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Butadiene cancer exposure–response modeling: Based on workers in the styrene–butadiene–rubber industry: Total leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia

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ABSTRACT

Cox regression is used to estimate exposure–response models (with cumulative 1,3-butadiene (BD) ppm-years as the exposure metric) based on the most recent data and validated exposure estimates from UAB's study of North American workers in the styrene–butadiene–rubber industry. These data are substantially updated from those in USEPA's 2002 risk assessment.

The slope for cumulative BD ppm-years is not statistically significantly different than zero for CML, AML, or, when any one of eight exposure covariates is added to the model, for all leukemias combined (total leukemia).

For total leukemia, the EC(1/100,000) is approximately 0.15 BD environmental ppm and the corresponding unit risk factor is approximately 0.00007 per BD environmental ppm. The excess risk for CML is approximately 15-fold less than for total leukemia. The maximum likelihood estimates suggest that there is no excess risk for AML from cumulative BD ppm-years.

For CLL, the slope is statistically significantly different than zero. The excess risk for CLL is approximately 2.5-fold less than for total leukemia.

For both total leukemia and CLL, the slope is not statistically significantly different than zero when the exposure–response modeling is based on the person-years with cumulative BD ppm-years less than or equal to 300 ppm-years.

1. Introduction

Numerous publications have examined the evidence related to 1,3-butadiene (BD) and carcinogenicity in worker populations. These publications relate to five independent cohorts used primarily for long-term mortality cohort studies: a diverse rubber manufacturing plant in Ohio (e.g., McMichael et al., 1976), three different facilities involving monomer production (e.g., Divine and Hartman, 2001), and multi-center studies of largely overlapping cohorts of styrene–butadiene–rubber (SBR) workers (e.g., Delzell et al., 2006). For the purposes of exposure–response modeling, quantitative exposure information is critical – not only on the chemical of concern (here, BD), but also on potential confounding exposures (here, styrene (STY), benzene, and dimethyldithiocarbamate (DMDTC)). In this regard, the University of Alabama at Birmingham (UAB) epidemiological study of North American male workers in the SBR industry provides the best available data. For the other studies, the exposure information is limited and generally qualitative. For example, in the recent monomer studies the exposure has been characterized by a qualitative cumulative exposure score based on job classes, calendar time, and length of time in the job, and there were no data available on the peak exposures (Divine and Hartman, 2001).

Sections 7.4, 8.2.4.2, and 10.1.1 in the 2002 USEPA "Health Assessment of 1,3-Butadiene" contain an extensive discussion of the studies related to BD workers and concluded that the UAB data provided the best published set of data to evaluate human cancer risk from BD inhalation exposure (USEPA, 2002). In 2009, the Texas Commission on Environmental Quality (TCEQ) reviewed the scientific literature and concluded that there were no other epidemiology studies that would be appropriate to evaluate human cancer risk from BD inhalation exposure (Grant et al. 2009).

To date, there have been three editions of the UAB epidemiological study database. The 1995 epidemiological data set (findings published in Delzell et al. 1996) included the original estimates of exposure for six of the eight plants and follow-up for workers from all eight plants through December of 1991. The 2000 edition of the epidemiological data set (Delzell et al. 2000, 2001) included revised estimates of exposure. The 2004 edition of the data (findings published in Cheng et al. 2007 and elsewhere) includes seven more years of follow-up than

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the 1995 data set, and includes the 2000 edition revised exposure estimates.

1995 Data Set – In 1995, Delzell et al. (1995) reported analyses (based on the exposure estimates described in Macaluso et al. 1996) performed in 17,964 men who worked at eight plants located in North America. All eight plants produced styrene–butadiene–rubber and related products. A majority (92%) of the 17,964 men had exposure history and could be used in exposure–response modeling.

2000 Data Set – In a 2000 report (published in 2004), Macaluso et al. indicated that the original exposure estimates (reported in 1995) were low and reported new extensively changed exposure estimates developed over approximately five years in a multi-phase review including two new sets of plant visits. The review involved plant engineering and technical staffs and an independent panel of industry experts including industrial hygienists, epidemiologists, and engineers. The review identified new tasks for which exposure estimates were needed, made the exposure scenarios more specific by separating multiple tasks previously grouped into broadly defined background exposures, developed further questions about operations and exposure potential, provided reference materials on emission rates from pumps, compressors, and tank vents, provided measurements and refined estimates of airflow, and recommended changes in assumptions, parameters, and models used to estimate exposures. The relative ranking of exposures across workers was largely unchanged. However, the upper 50% of the distribution of task- and calendar-year-specific exposure estimates shifted upwards. The median cumulative exposure to BD was almost five times higher than the original estimate. The revised BD exposure estimates are up to one order of magnitude greater than the original estimates, particularly for the 1940–1960s. The revised STY exposures also increased but not as much as the BD exposures did. In 2000, UAB also developed estimates of exposures to DMDTC and additional measures of BD and STY exposures. Specifically, the BD and STY exposure estimates were expanded to include a new definition of "peak" exposures and the exposures to BD and STY were partitioned into exposures either above or below a nominal threshold of 100 ppm for BD and 50 ppm for STY.

2004 Data Set – In 2004, the UAB updated the epidemiological data to include seven more years of follow-up (through 1998) and the most recent estimates of exposures developed in 2000 (Sathiakumar et al. 2005). The 2004 epidemiological data includes 81 decedents with leukemia as opposed to 58 decedents with leukemia in the 1995 and 2000 data sets. In the 2004 data set there are a total of 16,585 workers and 5593 decedents with exposure estimates for BD, STY and DMDTC. Exposure estimates are available for 6 of the 8 plants, and the exposure–response modeling is based on these 6 plants. Additionally, a substantial effort was made to validate the BD exposure estimates developed by Macaluso et al. (2004) against job- and calendar-year specific exposure-monitoring measurements from 1977 to 1991 at the largest of the six plants (Sathiakumar et al. 2007). This validation plant was the only plant with both typical SBR operations and extensive other operations. Most of the other five plants had typical SBR operations only. Sathiakumar et al. stated that the exposure misclassification may have been more severe at the validation plant, and that, although the general procedures for estimating exposure were the same for all six plants, data on determinants of exposure were plant-specific. For jobs that were well-defined by a specific set of tasks and typically found in all SBR plants, the correlation between estimates and measurements was relatively high (0.81), and the difference (measurement–estimate) was noticeably greater in the earlier years (1977–1983) and much smaller in the later years (1984–1991). For BD ppm, over all years combined, the measurements and estimates had means 11.3 and 6.0, respectively, and medians 2.9 and 0.23, respectively.

