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Quantitative risk assessment of exposures to butadiene in EU occupational settings based on the University of Alabama at Birmingham epidemiological study

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ABSTRACT

The excess risks due to 1,3-butadiene (BD) inhalation in EU occupational settings are quantified for leukemia, AML, CLL, CML, lymphoid neoplasms, and myeloid neoplasms. The most recent data from the University of Alabama at Birmingham epidemiological study of North American workers in the styrene-butadiene rubber industry are modeled.

The number of high-intensity tasks (HITs) and other exposure covariates may be more important predictors than cumulative BD ppm-years alone. For example, all of the 71 leukemia decedents in the UAB study who were exposed to BD had some BD HITs. None of the 1192 exposed workers without BD HITs had leukemia mortalities.

The authors' best estimate (consolidated over all endpoints) of the average occupational BD exposure concentration for 45 years of exposure starting at age 20 corresponding to an added risk of 1/10,000 by age 70 is 7.2 ppm.

Cumulative BD ppm-years is not statistically significantly associated with CML, AML, or myeloid neoplasms or (after any one of eight exposure covariates is included in the modeling) leukemia. The statistical significance of the slopes for leukemia, CLL, and lymphoid neoplasms unadjusted for covariate effects disappears when modeling is restricted to person years with less than 200 cumulative BD ppm-years.

1. Introduction

The 2002 USEPA "Health Assessment of 1,3-Butadiene" concluded that the University of Alabama at Birmingham (UAB) epidemiological study of North American workers in the styrene-butadiene rubber industry provided the best published set of data to evaluate human cancer risk from 1,3-butadiene (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) was updated in 2000 (Delzell et al., 2000, 2001) to include revised estimates of exposure. 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 (Macaluso et al., 2004; Sathiakumar et al., 2005). Exposure estimates are available for 6 of the 8 plants, and the exposure–response modeling is based on these 6 plants. In these six plants, 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, styrene (STY) and dimethyldithiocarbamate (DMDTC).

Mortality from leukemia and other lymphohematopoietic cancers has consistently been the health endpoint of interest. Early analyses of other mortality endpoints (e.g., all causes, all cancers, and lymphosarcoma (currently classified as non-Hodgkin's lymphomas (NHL)) and cancer incidence did not indicate increases for these endpoints associated with occupational exposures (Delzell et al., 1996). Herein, leukemia (all leukemia types combined) and three subclassifications of leukemia (acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic

Abbreviations: AML, acute myelogenous leukemia; BD, 1,3-butadiene; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; EU, European Union; DMDTC, dimethyldithiocarbamate; HIT, high-intensity task; mle, maximum likelihood estimate; MoA, mode of action; NHL, non-Hodgkin's lymphoma; ppm, part per million; ppm-years, part per million concentration multiplied by a number of person years; RR, rate ratio; SAB, USEPA's Science Advisory Board; SCOEL, Scientific Committee on Occupational Exposure Limits; SMR, standardized mortality ratio; Std Dev, standard deviation; STY, styrene; TCEQ, Texas Commission on Environmental Quality; UAB, University of Alabama at Birmingham; URF, unit risk factor; USEPA, United States Environmental Protection Agency.

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myelogenous leukemia (CML)) as well as the group of lymphoid neoplasms and the group of myeloid neoplasms are each considered. The 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. The lymphoid neoplasms and myeloid neoplasms are considered because they include a larger number of decedents than the three subclassifications of leukemia.

As noted in Sielken et al. (2007), two important caveats associated with the analyses of myeloid and lymphoid neoplasms are (1) diagnoses based on death certificates and missing or nonspecific medical records often are missing the level of specificity needed for making distinctions among types of neoplasms and (2) using this classification for myeloid and lymphoid neoplasms assumes common etiology for the groupings, which has not been confirmed in epidemiologic studies.

Exposure–response models for the excess risk of mortality with leukemia, AML, CML, CLL, lymphoid neoplasms, and myeloid neoplasms using cumulative BD ppm-years as the primary dose metric are presented. These models are based on the most recent data set (the 2004 data). All models have cumulative BD ppm-years as the predictive variable either alone or with a covariate that has a statistically significant effect on the goodness of fit of the exposure–response model to the data. Although the impact of cumulative BD ppm-years in the exposure–response model depends on the presence or absence of any covariates, the numerical value of the cumulative BD ppm-years exposure does not depend on the presence or absence of any covariates.

Estimates of excess risks are calculated using life-table methodology with European mortality rates, European survival probabilities, and cumulative exposures that (1) exclude exposures received 40 or more years from the current age and (2) include all exposures.

2. Methods

2.1. Endpoints

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 using analyses similar to those used for all 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" 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 the results for subtypes hardly change.

A further sensitivity analysis was performed by considering two additional endpoints, namely, all lymphoid neoplasms (ICD9 codes 200 through 204) and all myeloid neoplasms (ICD9 codes 205 and 206). The numbers of deaths that have these responses listed as the cause of death or contributing cause of death are 120 and 56, respectively. These endpoints have been considered previously in Cheng et al. (2007) and Sielken et al. (2007).

2.2. Exposure–Response modeling

There was a May 2002 document entitled "RISK ASSESSMENT FOR 1,3-BUTADIENE," prepared by C. Zocchetti, Sc.D., Institute of Occupational Health and Lombardy Region Health Directorate, Epidemiology Office, Milan, Italy. This document was referenced as "1,3-Butadiene," Luxembourg, June 2002, EMPL D/5 D(1) SKZ/pg, SCOEL/INF/521, Scientific Committee Group on Occupational Exposure Limits and was received by Sielken & Associates from Prof. A. Bertazzi. On page 4 in this reference, the following is stated (emphasis added):

> Exposure to butadiene (ppm) can occur at a constant level between the ages 20 and 65. After this age, exposure is not considered. Each subject is allowed a working life period of cumulative exposure for a maximum of forty years: exposure received earlier than 40 years before the current age are assumed not to be relevant.

Sielken & Associates has done exposure–response modeling and added risk calculations two ways: that is, (1) excluding exposure received earlier than 40 years before the current age and (2) including all exposures. In the first approach, all of the cumulative exposure metrics for ages T greater than 60 years are cumulated only over the preceding 40 years – that is, between T-40 and T – so that, the worker's exposures more than 40 years in the past are not included in the accumulation. This approach is also consistent with the US EPA's Science Advisory Board (SAB) (USEPA, 1998b) recommendation that, in addition to exploring the importance of the number of BD high intensity tasks (HITs), the effects of the dose-time relationship be explored. The SAB suggested considering "a model that assumes a limited effect time (i.e., that leukemia risk during a given year of age is affected largely by the butadiene exposures received during the previous, say, 20 years, and only slightly or not at all by more distant ones)." In the second approach all exposures are accumulated in the calculation of the exposure metrics. Results are tabled for both approaches. The results for both approaches are similar. Results are discussed in the body of the text only for the first approach.

In Cox analyses, the cancer mortality hazard rate is modeled as the background rate multiplied by a rate ratio (RR), and the RR is modeled as a function of the individual's age-dependent cumulative exposure:

$$\text{Hazard Rate} = \text{BG} \times \text{NECV} \times \text{OECV} \times \text{F}(\text{BDppm-years})$$

where, BG = background hazard rate; NECV = categorical effect of non-exposure covariates; OECV = categorical effect of other