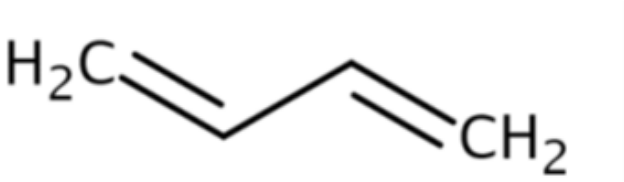
United States
Environmental Protection Agency

November 2024
Office of Chemical Safety and
Pollution Prevention

Data Quality Evaluation Information for Human Health Hazard Epidemiology for 1,3-Butadiene

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 106-99-0



November 2024

This supplemental file contains the data quality evaluation results for epidemiology data sources that (1) met PECO screening criteria and (2) passed further filtering. For a detailed description on these criteria, see the *Draft Risk Evaluation for 1,3-Butadiene - Systematic Review Protocol*. EPA conducted data quality evaluation based on author-reported descriptions and results; additional analyses (*e.g.*, statistical analyses performed during data integration into the risk evaluation) potentially conducted by EPA are not contained in this supplemental file. EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol are described in the *Draft Risk Evaluation for 1,3-Butadiene - Systematic Review Protocol*.

Table of Contents

Study Citation:	Cheng, H., Sathiakumar, N., Graff, J., Matthews, R., Delzell, E. (2007). 1,3-Butadiene and leukemia among synthetic rubber industry workers: Exposure-response relationships. Chemico-Biological Interactions 166(1-3):15-24.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Leukemia mortality, lymphoid neoplasms mortality, myeloid neoplasms mortality, Cancer; Immune/Hematological- Leukemia mortality, lymphoid neoplasms mortality, myeloid neoplasms mortality, Cancer; Mortality- Leukemia mortality, lymphoid neoplasms mortality, myeloid neoplasms mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	646899

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	This study analyzed associations between occupational exposure to 1,3-butadiene and mortality from select cancers including leukemia. Subjects were men who worked at varying times starting in 1944 through January 1992, employed for at least one year at any of six synthetic rubber plants (2 plants located in Texas, 2 in Louisiana, 1 in Kentucky, and 1 in Canada). Vital status ascertainment through 1998 was about 97% complete. Of the 16,579 subjects considered for this study, 16,091 were deemed eligible. 488 were excluded as they were lost follow up at ages younger than the youngest leukemia decedent (33 years of age). Subject data were gathered from plant records and data collected from previous follow-up studies (Macaluso et al., 1996 HERO: 051490). Descriptive characteristics of leukemia decedents and of other subjects are provided in Table 1. Mean duration since hire was about 30 years; mean duration employed was not described in this paper. A potential concern is that limiting the eligible population to workers employed for at least one year may have induced some risk of healthy worker bias if turnover of short-term workers was high. However, there was no direct evidence of such bias.
Domain 2: Exposure Characterization			
	Metric 2A: Exposure Measurement	Medium	Estimated exposure to butadiene (BD) was based on job-exposure matrices (JEMs) that captured work area/job groups per plants, work area/job group-specific component tasks that entailed exposure and associated historical changes in those tasks, and plant-, work area/job group- and time-specific average exposure indices (8 h time-weighted average concentration). To calculate exposure estimates, these plant-, work area/job group- and time-specific exposure estimates were linked with each subject's work history. Validation data are not discussed. Further details on estimation methods, and the limited availability of objective measures due to the lack of industrial hygiene monitoring prior to the 1970s, are described elsewhere (Macaluso et al., 2004 646914). Exposure variables analyzed in this paper included estimates of cumulative exposure in ppm-years, frequency of exposure to "peak" concentrations > 100 ppm and estimated average intensity of exposure. All exposure variables were time dependent. There was no evidence of bias in estimation of exposure.
Domain 3: Outcome Assessment			

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	646899

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Outcomes were mortality from leukemia, any lymphoid neoplasms (including lymphoid leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma) and any myeloid neoplasms (including myeloid and monocytic leukemia, myelofibrosis, myelodysplasia, myeloproliferative disorders, polycythemia vera). Leukemia subtypes were not analyzed separately. Multiple linked national databases were used to ascertain a subject's vital status as of end of 1998. Vital status ascertainment was largely complete (97%). Death certificates, the US National Death Index, and the Canadian Mortality Data Base were used to determine cause of death. Previous publications mention the use of ICD codes to identify outcomes (Delzell et al., 1996: HERO 51390). Authors mentioned they sought medical records for subjects whose death certificate mentioned leukemia or any other lymphatic and hematopoietic-related cancers. The authors do not specify if obtaining medical records for the 81 decedents represents a 100% success rate in locating such records and did not discuss the outcome of medical records review. There was no evidence of error or bias in outcome ascertainment. However, since mortality was analyzed, any participants with prevalent cases of these outcomes were not identified.
	Metric 3B:	Selective Reporting	High	All analyses described in the methods seem to be reported in all aspects of the report. Methodologies are clearly outlined. Penalized spline regression results are illustrated in Figure 1 but do not include butadiene average intensity; however, ln hazard ratio is reported in Section 3.1. Effect estimates by decile of exposure for each of the three butadiene variables are presented in Table 2. Effect estimates from exposure-response models using continuous, untransformed butadiene variables are presented in Tables 3-5. The use of transformed [ln and square root]) butadiene variables were considered in Table 3. Effects of lagged exposure were analyzed in Table 4.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Confounders were included in analyses. Effect estimates from one set of models adjusted age only, whereas effect estimates from another set adjusted a priori for age, year of birth, race, co-exposure to dimethyldithiocarbamate (DMDTC), years since hire and plant (facility). The authors briefly discussed the rationale for including or excluding several confounders. For example, they described the influence of adjusting for co-exposure variables (DMDTC, styrene), and discussed accounting for the potential influence of unmeasured workforce characteristics by adjusting for plant. While the sensitivity of plant to capture unmeasured factors is uncertain, there was no evidence of important residual confounding.
Domain 5: Analysis				