The 2002 USEPA assessment was based on the original exposure data developed prior to 1996. Although the EPA has not updated its assessment, the UAB researchers, TCEQ, and Sielken & Associates have all based their more recent analyses on the most recent updated data. Sielken & Associates was greatly impressed by the considerable efforts made by UAB during the exposure re-evaluation and strongly believes that the revised exposure estimates are much more appropriate for exposure–response analyses than the original estimates.

Mortality from leukemia and other lymphohematopoietic cancers has consistently been the health endpoint of interest. Early analyses of mortality from all causes, all cancers, and lymphosarcoma (currently classified as non-Hodgkin's lymphoma (NHL)) and cancer incidence did not indicate increases associated with occupational exposures to BD (Delzell et al. 1996). Herein, leukemia (total leukemia) and three subclassifications of leukemia (acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML)) will each be considered. These three subclassifications are considered because they have been previously identified as potentially of interest and there are sufficient mortalities with each of these endpoints for model fitting and risk characterization.

2. Methods

While it is generally agreed that BD produces toxicity when it is metabolized to its reactive metabolites after exposure, the data needed to conduct a detailed mechanism of action analysis and construct an accepted biologically based exposure–response model are not available (Grant et al. 2009).

The statistical exposure–response modeling herein is done separately for total leukemia, AML, CLL, and CML mortality. Although the regulation of environmental BD inhalation exposure has thus far been based on cumulative BD ppm-years (USEPA (2002) and TCEQ (Grant et al., 2009)), the 2004 UAB data set also contains five non-exposure variables (age, years since hire, calendar year, race, and plant) and eight other exposure variables (cumulative STY ppm-years, cumulative DMDTC mg/cm-years, cumulative number of BD high intensity tasks (HITs), cumulative number of STY HITs, cumulative ppm-years with BD $\leqslant$100 ppm, cumulative ppm-years with BD >100 ppm, cumulative ppm-years with STY $\leqslant$50 ppm, and cumulative ppm-years with STY >50 ppm). Each worker's exposure history is partitioned into person-years based on UAB's plant and calendar year specific job-exposure-matrix (JEM). Each person-year has an associated value for all exposure and non-exposure variables. Cox regression modeling of these person-years is used to estimate the roles of cumulative BD ppm-years and the other exposure and non-exposure variables with respect to the response. For each occurrence of the specified response, Cox regression notes the age of the corresponding worker, evaluates the proportion of the workers with that response among the set of all workers at risk at that age, and models the impacts of the exposure and non-exposure variables on these proportions. Cox regression (unlike Poisson regression) incorporates each specific age rather than categories of age and allows cumulative BD ppm-years to be treated as a continuous variable rather than being required to be grouped into categories. Maximum likelihood criteria are used to judge statistical significance at the 5% significance level.

Exposure–response modeling considered both simple lags (in which exposures in the preceding specified number of years are

excluded) as well as restrictions to exposure windows (in which exposures in the preceding specified number of years are excluded in addition to excluding exposures more than a specified number of years into the past).

The primary excess risk characterization is the estimated effective concentration (EC) in environmental ppm concentrations corresponding to an extra risk of 1/100,000 and the unit risk factor (URF_{mle}) corresponding to a linear extrapolation below the EC(1/100,000). The secondary excess risk characterization is the 95% lower confidence limit (LEC(1/100,000)) on the concentration corresponding to an extra risk of 1/100,000 and the upper-bound unit risk factor (URF_{ub}) corresponding to a linear extrapolation below the LEC(1/100,000).

Life-table methods are used to calculate excess risks (ECs and LECs). These calculations are sequential calculations beginning at age zero that step through the years in a lifetime. The calculation incorporates the background age-specific hazard rate for all-cause mortality, the background age-specific hazard rate for the specified response, the age-specific values for the exposure metrics, and the corresponding Cox exposure–response model (i.e., the age-specific multiplier of the background age-specific hazard rate for the specified response determined by the Cox exposure–response model and the values of the age-specific exposure metrics).

Although the details in the calculations of ECs, and LECs can differ among authors, the preferred BEIR IV methodology (NRC, 1988) is used herein to do the life-table calculations. Also, the calculations include recent US survival rates (Arias, 2010) and recent leukemia mortality rates (2005 mortality from CDC WONDER – http://wonder.cdc.gov/cancermort-v2005.HTML – accessed on June 29, 2010). Furthermore, the ECs and LECs are calculated using the methodology and default age-dependent adjustment factors (ADAFs) described in USEPA 2005a,b (see also Sielken and Valdez-Flores (2008) (Appendix 5) and Sielken and Valdez-Flores (2009)).

3. Exposure–response models for total leukemia

Table 1 identifies the features of the occupational exposures that make a statistically significant improvement in the Cox model's ability to predict occupational leukemia by including a second variable (given that cumulative BD ppm-years is the first variable). Table 1 indicates that any one of

1) cumulative DMDTC mg/cm-years,
2) cumulative BD HITs,
3) cumulative STY HITs,
4) cumulative ppm-years with BD >100 ppm,
5) cumulative ppm-years with STY ⩽50 ppm, and
6) cumulative ppm-years with STY >50 ppm

makes a statistically significant improvement in the maximum likelihood if that single covariate is added to the exposure–response model with cumulative BD ppm-years as the predictive variable. These six covariates are not part of the regulated environmental exposures; therefore, it is important that the occupational leukemia risk attributed to cumulative BD ppm-years be adjusted to account for the effects that other co-occurring exposures may have on the occupational leukemia risk.

