Chemico-Biological Interactions xxx (2015) 1–10

Contents lists available at ScienceDirect

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint

1,3-Butadiene, styrene and lymphohematopoietic cancer among male synthetic rubber industry workers – Preliminary exposure-response analyses

Nalini Sathiakumar*, Ilene Brill, Mark Leader, Elizabeth Delzell

Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, United States

ARTICLE INFO

Article history:
Available online xxx

Keywords:
1,3-Butadiene
Styrene
Leukemia
Non-Hodgkin lymphoma
Multiple myeloma
Synthetic rubber industry workers

ABSTRACT

We updated the mortality experience of North American synthetic rubber industry workers to include follow-up from 1944 through 2009, adding 11 years of mortality data to previous investigations. The present analysis used Cox regression to examine the exposure-response relationship between 1,3-butadiene (BD) and styrene (STY) parts per million (ppm)-years and leukemia (N = 114 deaths), non-Hodgkin lymphoma (NHL) (N = 89) and multiple myeloma (MM) (N = 48). A pattern of largely monotonically increasing rate ratios across deciles of BD ppm-years and a positive, statistically significant exposure-response trend were observed for BD ppm-years and leukemia. Using continuous, untransformed BD ppm-years the regression coefficient (β) adjusted only for age was 2.6×10^{-4} ($p < 0.01$); the regression coefficient adjusted for age, year of birth, race and plant was 2.9×10^{-4} ($p < 0.01$). STY ppm-years also displayed a positive exposure-response association with leukemia. STY and BD were strongly correlated, and the separate effects of these two agents could not be estimated. For NHL, a pattern of approximately monotonically increasing rate ratios across deciles of exposure was seen for STY but not for BD; the test of trend was statistically significant in one of five models that used different STY exposure metrics and adjusted for age and other covariates. BD ppm-years and STY ppm-years were not associated with MM. The present analyses indicated a positive exposure-response relationship between BD cumulative exposure and leukemia. This result along with other research and biological information support an interpretation that BD causes leukemia in humans. STY exposure also was positively associated with leukemia, but its independent effect could not be delineated because of its strong correlation with BD, and there is no external support for a STY-leukemia association. STY, but not BD, was associated positively with NHL. The interpretation of this result is uncertain because the exposure-response data were statistically imprecise and because consistent support for causality from other studies is lacking. The current study provides no support for an association between BD or STY and MM.

1. Introduction

Synthetic rubber production workers are exposed to many chemicals, including 1,3-butadiene (BD) and styrene (STY) monomers, shortstops, emulsifiers, activators, modifiers, catalysts, dilute acids, antioxidants, oils, carbon black and solvents. The International Agency for Research on Cancer (IARC) has classified BD as carcinogenic to humans (Group 1), based on sufficient evidence both in humans and in animals [1,17]. In 2012, IARC reviewed new data and concluded that there is sufficient evidence that BD causes cancer of the hematolymphatic organs in humans based on the increased risk of leukemia in epidemiologic studies among styrene-butadiene rubber (SBR) industry workers and on the increased risk of leukemia and lymphoma among BD monomer industry workers [18]. The National Toxicology Program (NTP) [31] has classified BD as 'known to be a human carcinogen' based on sufficient evidence of carcinogenicity in humans and mechanistic studies; the cancer end points included leukemia, lymphosarcoma and reticulosarcoma.

The IARC has classified STY as possibly carcinogenic to humans (Group 2B) based on limited evidence in experimental animals and on inadequate evidence in humans [16]. Bofetta et al. [2] reviewed epidemiologic studies of STY and cancer and concluded that there is

* Corresponding author.
E-mail address: nalini@uab.edu (N. Sathiakumar).

http://dx.doi.org/10.1016/j.cbi.2015.09.003
0009-2797/

no consistent evidence of an association between STY exposure and lymphohematopietic cancer (LHC) overall, or for lymphoma or leukemia. Huff and Infante [15] in another review, suggested that STY and styrene-7,8-oxide should be considered as potential carcinogens to humans based on both animal and human data. The NTP [31] has classified styrene as 'reasonably anticipated to be a human carcinogen' based on increased mortality or incidence of leukemia, lymphoma or all LHC and an increased level of DNA adducts and genetic damage in exposed workers.

We previously assembled and analyzed epidemiologic data on men employed in the North American synthetic rubber industry and reported on their mortality experience [4,9–11,13,25,26,34,35]. An earlier analysis of the study of male workers [13,35] evaluated mortality during the time period 1944 through 1998 among 17,924 men employed at eight plants and found an excess of leukemia that was likely to have been due to exposure to BD or BD plus other chemicals. The study did not find any clear relation between exposure to BD or STY and non-Hodgkin lymphoma (NHL) or multiple myeloma (MM).