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Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Leukemia mortality, lymphoid neoplasms mortality, myeloid neoplasms mortality, Cancer; Immune/Hematological- Leukemia mortality, lymphoid neoplasms mortality, myeloid neoplasms mortality, Cancer; Mortality- Leukemia mortality, lymphoid neoplasms mortality, myeloid neoplasms mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	646899

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	High	Descriptive data were presented for leukemia decedents vs the remaining cohort, and associations between BD and mortality outcomes were analyzed using Cox regression models. The proportional hazard assumption was tested using age-exposure interaction terms. The exposure-response relationship analysis in this study was very detailed and robust. The study compared results using alternative approaches to analyze dose-response patterns for three different butadiene exposure variables (ppm-years, peaks, and average intensity). This included the use of continuous untransformed variables, continuous ln-transformed and square-root-transformed variables, deciles, and continuous mean-scored deciles. Deciles were defined based on the distribution among leukemia cases. Justification for all methods is provided (e.g., use of penalized spline regression to inform adequacy of Cox regression models, comparison of categorical v. continuous exposure variables). Quantitative results are adequately presented, including the effect estimates, confidence intervals, variability (standard error for exposure-response models using continuous butadiene variables only). Fit was evaluated and compared across models based on -2 log likelihood values. Results were presented for age-adjusted and multivariate-adjusted models. Supplementary analyses excluded potentially influential exposures above the 95th percentile and analyzed exposure using lags ranging from 0 to 20 years.
	Metric 5B:	Sensitivity	Medium	This study assessed associations between BD exposure and several cancer mortality outcomes in a cohort of workers with known exposure to butadiene, styrene, and DMDTC. The length of follow-up was appropriate given the expected latency for cancer development (median of about 30 years since hire, mean age $>$ 60 years). The cohort was large, there was variability in estimated exposure, and analyses included up to 81 leukemia cases. There was no evidence of inadequate sensitivity.

Additional Comments: This retrospective study of more than 16,000 synthetic rubber cohort workers examined the association between occupational exposure to 1,3 butadiene and mortality from leukemia, lymphoid neoplasms, and myeloid neoplasms through 1998. The authors analyzed cumulative exposure, frequency of peak exposures, and average intensity of exposure. Analyses of dose-response relationships were very detailed and robust, comparing findings from models that analyzed exposure as continuous variables with different transformations as well as using categorical variables. Authors provided comprehensive justification for their choice of methods. Findings supported a positive exposure–response relationship between occupational BD exposure and leukemia mortality, but not with lymphoid or myeloid neoplasm mortality. Multivariate-adjusted associations between cumulative BD exposure and leukemia were significant using continuous untransformed, square root transformed and mean-scored decile exposure variables. Estimates were more robust in the sample below the 95th percentile of exposure among cases. However, results did not clearly indicate superior fit of a particular exposure variable specification, and reasons for some variation in the magnitude of effect estimates were uncertain.

Overall Quality Determination Medium

Study Citation:	Danysh, H. E., Mitchell, L. E., Zhang, K., Scheurer, M. E., Lupo, P. J. (2015). Traffic-related air pollution and the incidence of childhood central nervous system tumors: Texas, 2001-2009. Pediatric Blood & Cancer 62(9):1572-1578.
Health Outcome(s) Assessed:	Neurological/Behavioral- All central nervous system tumors, juvenile pilocytic astrocytoma, other astrocytomas, ependymoma, medulloblastoma, primitive neuroectodermal tumors, Cancer; Cancer/Carcinogenesis- All central nervous system tumors, juvenile pilocytic astrocytoma, other astrocytomas, ependymoma, medulloblastoma, primitive neuroectodermal tumors, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	3011004