Some previous BD and STY exposure characterizations have included "peaks." However, the term "peaks" can be misleading because the variable actually refers to the "number of high-intensity tasks (HITs)" rather than the specific numerical value of the maximum ppm exposure level. Also, HITs was defined one way in 1995 and then redefined in 2000. In 1995, HITs was defined by evaluating task-specific and background exposures to determine the number of 15 min periods in a shift during which the average intensity of exposure was at or above a threshold (100 ppm for butadiene and 50 ppm for styrene) and then this number of high-intensity tasks per shift was multiplied by 225 (days at work in a year) to obtain the annual HITs value (Delzell et al. 1995). In 2000, HITs was redefined as "...multiplying the per-shift frequency of tasks entailing exposure >100 ppm (for BD) and >50 ppm (for STY) by 225 shifts/year" (Macaluso et al. 2004). In the 2000 definition, the 15 min averaging period in the 1995 definition was eliminated – "To capture high exposures of very short duration, this definition did not take exposure duration into account" (Macaluso et al. 2004). With regard to the 100 and 50 ppm levels, "These arbitrary values for the peak threshold appear sensitive enough to capture intensity and specific enough to exclude small excursions compatible with the imprecision of our estimation procedures" (Macaluso et al. 2004).

The statistical analysis of covariates herein only gives a limited indication of the possible improvement in the Cox model's ability to predict leukemia if the model based on cumulative BD ppm-years is expanded to include other variables. The statistical

Table 1
Total leukemia: Increase in the maximum log likelihood when one of the non-exposure or exposure covariates is added to the Cox proportional hazards model with the rate ratio being a log-linear function of cumulative BD ppm-years: Statistically significant increases are shaded.

Covariate considered for inclusion in the Cox model	Slope of cumulative BD ppm-years in the log-linear rate ratio model (std error)	Maximum log likelihood		Chi square statistic (d. f.)	*p*-Value for including covariate
		Covariate included	Covariate excluded		
None[a]	2.90×10^{-4} (1.03×10^{-4})	Not applicable			
Years since hire[b]	2.92×10^{-4} (1.04×10^{-4})	−689.90	−692.08	4.36 (4)	0.3591
Calendar year[b]	2.84×10^{-4} (1.03×10^{-4})	−689.48	−692.08	5.20 (4)	0.2672
Race[b]	2.59×10^{-4} (1.16×10^{-4})	−691.88	−692.08	0.40 (1)	0.5286
Plant[b]	3.88×10^{-4} (1.16×10^{-4})	−687.93	−692.08	8.31 (5)	0.1399
STY (ppm-years)	2.15×10^{-4} (1.31×10^{-4})	−688.45	−692.08	6.64 (5)	0.2491
DMDTC (mg/cm-years)	1.79×10^{-4} (1.23×10^{-4})	−681.39	−692.08	21.68 (5)	0.0006**
# of BD HITs	2.01×10^{-4} (1.30×10^{-4})	−679.23	−692.08	23.49 (5)	0.0003**
# of STY HITs	1.13×10^{-4} (1.40×10^{-4})	−679.77	−692.08	24.83 (5)	0.0002**
BD ⩽ 100 ppm (ppm-years)	2.03×10^{-4} (1.36×10^{-4})	−688.49	−692.08	7.18 (5)	0.2078
BD > 100 ppm (ppm-years)	1.39×10^{-4} (1.57×10^{-4})	−684.63	−692.08	14.90 (5)	0.0108*
STY ⩽ 50 ppm (ppm-years)	2.18×10^{-4} (1.32×10^{-4})	−685.90	−692.08	11.54 (5)	0.0417*
STY > 50 ppm (ppm-years)	1.59×10^{-4} (1.40×10^{-4})	−678.64	−692.08	27.82 (5)	3.94×10^{-5}**

[a] Cox model with only cumulative BD ppm-years.
[b] Categories for years since hire and Calendar year were based on quintiles of leukemia decedents, and race was categorized as black and others, while covariates for cumulative exposures were partitioned as controls and quintiles of exposed leukemia decedents.
* Statistically significant improvement in the likelihood at the 5% significance level.
** Statistically significant improvement in the likelihood at the 1% significance level.

analysis is not a biological or mechanistic analysis and only considers the simplest linear model for the effects of these variables individually. As is clear from Fig. 1, which shows the joint relationship between cumulative BD ppm-years and the cumulative number of BD HITs at the end of follow-up, the relationship between variables goes well beyond correlation and is not simple. These two correlated variables can jointly contribute to the Cox's models ability to predict leukemia (as evidenced by the statistically significant increase in the maximum likelihood when BD HITs is added to the model). Several variables may in fact be involved in the observed leukemia.

Table 2 indicates the excess risk characterizations for total leukemia based on the most scientifically defensible exposure–response modeling of the effect of cumulative BD ppm-years either alone or after adjusting for the effects of a statistically significant covariate. The average and geometric mean of the EC(1/100,000)s and corresponding URF_{mle}s are approximately 0.15 ppm environmental BD and 0.00007 per ppm environmental BD, respectively – either for the six models with an added covariate or all seven models (including the model with no covariate). The average and geometric mean of the LEC(1/100,000)s and URF_{ub} are approximately 0.06 ppm and 0.00016 per ppm, respectively. The benchmark response level of 1/100,000 (rather than, say, 1/million) was chosen so that the EC and LECs would still be in the heart of the observed data and not be unnecessarily dependent upon the assumed shape of the exposure–response model.

In order for the ECs and LECs to be reasonable points of departure (PODs), they need to be in the midst of the study data and not too close to zero. There were 12,819 exposed workers among the 16,585 workers in the entire cohort. Of the 81 leukemia mortalities, there were 71 among the exposed workers. The BD ECs and LECs in Table 2 are all between 0.05 and 0.22 environmental ppm. These environmental ppm concentrations are equivalent to 10.65 and 46.85 occupational BD ppm-years assuming that the environmental exposure was for 70 years. Among the 12,819 exposed workers, 22% have cumulative BD ppm-years at the end of their follow-up less than 10.65 occupational BD ppm-years, and these workers had 7% of the corresponding 71 leukemia mortalities. Also, among the 12,819 exposed workers, 47% have cumulative BD ppm-years at the end of their follow-up less than 46.85 occupational BD ppm-years, and these workers had 34% of the corresponding 71 leukemia mortalities. Thus, the ECs and LECs in Table 2 corresponding to an extra risk of 1/100,000 are well within the range of the cumulative BD exposures observed in the UAB epidemiological data.