The research described here extended the mortality follow-up through 2009, adding 11 years to the previous update. In this paper, we present a preliminary analysis of exposure-response relationships between BD or STY ppm-years and leukemia, NHL and MM, based on data obtained for the study as of October, 2014. Data collection for the update is still ongoing; however, because only a few additional death certificates will be obtained, future publications will contain results only slightly different from those reported here.

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 for men [11,13,35]. The present study included 16,579 men who had worked before January 1, 1992, for at least 1 year at any of the six synthetic rubber plants located in Texas (two plants), Louisiana (two plants), Kentucky (one plant) and Canada (one plant), and for whom detailed work histories and historical exposure information were available.

As described previously [25,26], we developed quantitative estimates of each subject's exposure to BD and STY 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.

In developing exposure estimates, we did not use industrial hygiene data for several reasons [26]. Extensive changes in production and engineering controls have occurred in the synthetic rubber industry since the 1940s, historical exposure measurements were sparse before 1975, and exposure measurements taken since 1975 did not cover all work area/job title groups at all plants. However, data from a validation study at one of the plants included in the present investigation found that the correlation between estimated and measured BD ppm was moderate overall (Spearman's $r = 0.45$, $p < 0.0001$) and was high for jobs that pertained to typical SBR operations ($r = 0.81$, $p < 0.0001$) [36].

The BD and STY exposure indices analyzed for this paper pertained to cumulative exposure to BD or STY in parts per million (ppm)-years. All work history and exposure data covered the time period included in our initial investigation of the study cohort, 1943–1991 [11,25,34]. As of the end of 1991, 3763 (21%) men were still actively employed at the study plants. Post-1991 work history information was not available to update the work histories or exposure estimates of these men.

Our previous investigations (1944–1998) of men employed at eight synthetic rubber plants identified 6237 men as deceased before 1999, 11,117 as presumed living and 570 (US plants) as having unknown vital status. We used linkages with several national databases to determine subjects' vital status as of the end of 2009 for the present study. Vital status ascertainment was about 99% complete. Cause of death information came from death certificates, the United States (US) National Death Index and the Canadian Mortality Data Base. In total (1944–2009 time period) among men employed at six plants, we identified 114 decedents with leukemia, 89 with NHL and 48 with MM reported as the underlying (leukemia, 85%; NHL, 75%; MM, 85%) or a contributing (leukemia, 15%; NHL, 25%; MM, 15%) cause of death. Only 14 decedents had Hodgkin lymphoma, and therefore it was not possible to conduct any meaningful exposure-response analyses for this malignancy.

Of the total cohort of 16,579 men, exclusions for Cox regression analyses of each of the above forms of LHC were: leukemia − 168 men who dropped out of follow-up at ages younger than the youngest leukemia decedent (age 32 years); NHL − 372 men who dropped out of follow-up at ages younger than the youngest NHL decedent (age 41 years); MM − 1144 men who dropped out of follow-up at ages younger than the youngest MM decedent (age 49 years). Thus, results were based on 16,411 subjects and 611,880 person-years of observation for leukemia; 16,207 subjects and 609,711 person-years for NHL; and 15,435 subjects and 595,013 person-years for MM.

We used Cox regression, with age as the time variable, to obtain an estimate of the rate ratio (RR) and the 95% CI for each disease category in each decile of BD or STY exposure, compared to the unexposed; and to estimate the slope of the exposure-response trend using continuous BD or STY variables. The measure of association in these analyses was the hazard ratio, which can be interpreted as a RR. The exposure variables, as well as the covariates, age and years since hire, were time-dependent. The Cox regression models provided maximum partial likelihood estimates of disease-specific RRs across the exposure range experienced by subjects in the study. We present the results of two sets of models. One set estimated the association between the exposure variable and the outcome of interest, adjusting only for age. The second set estimated the association between the exposure variable and the outcome of interest, adjusting for age, as well as other potential confounders (see below).

We examined the trend in exposure-response relationships using: (a) deciles of BD or STY ppm-years; (b) continuous, untransformed BD or STY ppm-years; (c) natural logarithm (ln)-transformed, log base 10 and square-root transformed continuous BD or STY ppm-years. For the log transformations, to avoid zero exposure values, we added 1 ppm-day (0.0027 ppm-years) to each exposure value and obtained the log of the resulting value.

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 of exposure avoid assumptions about the functional form of a continuous exposure-response relationship and may reduce the influence of data at extreme exposure values; in particular, it may reduce the impact of misclassification that some investigators have suggested might selectively affect the upper range of exposure estimates

Please cite this article in press as: N. Sathiakumar, et al., 1,3-Butadiene, styrene and lymphohematopoietic cancer among male synthetic rubber industry workers – Preliminary exposure-response analyses, Chemico-Biological Interactions (2015), http://dx.doi.org/10.1016/j.cbi.2015.09.003