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	High	This ecological study examined associations between census-tract level estimated exposure to 1,3-butadiene and incidence of several forms for central nervous system (CNS) tumors among children living in Texas. The study included all children age <15 in Texas with incident CNS tumors, 2001-2009 (n=1,949) identified from the population-based Texas Cancer Registry. As the denominator / at-risk population, the study also included all children age <15 living in Texas in the year 2000 (n=5,797,483). Children with CNS tumors were excluded if they invalid county and census tract code combinations or if the population estimate for their census tract was 0. Exclusion criteria reduced the number of included cases only slightly, from n=2,019 to n=1,949. Excluded cases were similar to included cases on age at diagnosis, sex, and area-level poverty, but were more likely to be non-Hispanic Black and less likely to be non-Hispanic white than included cases. Overall, concern for selection bias is minimal.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Low	Census-tract-level annual exposure estimates for 1,3-butadiene were obtained for the year 2005 from the U.S. Environmental Protection Agency's Assessment System for Population Exposure Nationwide (ASPEN), a "computer simulation model derived from the U.S. EPA's Industrial Source Complex Long Term model" and describe in detail in Rosenbaum et al. 1999, HERO ID 1383. Several concerns reduce confidence in this domain. First, some exposure misclassification is likely given the use of census tract-level estimates to represent individual exposure. Second, exposure estimates were assigned based on address at time of diagnosis, potentially leading to further exposure misclassification. Third, exposure estimates for the year 2005 were used for all cases diagnosed 2001-2009; as such, exposures may not represent the etiologically relevant time window.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	High	The outcomes of interest were all central nervous system (CNS) tumors, juvenile pilocytic astrocytoma (JPA), other (non-JPA) astrocytomas, ependymoma, medulloblastoma, and primitive neuroectodermal tumors (PNET). Cases of these outcomes were identified from the Texas Cancer Registry, a population-based cancer registry "with a gold certification from the North American Association of Central Cancer Registries during the study period." Cases were identified usings International Classification of Childhood Cancer, 3rd edition and International Classification of Diseases for Oncology, 3rd edition codes. Cases were limited to those with a CNS tumor as their first malignancy. Outcome misclassification is expected to be minimal.

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Health Outcome(s) Assessed:	Neurological/Behavioral- All central nervous system tumors, juvenile pilocytic astrocytoma, other astrocytomas, ependymoma, medulloblastoma, primitive neuroectodermal tumors, Cancer; Cancer/Carcinogenesis- All central nervous system tumors, juvenile pilocytic astrocytoma, other astrocytomas, ependymoma, medulloblastoma, primitive neuroectodermal tumors, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	3011004

Domain	Metric		Rating	Comments
	Metric 3B:	Selective Reporting	Medium	All primary analyses described in the methods section are presented in the results section.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	Potential confounders were selected a priori, but no further detail regarding selection strategy was provided. Selected confounders were: sex, age at diagnosis, race/ethnicity, and census-tract level poverty (as a proxy for SES). Information on confounders was obtained from Texas Cancer Registry records (sex, age, race/ethnicity) and from the 2000 U.S. Census (census tract-level poverty). Census tract exposure estimates for 1,3-butadiene were higher near major metropolitan areas, but a measure of urban/rural status was not evaluated as a potential confounder. Additionally, 1,3-butadiene was highly correlated with other chemicals assessed as exposures in the study, but confounding by co-exposures was not evaluated (Spearman's rank correlation with benzene = 0.84, p <0.0001; with diesel particulate matter = 0.086, p <0.0001). The potential for bias due to residual confounding is likely high.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Incidence rate ratios for each tumor type were estimated using Poisson regression. Models were examined for over-dispersion, and negative binomial regression was used instead in such cases. Estimated exposure to 1,3-butadiene was categorized into quartiles for analysis. Sensitivity analyses included models restricted to only cases diagnosed in 2004-2006 for better alignment with the timing of exposure estimates (2005). Potential confounding by race/ethnicity was further analyzed by restricting the model for other astrocytomas to non-Hispanic white study subjects.
	Metric 5B:	Sensitivity	Medium	The sample size was adequate (n=1,949 cases), although numbers were small for some specific tumor types (e.g., n=47 cases of primitive neuroectodermal tumors). No other concerns regarding study sensitivity were identified.

Additional Comments: This ecologic study estimated associations between 1,3-butadiene exposure and several forms of central nervous system tumors among children age <15 in Texas. Strengths include the use of a population-based cancer registry to identify cases. Concerns include the potential for exposure misclassification due to the use of census-tract level estimates for children's address at time of diagnosis, uncertainty regarding whether exposure was assessed during the etiologically relevant time window, limited information on confounder identification and selection strategy, and the potential for residual confounding (e.g., by other demographic characteristics or by co-exposures). The study found significant associations between medium (Q2) and medium-high (Q3) exposure to 1,3-butadiene and other (non-juvenile pilocytic astrocytoma) astrocytoma compared to low (Q1) exposure.