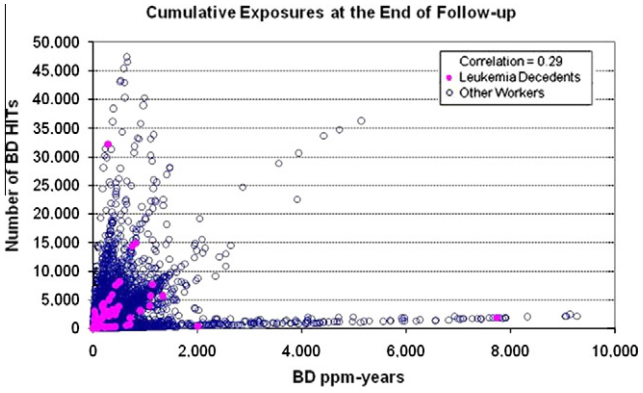

Fig. 1. Scatter plot of the cumulative BD ppm-years and the cumulative number of BD HITs at the time of follow-up for all workers.

4. Results for acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia

The leukemia diagnoses among workers were pathologically confirmed by Delzell et al. (2006) based on medical records. The 81 leukemia deaths observed in the UAB data were classified as one of nine mutually exclusive types.

Category	Description	Number	ICD9
1	Acute lymphocytic leukemia	3	204.0
2	***Acute myelogenous or monocytic leukemia***	***26***	***205.0, 206.0***
3	Acute leukemia – other/ unknown	4	207.0
4	***Chronic lymphocytic leukemia***	***25***	***204.1***
5	***Chronic myelogenous leukemia***	***16***	***205.1***
6	Chronic leukemia – other/ unknown	1	207.1
7	Non-AML – unspecified lymphocytic	2	204.9
8	Non-AML – unspecified myelogenous	3	205.9
9	Non-AML – other non-AML/ unknown	1	207.8

Three of these nine types (acute myelogenous leukemia (AML) (category 2), chronic lymphocytic leukemia (CLL) (category 4), and chronic myelogenous leukemia (CML) (category 5)) are well-defined endpoints and include sufficient numbers of decedents in the UAB data to develop models and analyses similar to those used above for total leukemia. Table 3 shows the excess risk characterizations for AML, CML, and CLL we obtained with the same exposure–response modeling methodology used for total leukemia. Leukemia and the CLL, CML, and AML subsets were also analyzed in Graff et al. 2005, although the focus there was on relative rates (RRs) for specified exposure categories and no exposure–response models were estimated.

Sensitivity analyses of the modeling and excess risk characterizations to either including or excluding other/unknown and unspecified leukemia types as part of the three well-defined leukemia types (i.e., AML, CML, and CLL) were performed. (Adding categories 3 or 8 or both to AML, adding categories 6 or 7 or both to CLL, and adding categories 6 or 8 or both to CML were evaluated.) The sensitivity analyses show that these subtypes hardly change the results.

5. Discussion

The primary objective herein is to develop, identify and provide scientific support for the best, most scientifically defensible point estimate of excess risk. A secondary objective is to describe how this point estimate fits in with the other available estimates.

All estimates in Sections 3 and 4 are based on the most recent data from the preferred occupational epidemiological study. In addition, the scientific defensibility of these estimates stems from being based on (1) Cox rather than Poisson regression, (2) consideration of both non-exposure and exposure covariates and their interaction with the cumulative BD ppm-years exposure metric, (3) the more flexible treatment of these co-variables as categorical variables using nonparametric techniques rather than as continuous variables using parametric techniques, (4)

Table 2
Excess risk characterizations for total leukemia: Models ordered with the largest maximum log likelihood first and the smallest maximum log likelihood last: Models with maximum log likelihoods statistically significantly improved over the maximum log likelihood for the model with exposure characterized only by cumulative BD ppm-years are shaded.

Model:exposure variables[a]	Maximum log likelihood	Beta[b]: MLE, *p*-Value SS[g] or NS[h]	Beta[b] (95% UCL)	EC[c] 1/100,000 (env. ppm)	LEC[d] 1/100,000 (env. ppm)	Linear slope[e] (URF_{mle}) per ppm below EC (1/100,000)	Linear slope[f] (URF_{ub}) per ppm below LEC (1/100,000)
Cumulative BD ppm-years and cumulative STY > 50 ppm (ppm-years)	−678.64	0.000159 0.256 NS	0.000389	0.155	0.063	0.000065	0.000158
Cumulative BD ppm-years and cumulative BD HITs	−679.23	0.000201 0.122 NS	0.000415	0.122	0.059	0.000082	0.000169
Cumulative BD ppm-years and cumulative STY HITs	−679.77	0.000113 0.420 NS	0.000343	0.217	0.072	0.000046	0.000140
Cumulative BD ppm-years and cumulative DMDTC (mg/cm-years)	−681.39	0.000179 0.146 NS	0.000381	0.137	0.064	0.000073	0.000155
Cumulative BD ppm-years and cumulative BD > 100 ppm (ppm-years)	−684.63	0.000139 0.376 NS	0.000397	0.177	0.062	0.000057	0.000162
Cumulative BD ppm-years and cumulative STY ⩽ 50 ppm (ppm-years)	−685.90	0.000218 0.099 NS	0.000435	0.113	0.056	0.000089	0.000177
Cumulative BD ppm-years	−692.08	0.000290 0.005 SS	0.000459	0.085	0.054	0.000118	0.000187
Shaded models	Average			0.154	0.063	0.000069	0.000160
Shaded models	Geometric mean			0.150	0.062	0.000067	0.000160
All models	Average			0.144	0.061	0.000076	0.000164
All models	Geometric mean			0.138	0.061	0.000073	0.000163

[a] All models use cumulative BD ppm-years as the predictive dose metric. Some models include categorical covariate effects. The range of positive covariate values is partitioned into quintiles with approximately equal numbers of leukemia mortalities in each quintile.
[b] Beta is the coefficient of occupational cumulative BD ppm-years in the exposure–response models. Occupational exposure is assumed to be at 10 m^3 per day for 240 days per year. Environmental exposure is assumed to be at 20 m^3 per day for 365 days per year. An environmental ppm-year is assumed to be equivalent to 3.042 occupational ppm-years [(20/10) × (365/240) = 3.042].
[c] EC(1/100,000) is the estimated effective concentration (EC) corresponding to an increase in the extra risk of 1/100,000 by age 70. ECs are in environmental ppm and are for environmental exposures.
[d] LEC(1/100,000) is the 95% lower confidence limit on the effective concentration (EC) corresponding to an increase in the extra risk of 1/100,000. LECs are in environmental ppm and are for environmental exposures.
[e] Slope for a linear extrapolation below EC(1/100,000); namely, slope = 0.00001/EC(1/100,000).
[f] Slope for a linear extrapolation below LEC(1/100,000); namely, slope = 0.00001/LEC(1/100,000).
[g] Statistically significantly different than zero at the 5% significance level.
[h] Not statistically significantly different than zero at the 5% significance level.

calculating cumulative BD ppm-years from best estimates of BD exposure rather than mean scored deciles, (5) more thorough evaluation of the impacts of potential restrictions to the lower exposure range, and (6) recent exposure validation reported in Sathiakumar et al. (2007) and our sensitivity analyses that suggest that the slope and corresponding excess risks would be less under several alternative exposure characterizations based on Sathiakumar et al. (2007).

