2.8, 7.7	2032.10
BD average intensity (ppm), continuous				
Model 1	0.8 (1.8)	0.65	−2.7, 4.3	2048.55
Model 2	−0.4 (2.1)	0.85	−4.6, 3.8	2032.79
Myeloid neoplasms				
BD ppm-years, continuous				
Model 1	1.5 (1.8)	0.39	−2.0, 5.1	955.51
Model 2	1.1 (2.4)	0.64	−3.6, 5.9	931.89
BD peaks, continuous				
Model 1	5.1 (2.5)	0.04	0.1, 10.0	653.30
Model 2	4.0 (3.2)	0.21	−2.3, 10.3	930.85
BD average intensity (ppm), continuous				
Model 1	3.1 (1.9)	0.10	−0.5, 6.7	954.00
Model 2	3.9 (2.5)	0.12	−1.0, 8.8	930.00

[a] Model 1 controlled only for age; model 2 controlled for age, year of birth, race, DMDTC, years since hire and plant.
[b] β, S.E. and CI are $\times 10^{-4}$ for BD ppm-years, $\times 10^{-5}$ for BD peaks, and $\times 10^{-3}$ for BD average intensity.

sion coefficients for BD as compared with models using the continuous, untransformed exposure variable. This is because the former reduced the impact of data in the upper part of the BD exposure range (e.g., above the 95% percentile), where the slope of the exposure–response relationship was irregular. Reasons for the latter pattern, other than random variability, are speculative. Others have suggested that exposure misclassification may be most severe, and may distort the exposure–response relationship, in the upper end of the exposure range [12,13]. Data from a validation study that compared estimated with measured BD concentrations at one of the plants included in the present investigation were suggestive of this pattern of misclassification [15]. However, we cannot rule out distortion of the exposure–response relationship by misclassification throughout the exposure range. Exposure misclassification also could be responsible for the slightly better fit provided by categorical and ln- or square root-transformed BD variables, as compared to the continuous, untransformed exposure variables. Because of these uncertainties, we prefer the estimate of the exposure–response trend that is based on the continuous, untransformed form of the BD variables and the full range of exposure data. Due to the high potential for distortion of the exposure–response

relationship as a result of exposure misclassification, it may be useful to incorporate uncertainty analyses into any risk assessment that uses these data.

The finding that lagging BD exposure had little impact on the exposure–response relationship with leukemia reflects the tendency for relatively little exposure to have occurred during the lag periods. BD exposure was relatively low during lag periods because those periods occurred after many subjects were no longer working and because, among those still working, exposure tended to be low during the lag periods due to the general decline in BD exposure over time [9].

The results of our study appear to be reasonably consistent with those of Albertini et al. [16], who found no evidence that low-intensity exposure to BD was associated with structural changes in chromosomes or gene mutations among BD monomer and synthetic rubber workers in the Czech Republic. The Czech workers were exposed to BD concentrations that were on average below 5 ppm, and their duration of employment was on average 15–18 years. Assuming exposure to 5 ppm BD over a 20-year period (cumulative exposure, 100 ppm-years), our present analyses yielded an RR for leukemia that was consistent with a minimal effect of BD on leukemia mortality (RR = 1.03, that is, $e^{(0.00029 \times 100)}$,

for the untransformed, continuous BD ppm-years variable).

This study did not resolve questions about the association between DMDTC and leukemia. It is not clear if DMDTC causes leukemia, if it is correlated with some unknown cause present in synthetic rubber industry workers, if it measures some aspect of BD not captured in our BD exposure estimates or if the apparent association with DMDTC seen in some of our analyses is non-causal. Adjustment of the association between BD and leukemia for DMDTC is appropriate only if one of the first two interpretations is correct.

The evidence of a causal association between DMDTC and leukemia is limited and is based on observations of immune system toxicity [5,6] and on the results of research on synthetic rubber industry workers included in the present analyses [2]. The absence of a linear exposure–response relationship in the present study, of confirmatory evidence of an association from studies of other exposed populations and of demonstrated carcinogenicity in animals precludes a conclusion that DMDTC causes leukemia. If DMDTC is not causal but is instead correlated with a cause of leukemia other than BD, that causal factor has not been identified. On balance, it seemed reasonable to present the results of the present study both with and without adjustment for DMDTC. In summary, the present analyses support the presence of a positive exposure–response relationship between several indices of BD exposure and leukemia. Evidence of an association between BD and all lymphoid neoplasms or all myeloid neoplasms is less persuasive.

Acknowledgement

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