Overall Quality Determination Medium

Study Citation:	Delfino, R. J., Gone, H., Linn, W. S., Pellizzari, E. D., Hu, Y. (2003). Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. Environmental Health Perspectives 111(4):647-656.
Health Outcome(s) Assessed:	Lung/Respiratory- Asthma symptom severity, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	50460

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This panel study of Hispanic children with asthma examined associations between daily measurements of air pollution (including 1,3-butadiene) and daily measures of asthma symptoms over a 3-month period from November 1999 to January 2000. Participants were recruited though referral from area schools in east Los Angeles. Inclusion criteria were: at least a 1-year history of physician diagnosed asthma, age 10-15, non-smokers/non-smoking households, home and school addresses within a 3-mile radius of the central air monitoring site used for exposure assessment, and reporting at least 2 symptomatic days per week requiring as-needed beta-agonist inhaler use. Participation rates were not provided. Several inclusion criteria were relaxed during the study in order to meet the enrollment target of 24 children (one study subject lived 3.8 miles from the monitor, two 16-year olds were included, and the inhaler criterion was relaxed to include children with intermittent asthma). Of the 26 children recruited, 2 were excluded because they did not complete symptom diaries, 2 were excluded due to apparently falsified peak expiratory flow data, and 2 were excluded from analyses adjusted for respiratory infections due to a "frequent off-and-on appearance of responses, which is inconsistent with the usual course and frequency of respiratory infections." These further exclusions left 22 and 20 participants for models without and with a term for respiratory infections, respectively. While not all aspects of participant selection were reported (e.g., participation rate), concern for selection bias is minimal.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Daily 1,3-butadiene concentrations assessed at a single monitoring site. Exposure was measured using outdoor 24-hour air samples of 1,3-butadiene collected in canisters and analyzed using "U.S. EPA TO-14 methodology (SCAQMD, 2000)." There is some concern for exposure misclassification as the monitoring site was initially specified to be a site in Huntington Park, but prior to analysis was changed to "an alternate site nearer to eight volunteers in Maywood" due to a delay in the sampling start date at the Huntington Park site. It is not clear how far this site was from the study population as a whole, and the study did not state whether the Maywood site was used for the entirety of the study or only for the missing days at the start of the study period.
Domain 3: Outcome Assessment				

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Health Outcome(s) Assessed:	Lung/Respiratory- Asthma symptom severity, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	50460

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Low	Asthma symptom severity was self-reported daily by participants in a diary using a scale "that incorporates the impact of the clinical severity of asthma symptoms on daily activities." Specifically, symptoms (cough, wheeze, sputum production, shortness of breath, chest tightness) were rated in terms of combined severity on a six-level ordinal scale. Analyses evaluated 2 dichotomous outcomes: a) of no symptoms or symptoms not bothersome (score 0 or 1) versus bothersome or more severe asthma symptoms (scores $>$ 1), and b) none-to-bothersomesymptoms but no interference with daily activities (score 0–2) versus asthma symptoms that interfered with daily activities (scores $>$ 2). Supporting references are provided for appropriateness of the approach to detect detect associations of these clinically relevant symptom outcomes with criteria air pollutantsPeak expiratory flow (L/min) was measured daily by study participants using Mini-Wright peak flow meters before use (if any) of bronchodilator medication. Participants recorded three values in the morning and three in the evening, with the highest value from each morning and evening retained. PEF measurements that did not meet the reproducibility criterion of $\leq$ 10% difference between the highest and second highest PEF were excluded. Trained research assistants also administered baseline and an end-of study spirometryReliance on self-reported measurements and non-electronic PEF raises concern for outcome misclassification.
	Metric 3B:	Selective Reporting	Medium	The primary analyses described in the methods section were presented in the result section. However, multi-pollutant models were only shown for select air pollutant models and did not include results for models including 1,3-butadiene.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Confounders evaluated were weekend vs. weekday, temperature, and respiratory infections; variables were retained in models if they led to a 10% or larger change in the effect estimate. Factors that vary between individuals that are frequently evaluated as potential confounders in other study designs (e.g., age, sex, socioeconomic status) are controlled for by design in this study, as comparisons are made within rather than across individuals. Seasonal/long-term time trends were not considered as a potential confounder, but this is not a major concern given the short study period (3 months). The strategy for identifying potential confounders was not provided, but confounders evaluated are generally consistent with those typically included in studies examining the short-term effects of air pollution in panel studies
Domain 5: Analysis				

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Health Outcome(s) Assessed:	Lung/Respiratory- Asthma symptom severity, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	50460

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Analytic methods were appropriate for examining longitudinal exposures and outcomes within individuals. Association of daily 1,3-butadiene exposure with daily asthma symptoms were assessed using generalized estimating equations.. Models were constructed for individual lag days 0 through 4; only results from lag days 0 and 1 were provided; authors state that these were the lag days with the strongest associations. Additional models were constructed testing interactions with respiratory infections and anti-inflammatory medication use, excluding one individual at a time to determine whether particular individuals were especially influential, and including multiple air pollutants in the model simultaneously. The number of days with missing exposure data was provided.
	Metric 5B:	Sensitivity	Low	The overall sample size was small (n=22), with even smaller sample sizes for analyses of self-reported asthma symptom severity measures (asthma symptoms scores >1 analysis: n=16; asthma symptoms scores >2 analysis: n=7). The mean (SD) concentration of 1,3-butadiene was 0.51 (0.28) ppb.