The advantages of Cox regression over Poisson regression have already been mentioned.

5.1. Covariates

The SBR exposure scenarios are fairly complicated and involve not only potentially important exposures to compounds other than BD but also highly diverse exposures to BD in terms of magnitude, intensity, and duration. The exposure characteristics differ substantially from one work area to another. Some tasks involve very high intensity exposures of short duration. Very few tasks involve simple exposures that would allow the effects of different compounds and different intensities and durations to be easily separated. Correlation and collinearity among exposure variables complicates and adversely impacts the exposure–response modeling. However, as exemplified by cumulative BD ppm-years and the cumulative number of BD HITs in Fig. 1, two variables can be correlated and still contribute different exposure information. So far, the USEPA has regulated environmental exposure to BD based solely on cumulative BD ppm-years; therefore, any exposure–response modeling that hopes to impact such regulations must include cumulative BD ppm-years. We have used a forward selection version of stepwise regression to determine the variables to add to the exposure–response model given the condition that cumulative BD ppm-years is always part of the model. After expanding the model from cumulative BD ppm-years to cumulative BD ppm-years plus one other variable, no further addition made a statistically significant increase in the maximum likelihood.

As indicated in Table 1, none of the non-exposure covariates (years since hire, calendar year, race, or plant) make a statistically significant improvement in the maximum log likelihood.

The improvements in the maximum log likelihood indicated in Table 1 for six exposure covariates (DMDTC, BD HITs, STY HITs, BD >100 ppm, STY ⩽50 ppm, and STY >50 ppm) strongly suggest that, from a statistical perspective, there are exposure factors other than cumulative BD ppm-years in the occupational setting potentially affecting leukemia.

This suggestion is also supported by analyses of the data not involving exposure–response modeling. For example, consider BD HITs. All of the 71 exposed workers who had leukemia mortalities had some BD HITs. None of the 1192 exposed workers without BD

Table 3
Excess risk characterizations for CLL, CML, and AML: Models ordered with the largest maximum log likelihood first and the smallest maximum log likelihood last: Models with maximum log likelihoods statistically significantly improved over the maximum log likelihood for the model with exposure characterized only by cumulative BD ppm-years are shaded.

Model:exposure variables[a]	Maximum log likelihood	Beta[b] (MLE)	Beta[b] (95% UCL)	EC[c] 1/100,000 (env. ppm)	LEC[d] 1/100,000 (env. ppm)	Linear slope[e] (URF_{mle}) per ppm Below EC (1/100,000)	Linear slope[f] (URF_{ub}) per ppm Below LEC (1/100,000)
Chronic Lymphocytic Leukemia (CLL)							
Cumulative BD ppm-years	−205.66	0.000417 (SS[g])	0.000628	0.375	0.249	0.000027	0.000040
Chronic Myelogenous Leukemia (CML)							
Cumulative BD ppm-years and cumulative BD HITs	−134.71	−0.000168 (NS[g])	0.000890	Infinite	0.543	0	0.000018
Cumulative BD ppm-years	−140.95	0.000213 (NS[h])	0.000683	2.269	0.708	0.000004	0.000014
Acute Myelogenous Leukemia (AML)							
Cumulative BD ppm-years and cumulative STY HITs	−215.41	−0.000801 (NS[h])	0.000512	Infinite	0.106	0	0.000094
Cumulative BD ppm-years and cumulative STY >50 ppm (ppm-years)	−215.91	−0.000795 (NS[h])	0.000554	Infinite	0.098	0	0.000102
Cumulative BD ppm-years and cumulative DMDTC (mg/cm-years)	−216.06	−0.000275 (NS[h])	0.000714	Infinite	0.076	0	0.000132
Cumulative BD ppm-years	−224.12	−0.00001 (NS[h])	0.000666	Infinite	0.082	0	0.000122

[a] All models use cumulative BD ppm-years as the predictive dose metric. Some models include categorical covariate effects. The range of positive covariate values is partitioned into quintiles with approximately equal numbers of leukemia mortalities in each quintile.
[b] Beta is the coefficient of occupational cumulative BD ppm-years in the exposure–response models. Occupational exposure is assumed to be at 10 m^3 per day for 240 days per year. Environmental exposure is assumed to be at 20 m^3 per day for 365 days per year. An environmental ppm-year is assumed to be equivalent to 3.042 occupational ppm-years [(20/10) × (365/240) = 3.042].
[c] EC(1/100,000) is the estimated effective concentration (EC) corresponding to an increase in the extra risk of 1/100,000 by age 70. ECs are in environmental ppm and are for environmental exposures.
[d] LEC(1/100,000) is the 95% lower confidence limit on the effective concentration (EC) corresponding to an increase in the extra risk of 1/100,000. LECs are in environmental ppm and are for environmental exposures.
[e] Slope for a linear extrapolation below EC(1/100,000); namely, slope = 0.00001/EC(1/100,000).
[f] Slope for a linear extrapolation below LEC(1/100,000); namely, slope = 0.00001/LEC(1/100,000).
[g] Statistically significantly different than zero at the 5% significance level.
[h] Not statistically significantly different than zero at the 5% significance level.

HITs had leukemia mortalities. This absence is very unlikely unless BD HITs is a contributing factor to leukemia. The four potential alternative explanations for this absence can be dismissed as follows: First, the distribution of cumulative BD ppm-years at the end of follow-up is similar for the 1192 exposed workers without BD HITs and the 11,627 exposed workers with BD HITs. Second, the location of the 71 leukemia mortalities among exposed workers relative to the distribution of cumulative BD ppm-years at the end of follow-up is similar for the 1192 exposed workers without BD HITs and the 11,627 workers with BD HITs.

Third, the 9000 workers with BD HITs who had cumulative BD ppm-years in the same range as the exposed workers without BD HITs had 58% of the leukemia mortalities among exposed workers. Thus, if cumulative BD ppm-years were the cause of leukemia mortalities, then the 1192 exposed workers without BD HITs had sufficient BD ppm-years to cause leukemia mortalities. However, they had no leukemia mortalities. Furthermore, if the leukemia mortality rate (41 out of 9000) among the 9000 workers with BD HITs who had cumulative BD ppm-years at the end of follow-up in the same range as the exposed workers without BD HITs were assumed to apply to the exposed workers without BD HITs, then more than five leukemia mortalities would have been expected among the 1192 exposed workers without BD HITs, and the probability of observing no leukemia mortalities among these 1192 exposed workers is less than 0.005.

Fourth, the distribution of age at the end of follow-up is similar for the exposed workers with and without BD HITs. Thus, there is no substantial difference in age that would explain why exposed workers without BD HITs had no leukemia mortalities but exposed workers with BD HITs did have leukemia mortalities.

5.2. Treatment of cumulative number of HITs

The number of HITs (BD or STY) depends on the types of jobs performed by the worker. The observed relationship between cumulative number of HITs and leukemia is not simple, smooth, or monotone. Hence, a categorical and nonparametric treatment of the cumulative number of HITs is less restrictive and more appropriate than a continuous and parametric treatment.

5.3. Treatment of cumulative BD ppm-years

Because regulatory procedures for environmental risk assessment need to be able to characterize a continuous spectrum of low levels of BD exposure in a consistent manner, the treatment of cumulative BD ppm-years in the exposure–response modeling needs to be parametric. This can be done with cumulative BD ppm-years either treated as a continuous variable with each worker's specific exposure value treated as is (untransformed) or treated as a grouped variable with each worker's specific exposure value transformed to a common value for the group. The dose metric called "mean scored deciles" is an example of the latter treatment. Here, the range of the cumulative BD ppm-years values is partitioned into 10 groups or categories with approximately equal numbers of leukemia mortalities. Then, if a worker's actual cumulative BD ppm-years value at a specific evaluation time in the Cox modeling is in the group, then the mean in the group replaces the worker's actual cumulative BD ppm-years. The use of "mean-scored deciles" has been proposed as an attempt to offset exposure classification errors; however, using replacement grouped values does not improve the estimates of exposure. In addition, early

Table 4
The variability in the risk characterizations (exposure–response model slope and its significance) when the exposure–response modeling is restricted to different percentages of the exposure range.

Cox proportional hazards model with adjustment for HITs Restricted exposure range				Slope (Beta) of exposure–response model				Statistical significance of slope		
Person – years	Percentage among 71 leukemia mortalities with positive exposures (%)	Percentage among all workers (%)	# of leukemia mortalities	Maximum likelihood estimate	Standard error	95% Lower confidence limit	95% Upper confidence limit	Likelihood ratio test	Wald test	SS[a] or not SS
ALL (⩽9274)	100	100	81	0.00020	0.00013	−0.00001	0.00041	0.1931	0.1232	Not SS
⩽7750	100	99.9	81	0.00028	0.00014	0.00004	0.00052	0.1067	0.0529	Not SS
⩽2015	99	99	80	0.00050	0.00040	−0.00015	0.00115	0.2282	0.2057	Not SS
⩽1123	95	98	77	0.00058	0.00058	−0.00037	0.00153	0.3292	0.3137	Not SS
⩽401	75	91	63	0.00027	0.00162	−0.00240	0.00293	0.8695	0.8698	Not SS
⩽185	50	81	46	−0.00912	0.00483	−0.01706	−0.00118	0.0437	0.0593	SS and negative
⩽34	25	55	28	−0.02507	0.02667	−0.06894	0.01880	0.3349	0.3472	Not SS

[a] Statistically significant at 5% significance level.

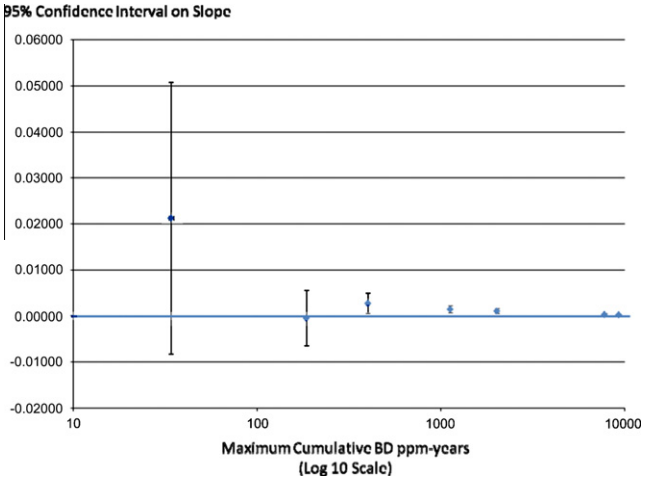

Fig. 2. The variability in the estimated slope in the exposure–response when the exposure range is restricted: Exposure–response model excluding HITs.

questions about exposure misclassification have now been largely resolved in recent publications. Such resolutions greatly reduce any value of using artificial replacement values instead of continuous exposures.

5.4. Impacts of restrictions to the lower exposure range

In response to some peer-reviewers' comments expressing concern over uncertainty in the estimates of job exposure levels and resultant values of cumulative BD ppm-years, especially at the highest levels, TCEQ considered Cheng et al.'s exposure–response modeling restricted to the lower 95% of the exposure range (i.e., below the 95th percentile of the cumulative BD ppm-years at the end of follow-up among the 71 workers with leukemia mortalities and positive exposure) (Grant, 2008). The problem here is that the resulting risk characterization is quite variable depending on the specific percentage of the exposure range utilized. For example, two-sided confidence intervals on the slope of cumulative BD ppm-years expand dramatically (indicating greater uncertainty) and increasingly suggest non-positive slopes as the exposure range is restricted (see Table 4 and Fig. 2).