Additional Comments: This longitudinal panel study evaluated associations between daily 1,3-butadiene exposure, self-reported asthma symptom severity, and peak expiratory flow. Major concerns contributing to reduced confidence were the lack of information validation of outcome measures and the small sample size (n=22).

Overall Quality Determination Low

Study Citation:	Delfino, R. J., Gone, H., Linn, W. S., Pellizzari, E. D., Hu, Y. (2003). Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. Environmental Health Perspectives 111(4):647-656.
Health Outcome(s) Assessed:	Lung/Respiratory- Peak expiratory flow, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	50460

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This panel study of Hispanic children with asthma examined associations between daily measurements of air pollution (including 1,3-butadiene) and daily measures of asthma symptoms over a 3-month period from November 1999 to January 2000. Participants were recruited though referral from area schools in east Los Angeles. Inclusion criteria were: at least a 1-year history of physician diagnosed asthma, age 10-15, non-smokers/non-smoking households, home and school addresses within a 3-mile radius of the central air monitoring site used for exposure assessment, and reporting at least 2 symptomatic days per week requiring as-needed beta-agonist inhaler use. Participation rates were not provided. Several inclusion criteria were relaxed during the study in order to meet the enrollment target of 24 children (one study subject lived 3.8 miles from the monitor, two 16-year olds were included, and the inhaler criterion was relaxed to include children with intermittent asthma). Of the 26 children ultimately recruited, 2 were excluded because they did not complete symptom diaries, 2 were excluded due to apparently falsified peak expiratory flow data, and 2 were excluded from analyses adjusted for respiratory infections due to a "frequent off-and-on appearance of responses, which is inconsistent with the usual course and frequency of respiratory infections." These further exclusions left 22 and 20 participants for models without and with a term for respiratory infections, respectively. While not all aspects of participant selection were reported (e.g., participation rate), concern for selection bias is minimal.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Daily 1,3-butadiene concentrations assessed at a single monitoring site. Exposure was measured using outdoor 24-hour air samples of 1,3-butadiene collected in canisters and analyzed using "U.S. EPA TO-14 methodology (SCAQMD, 2000)." There is some concern for exposure misclassification as the monitoring site was initially specified to be a site in Huntington Park, but prior to analysis was changed to "an alternate site nearer to eight volunteers in Maywood" due to a delay in the sampling start date at the Huntington Park site. It is not clear how far this site was from the study population as a whole, and the study did not state whether the Maywood site was used for the entirety of the study or only for the missing days at the start of the study period.
Domain 3: Outcome Assessment				

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Health Outcome(s) Assessed: Lung/Respiratory- Peak expiratory flow, Non-cancer

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 50460

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Low	The outcomes of interest were asthma symptom severity and peak expiratory flow. Asthma symptom severity was self-reported daily by participants in a diary using a scale "that incorporates the impact of the clinical severity of asthma symptoms on daily activities." Specifically, symptoms (cough, wheeze, sputum production, shortness of breath, chest tightness) were rated in terms of combined severity on a six-level ordinal scale. No information was provided on the validity of the asthma symptom scale. Peak expiratory flow (L/min) was measured daily by study participants using Mini-Wright peak flow meters before use (if any) of bronchodilator medication. Participants recorded three values in the morning and three in the evening, with the highest value from each morning and evening retained. No information was reported on the validation of this outcome (e.g., comparisons to spirometry conducted by a medical professional). There is some concern for outcome misclassification due to the absence of validation data for these self-reported outcomes.
	Metric 3B:	Selective Reporting	Medium	The primary analyses described in the methods section were presented in the result section. However, multi-pollutant models were only shown for select air pollutant models and did not include results for models including 1,3-butadiene.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	The strategy for identifying potential confounders was not provided, but confounders evaluated are generally consistent with those typically included in studies examining the short-term effects of air pollution using within-individual comparisons. Confounders evaluated were weekend vs. weekday, daily maximum temperature, and respiratory infections; variables were retained in models if they led to a 10% or larger change in the effect estimate. Factors that vary between individuals that are frequently evaluated as potential confounders in other study designs (e.g., age, sex, socioeconomic status) are controlled for by design in this study, as comparisons are made within rather than across individuals. Seasonal/long-term time trends were not considered as a potential confounder, but this is not a major concern given the short study period (3 months).
Domain 5: Analysis				
	Metric 5A:	Analysis	Low	Analytic methods were generally appropriate for examining longitudinal exposures and outcomes within individuals. Associations of daily 1,3-butadiene exposure with daily peak expiratory flow were assessed using general linear mixed models with a random intercept for each individual. Results for analyses of peak expiratory flow are presented only in terms of statistical significance (i.e., results were stated to be not statistically significant), with no effect sizes or confidence intervals provided. It is unclear whether sensitivity analyses (testing interactions with respiratory infections and anti-inflammatory medication use, excluding one individual at a time to determine whether particular individuals were especially influential, and including multiple air pollutants in the model simultaneously) were run for this outcome. The number of days with missing exposure data was provided.