Although thresholds were not explicitly considered in the exposure–response modeling herein, restrictions to the lower exposure range indicate that there is little to no risk at low exposure levels and certainly no statistically significant increasing exposure–response relationship (Tables 5 and 6). This was also previously described in Sielken et al. (2007) based on Poisson regression.

5.5. Exposure validation and sensitivity analysis

Sathiakumar et al. (2007) addresses the validation of the 1,3-butadiene exposure estimates for workers at a synthetic rubber plant. Based on this work, Appendix 7 in TCEQ's report (Grant, 2008; Grant et al., 2009) provides a sensitivity analysis of BD risk characterizations to possible exposure estimation errors. Table 7 herein clearly indicates the directionality of the impact of alternative exposure values (JEM values) on the estimated slope for cumulative BD ppm-years; namely, that the slope and corresponding

Table 5
Maximum likelihood estimate of the slope for cumulative BD ppm-years (in the Cox proportional hazards model with cumulative BD ppm-years as a continuous variable and the only exposure variable), standard error, confidence interval, and statistical significance for different maximum levels of cumulative BD ppm-years for deaths in which leukemia is the primary cause of death or a contributing cause of death: Total leukemia.

Cumulative Butadiene ppm-years intervals included in the estimation	Maximum likelihood estimate of the slope	Standard error of the estimate of the slope	95% Confidence interval on the slope		Likelihood ratio test that slope = 0 (p-value)
All	0.00029	0.00010	0.00009	0.00049	0.0263*
⩽1338 ppm-years	0.00121	0.00036	0.00051	0.00191	0.0024**
⩽1000 ppm-years	0.00145	0.00047	0.00054	0.00236	0.0045**
⩽500 ppm-years	0.00296	0.00086	0.00127	0.00465	0.0014**
⩽400 ppm-years	0.00283	0.00111	0.00065	0.00501	0.0156*
⩽300 ppm-years	0.00305	0.00155	0.00001	0.00609	0.0591
⩽200 ppm-years	0.00089	0.00267	−0.00434	0.00612	0.7415
⩽100 ppm-years	0.00224	0.00536	−0.00827	0.01275	0.6793

* Statistically significant at the 5% significance level.
** Statistically significant at the 1% significance level.

Table 6
Characteristics of the data sets evaluated in Table 5.

Cumulative butadiene ppm-years intervals included in the estimation	# of Person years	Observed # of leukemia deaths: leukemia is primary or contributing cause of death	Observed # of leukemia deaths: leukemia is primary cause of death	Expected[a] # of leukemia deaths: leukemia is primary cause of death	SMR[b]: observed/expected: leukemia is primary cause of death	Power[c] to detect a slope of 0.005	Power to detect a slope of 0.0099[d]
All	500,378 (100%)	81 (100%)	68 (100%)	55	124	0.97	1.00
⩽1338 ppm-years	494,348 (98.8%)	78 (96%)	65 (96%)	54	121	0.82	1.00
⩽1000 ppm-years	489,694 (97.9%)	75 (93%)	62 (91%)	53	117	0.78	1.00
⩽500 ppm-years	469,876 (93.9%)	68 (84%)	58 (85%)	50	116	0.41	0.97
⩽400 ppm-years	461,234 (92.2%)	63 (78%)	54 (79%)	49	111	0.44	0.96
⩽300 ppm-years	445,524 (89.0%)	57 (70%)	50 (74%)	46	108	0.37	0.89
⩽200 ppm-years	419,682 (83.9%)	48 (59%)	45 (66%)	43	105	0.26	0.70
⩽100 ppm-years	364,411 (73.8%)	41 (51%)	38 (56%)	36	106	0.10	0.25

[a] Using US male mortality rates.
[b] Standardized mortality ratio (SMR).
[c] Using the Beaumont and Breslow (1981) approach, the statistical power to detect increases in leukemia deaths in the UAB cohorts, when the expected number of cancer deaths is based on a specified slope (coefficient of BD cumulative ppm-years in the linear rate ratio model) is given by the probability of a standard normal random variable exceeding $1.645 - 2 \times (RR^{0.5} - 1) \times (Expected)^{0.5}$ where RR is the ratio of the number of leukemia deaths predicted to the number of leukemia deaths observed and *Expected* is the number of leukemia deaths expected to occur due to background leukemia rates.
[d] 0.0099 is the value of the slope used in USEPA (2002).

excess risks would be less under several alternative exposure values based on Sathiakumar et al. (2007).

Graff et al. 2009 (which is a portion of Delzell et al. 2006) evaluates the impact of potential inaccuracies in the 2000 exposure estimates and conducted uncertainty analyses of the relation between cumulative exposure to BD and leukemia. They found that the relation was maintained even when the entries in the JEM matrices were replaced by random percentiles from the approximate probability distributions for the plant-, work area/job group-, and year specific exposure values.

5.6. Review of other analyses

The analyses reported in Delzell et al. (1995, 1996), Sathiakumar et al. (1998) and USEPA (2002) are based on the outdated 1995 data set.

Delzell et al. (2001) and Sielken and Valdez-Flores (2001) are based on the outdated 2000 data set and Poisson regression modeling.

Cheng et al. (2007) is based on the 2004 data set and uses Cox regression. The paper considered BD HITs as well as cumulative BD ppm-years and concluded that high intensity exposure to BD is important for leukemia. Cheng et al. (2007) reported an estimated regression coefficient (2.9×10^{-4}) for cumulative BD ppm-years in the Cox regression with no covariates which is identical to the coefficient calculated and reported in Table 1 herein.

The analyses in our current paper refine and extend the analyses done in Sielken et al. (2007). Both papers use the same UAB study data. The numerical risk characterizations for total leukemia are quite similar; namely, an environmental EC(1/1000) in the 2007 paper of 11.2 ppm BD which, using linear extrapolation, corresponds to an EC(1/100,000) of 0.112 ppm BD that is approximately equal to the 0.15 ppm BD obtained herein. The 2007 analyses were based on Poisson regression (which treats all variables as categorical) and focused on ECs calculated using only one co-variable (BD Peaks which are now, more accurately, referred to as BD HITs). On the other hand, the current analyses are based on Cox regression (which treats cumulative BD ppm-years continuously instead of categorically and treats age exactly instead of categorically), and the ECs are calculated using each one of the six statistically significant co-variables. In both papers, for total leukemia, the statistical significance of the slope for cumulative BD ppm-years disappears when exposures are restricted to no more than 200 or 300 cumulative BD ppm-years, and the slope

Table 7
Impact of alternative exposure values (job-exposure-matrix (JEM) values) on the characterizations of the model slope parameter (β) and the excess risk estimates: Based on the exposure estimation error reported by Sathiakumar et al. (2007) and the distributional characterization of JEM values in the UAB dataset (Macaluso et al. 2004): Exposure–response modeling including cumulative BD ppm-years but no covariates.

Data set	Description of JEM values	β	Standard deviation of estimate of β	95% LCL on β	95% UCL on β
Original	Average in Macaluso distribution	2.911E-04	1.029E-04	1.218E-04	4.604E-04
First alternate	Sathiakumar average calendar-year correction before 1984 and average calendar-year correction after 1983	1.469E-04	5.210E-05	6.120E-05	2.326E-04
Second Alternate	Sathiakumar average calendar-year correction for 1977 through 1983 and average calendar-year correction for 1984 through 1991	2.478E-04	8.660E-05	1.054E-04	3.902E-04
Third alternate	Sathiakumar calendar-year specific correction for 1977 through 1991	2.468E-04	8.620E-05	1.050E-04	3.886E-04
Fourth Alternate	Sathiakumar overall 10% correction	2.620E-04	9.260E-05	1.097E-04	4.143E-04

Table 8
Maximum likelihood estimate of the slope for cumulative BD ppm-years (in the Cox proportional hazards model for CLL with cumulative BD ppm-years as a continuous variable and the only exposure variable), standard error, confidence interval, and statistical significance for different maximum levels of cumulative BD ppm-years for deaths in which CLL is the primary cause of death or a contributing cause of death.

Person-years and cumulative butadiene ppm-years intervals included in the estimation	Number of CLL deaths	Maximum likelihood estimate of the slope	Standard error of the estimate of the slope	95% confidence interval on the slope		Likelihood ratio test that slope = 0 (p-Value)
All	25	0.00042	0.00013	0.00017	0.00067	0.0195*
⩽1338 ppm-years	24	0.00160	0.00057	0.00048	0.00272	0.0145*
⩽1000 ppm-years	23	0.00210	0.00073	0.00067	0.00353	0.0110*
⩽500 ppm-years	20	0.00411	0.00147	0.00123	0.00699	0.0101*
⩽400 ppm-years	18	0.00403	0.00192	0.00027	0.00779	0.0505
⩽300 ppm-years	14	0.00033	0.00352	−0.00657	0.00723	0.9253
⩽200 ppm-years	12	−0.00560	0.00661	−0.01856	0.00736	0.3625
⩽100 ppm-years	11	−0.00195	0.01090	−0.02331	0.01941	0.8568

* Statistically significant at the 5% significance level.

for cumulative BD ppm-years in the models with one statistically significant co-variable are not statistically significantly different than zero. The current paper evaluates AML, CLL, CML, and total leukemia whereas the 2007 paper only evaluated total leukemia (as well as lymphoid and myeloid neoplasms in sensitivity analyses).

6. Conclusions

The fit of the final models for total leukemia, AML, CML, and CLL did not improve with lagged cumulative exposures.

In the final Cox models (Tables 1–3), the non-exposure covariates (years since hire, calendar year, race, and plant) did not significantly improve the maximum likelihood (although calendar year and plant are important determinants of the values in the job exposure matrices).

For total leukemia, six exposure covariates (cumulative BD HITs, cumulative STY HITs, cumulative STY >50 ppm, cumulative STY ⩽50 ppm, cumulative DMDTC, and cumulative BD >100 ppm) significantly improve the maximum likelihood. Before any of the exposure covariates are added to the Cox model for leukemia, the slope per cumulative BD ppm-years is statistically significantly different than zero; however, the slope per cumulative BD ppm-years is not statistically significantly different than zero after any one of the exposure covariates is added to the Cox model.

For CLL, the slope per cumulative BD ppm-years is statistically significantly different than zero. No exposure or non-exposure covariate significantly improves the maximum likelihood.

For CML, the slope per cumulative BD ppm-years is not statistically significantly different than zero. Cumulative BD HITs significantly improves the maximum likelihood for CML. When cumulative BD HITs is added to the Cox model, the maximum likelihood estimate of the slope per cumulative BD ppm-years is negative.

For AML, the slope per cumulative BD ppm-years is not statistically significantly different than zero. Three exposure covariates (cumulative STY HITs, cumulative STY >50 ppm, and cumulative DMDTC) significantly improve the maximum likelihood for AML. The maximum likelihood estimate of the slope per cumulative BD ppm-years is negative in the Cox models either with or without one of these three exposure covariates.

For both total leukemia (Tables 5 and 6) and CLL (Table 8), the slope in the model with cumulative BD ppm-years as the only exposure variable is not statistical significantly different than zero when the exposure–response modeling is based on the person-years with cumulative BD ppm-years less than or equal to 300 ppm-years. The sensitivity analyses of the modeling to either including or excluding other/unknown and unspecified leukemia types as part of CLL did not change this result.

For leukemia and CLL, the EC(1/100,000)s are approximately 0.15 ppm environmental BD and 0.375 ppm environmental BD, respectively, and the corresponding URF_{mle}s are approximately 0.00007 per ppm and 0.000027 per ppm, respectively. Thus, the excess risk for CLL is approximately 2.5-fold less than for total leukemia. Analogously, for leukemia and CLL, the LEC(1/100,000)s are approximately 0.06 and 0.25 ppm environmental BD, respectively, and the corresponding URF_{ub}s are approximately 0.00016 per ppm and 0.00004 per ppm, respectively. Comparing bounds instead of maximum likelihood estimates, the excess risk for CLL is approximately 4-fold less than for total leukemia.

Because the EC(1/100,000)s are approximately 0.15 and 2.3 ppm environmental BD for leukemia and CML, respectively, and the slope per cumulative BD ppm-years for CML is not significantly different than zero, the maximum likelihood estimates suggest that the excess risk for CML is approximately 15-fold less than for total leukemia.

The maximum likelihood estimates suggest that there is no excess risk for AML from cumulative BD ppm-years.

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