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Health Outcome(s) Assessed:	Lung/Respiratory- Peak expiratory flow, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	50460

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Low	The overall sample size was small (n=22). The mean (SD) concentration of 1,3-butadiene was 0.51 (0.28) ppb. No other concerns regarding sensitivity were identified.

Additional Comments: This longitudinal panel study evaluated associations between daily 1,3-butadiene exposure, self-reported asthma symptom severity, and peak expiratory flow. Major concerns contributing to reduced confidence were the lack of information validation of outcome measures, small sample size (n=22), and reporting of peak expiratory flow rates as significant/not-significant only.

Overall Quality Determination Low

Study Citation:	Delzell, E., Macaluso, M., Sathiakumar, N., Matthews, R. (2001). Leukemia and exposure to 1,3-butadiene, styrene and dimethyldithiocarbamate among workers in the synthetic rubber industry. Chemico-Biological Interactions 135-136:515-534.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- leukemia mortality, Cancer; Mortality- leukemia mortality, Cancer; Immune/Hematological- leukemia mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	737524

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This occupational cohort study examined the association between 1,3-butadeine exposure and leukemia mortality in an occupational population from 1944 through 1991. Male workers (n=17,694) who worked in synthetic rubber plants for at least one year were identified using plant records. Eight rubber plants were included (7 in the United States, 1 in Canada). The final study population included 13, 130 men. Men were excluded from the study if they worked at two plants, as the records lacked information on work area/job assignment information (used to estimate exposure levels). 12 duplicate records capturing men who worked at more than one plant in the study period were also excluded. 3,468 men were excluded because they died or follow-up ended before 40 years of age or before 10 years since hire. It is not clear whether bias could have arisen due to healthier workers remaining employed in exposed jobs for longer; however, the available information does not raise serious concerns regarding selection bias for analyses that do not use the general population as the reference group. There is no comparison of those included and excluded from the study population. However, a high percentage of the eligible population was included in the study with minimal loss to follow-up, which minimizes concern for selection bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Exposure to 1,3-butadiene was assessed by reviewing the job-exposure matrix approach used to estimate exposure from previous studies (Delzell et al., 1999, HEROID 5664525) and updating accordingly. During the review, experts (i.e., industrial hygienists and chemical engineers) visited the six synthetic rubber plants to obtain additional information on work practices, operations, and engineering controls, and additional data on air speeds throughout each plant. The JEM incorporated measures of time, task- and plant-specific information, and detailed job histories, although data validating the JEM is not provided. Although there is potential for exposure misclassification, this is expected to be nondifferential.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Leukemia mortality data were obtained from plant records and data from individual tracing and record linkages with national and private agencies. Death certificates provided information on cause of death. For those with leukemia or another blood disorder listed as the attributed cause of death, medical records or pathology data were obtained to confirm the diagnosis (n = 49 out of 59 cases). Personnel, medical, and death certificate records are expected to be reliable measures of leukemia deaths. However, measures of solely deaths due to leukemia do not capture those with incident leukemia. Misclassification is expected to be minimal.

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Study Citation:	Delzell, E., Macaluso, M., Sathiakumar, N., Matthews, R. (2001). Leukemia and exposure to 1,3-butadiene, styrene and dimethyldithiocarbamate among workers in the synthetic rubber industry. Chemico-Biological Interactions 135-136:515-534.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- leukemia mortality, Cancer; Mortality- leukemia mortality, Cancer; Immune/Hematological- leukemia mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	737524

Domain	Metric		Rating	Comments
	Metric 3B:	Selective Reporting	Medium	Results are reported for all analyses described in the methods.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	Age and years since hire were included in models as confounders. Additionally, the study was restricted to male workers, effectively controlling for sex. Styrene and sodium dimethyldithiocarbamate (DMDTC) were included in multiple pollutant models. Key confounders including smoking status, other co-exposures encountered in the occupational environment that are associated with leukemia, race, and SES, were not included in analyses.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The association between leukemia mortality and occupational 1,3-butadiene exposure was analyzed via Poisson regression models. Effect estimates and 95% CI are reported for all analyses, along with p for trend (where applicable). Analyses used tertiles of exposure (among exposed leukemia decedents), quartiles, or quintiles of exposure in analyses. Median exposure levels among cases are provided.Both single-pollutant and multiple pollutant models were used to assess associations. Additionally, a 5- or 10-year lag was applied in some analyses to assess cumulative exposures to account for the latency of leukemia disease.
	Metric 5B:	Sensitivity	Medium	The sample size was adequate (n = 13,130 men) to detect an effect, although the number of cases was fairly low due to the rare nature of leukemia (n = 59). The follow-up period was appropriate to detect the disease given the expected latency of leukemia. No other concerns related to study sensitivity.

Additional Comments: This occupational cohort study examined the association between leukemia mortality and 1,3-butadiene exposure in a population of male synthetic rubber plant workers (n = 13,130). The approaches to participant selection, outcome ascertainment, and statistical analyses were adequate and not expected to introduce substantial bias. There was some potential of exposure misclassification due to the exposure estimation approach (i.e., incorporating information on job history and plant/task/temporal data); however, such misclassification would not be expected to be differential by outcome status. Additionally, some key confounders (including smoking status, other occupational co-exposures, race, and SES) were not considered or incorporated in analyses. Overall, concerns about major sources of residual bias are minimal.

Overall Quality Determination Medium

Study Citation:	Delzell, E., Sathiakumar, N., Graff, J., Macaluso, M., Maldonado, G., Matthews, R., Health Effects Institute (2006). An updated study of mortality among North American synthetic rubber industry workers. Research Reports (Health Effects Institute) 62(132):1-63; discussion 65-74.
Health Outcome(s) Assessed:	Immune/Hematological- All lymphopoietic cancer (LHC) mortality. LHC mortality subtypes analyzed: leukemia (lymphocytic, myelogenous, other), non-Hodgkin's lymphoma, Hodgkins's disease, multiple myeloma,, Cancer; Cancer/Carcinogenesis- All cancers mortality, all benign neoplasm mortality. Lymphopoietic cancer mortality (leukemia, Hodgkin's disease, non-Hodgkin's disease, multiple myeloma), buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, prostate cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, other cancer mortality., Cancer; Mortality- All lymphopoietic cancer (LHC) mortality. LHC mortality subtypes analyzed: leukemia (lymphocytic, myelogenous, other), non-Hodgkin's lymphoma, Hodgkins's disease, multiple myeloma mortality. Prostate cancer mortality. Buccal cavity and pharynx cancer mortality; esophageal cancer mortality; stomach cancer mortality; colorectal cancer mortality; pancreatic cancer mortality. Pancreatic cancer mortality. Bladder cancer mortality, kidney cancer mortality. Lung cancer mortality. Brain cancer mortality., Cancer; Mortality- Circulatory disease mortality. Digestive disease mortality. Allergic, endocrine, metabolic, and nutritional disease mortality (combined). Non-malignant respiratory disease mortality. External causes mortality. Other and unknown causes of mortality., Non-cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disorders mortality., Non-cancer; Cardiovascular- Circulatory disease mortality., Non-cancer; Reproductive/Developmental- Prostate cancer mortality., Cancer; Reproductive/Developmental- Genitourinary disease mortality., Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality; esophageal cancer mortality; stomach cancer mortality; colorectal cancer mortality; pancreatic cancer mortality., Cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality., Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease mortality (combined)., Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality., Cancer; Lung/Respiratory- Lung cancer mortality., Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality., Non-cancer; Neurological/Behavioral- Brain cancer mortality., Cancer; External, other and unspecified causes of mortality.- External cause mortality; other and unknown causes of mortality., Non-cancer; Hepatic/Liver- Liver cancer mortality., Cancer; Renal/Kidney- Genitourinary disease mortality., Non-cancer; Thyroid- Allergic, endocrine, metabolic, and nutritional disease mortality (combined), Non-cancer; Immune/Hematological- Blood disorders mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	737525

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	HEROID 737525 analyzed mortality patterns in 17,924 men employed for at least one year at 8 synthetic rubber plants (7 in the US, 1 in Canada) at varying times between 1943 and 1991. Additional details were provided in HEROID 5554378 (hereafter original report). This study extended mortality follow-up from 1992 to 1998; median follow-up was 33 years. The analysis sample in this study was not limited to men working in styrene-butadiene rubber production. In this extended follow-up, 11,117 (62%) were living or presumed alive, 6,237 (35%) were deceased, and 570 (3%) were considered lost to follow-up (Table 1). The earlier report stated that workers terminated before 1979 were presumed alive when vital status was not ascertained (N not provided in this study). Because eligibility limited the sample to workers employed for at least 1 year, median employment duration through 1991 was 11 years (high turnover <1 year noted in original report). The primary concern is risk of healthy worker selection bias due to restricting eligibility to workers employed for at least one year. Overall, it cannot be ascertained to what extent excluded workers may have differed from those included in terms of 1,3 butadiene exposure and cancer mortality. However, selection bias due to excluding short term workers is an important concern and cannot be ruled out.
Domain 2: Exposure Characterization			

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Study Citation:	Delzell, E., Sathiakumar, N., Graff, J., Macaluso, M., Maldonado, G., Matthews, R., Health Effects Institute (2006). An updated study of mortality among North American synthetic rubber industry workers. Research Reports (Health Effects Institute) 62(132):1-63; discussion 65-74.
Health Outcome(s) Assessed:	Immune/Hematological- All lymphopoietic cancer (LHC) mortality. LHC mortality subtypes analyzed: leukemia (lymphocytic, myelogenous, other), non-Hodgkin's lymphoma, Hodgkins's disease, multiple myeloma,, Cancer; Cancer/Carcinogenesis- All cancers mortality, all benign neoplasm mortality. Lymphopoietic cancer mortality (leukemia, Hodgkin's disease, non-Hodgkin's disease, multiple myeloma), buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, prostate cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, other cancer mortality., Cancer; Mortality- All lymphopoietic cancer (LHC) mortality. LHC mortality subtypes analyzed: leukemia (lymphocytic, myelogenous, other), non-Hodgkin's lymphoma, Hodgkins's disease, multiple myeloma mortality. Prostate cancer mortality. Buccal cavity and pharynx cancer mortality; esophageal cancer mortality; stomach cancer mortality; colorectal cancer mortality; pancreatic cancer mortality. Pancreatic cancer mortality. Bladder cancer mortality, kidney cancer mortality. Lung cancer mortality. Brain cancer mortality., Cancer; Mortality- Circulatory disease mortality. Digestive disease mortality. Allergic, endocrine, metabolic, and nutritional disease mortality (combined). Non-malignant respiratory disease mortality. External causes mortality. Other and unknown causes of mortality., Non-cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disorders mortality., Non-cancer; Cardiovascular- Circulatory disease mortality., Non-cancer; Reproductive/Developmental- Prostate cancer mortality., Cancer; Reproductive/Developmental- Genitourinary disease mortality., Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality; esophageal cancer mortality; stomach cancer mortality; colorectal cancer mortality; pancreatic cancer mortality., Cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality., Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease mortality (combined)., Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality., Cancer; Lung/Respiratory- Lung cancer mortality., Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality., Non-cancer; Neurological/Behavioral- Brain cancer mortality., Cancer; External, other and unspecified causes of mortality.- External cause mortality; other and unknown causes of mortality., Non-cancer; Hepatic/Liver- Liver cancer mortality., Cancer; Renal/Kidney- Genitourinary disease mortality., Non-cancer; Thyroid- Allergic, endocrine, metabolic, and nutritional disease mortality (combined), Non-cancer; Immune/Hematological- Blood disorders mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	737525

Domain	Metric	Rating	Comments
	Metric 2A: Exposure Measurement	Medium	Exposure was not quantified in this study but was examined qualitatively. Variables included (i) ever vs. never-hourly workers' and (ii) years since hire x years employed (6 categories). The cross-classification of years since hire x duration employed provides a proxy indicator for accumulated exposure and adequate latency. The sample was also classified into 9 work area/job groupings with similar tasks and exposures. The authors described potential exposure patterns for BD, styrene (STY) and dimethyldithiocarbamate (DMDTC) for some work area/job groupings (discussion). Potentially high exposures: (i) production-polymerization = regular exposure to BD and styrene, some DMDTC; (ii) Production-coagulation = exposed to pall 3 chemicals; (iii) maintenance-field = variable with potentially high exposures in some workers; (iv) labor-production = not discussed specifically from other laborers; (v) labor-maintenance = high exposures to all 3 during cleaning; and (vi) laboratories = high exposures to all 3 chemicals depending on tasks. Potentially lower exposures: (i) production-finishing= lower BD exposure; (ii) maintenance-shop = potentially lower exposures; (iii) other operations (ex. warehouses) = lower exposures likely.

Domain 3: Outcome Assessment

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Study Citation: Delzell, E., Sathiakumar, N., Graff, J., Macaluso, M., Maldonado, G., Matthews, R., Health Effects Institute (2006). An updated study of mortality among North American synthetic rubber industry workers. Research Reports (Health Effects Institute) 62(132):1-63; discussion 65-74.

Health Outcome(s) Assessed: Immune/Hematological- All lymphopoietic cancer (LHC) mortality. LHC mortality subtypes analyzed: leukemia (lymphocytic, myelogenous, other), non-Hodgkin's lymphoma, Hodgkins's disease, multiple myeloma,, Cancer; Cancer/Carcinogenesis- All cancers mortality, all benign neoplasm mortality. Lymphopoietic cancer mortality (leukemia, Hodgkin's disease, non-Hodgkin's disease, multiple myeloma), buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, prostate cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, other cancer mortality., Cancer; Mortality- All lymphopoietic cancer (LHC) mortality. LHC mortality subtypes analyzed: leukemia (lymphocytic, myelogenous, other), non-Hodgkin's lymphoma, Hodgkins's disease, multiple myeloma mortality. Prostate cancer mortality. Buccal cavity and pharynx cancer mortality; esophageal cancer mortality; stomach cancer mortality; colorectal cancer mortality; pancreatic cancer mortality. Pancreatic cancer mortality. Bladder cancer mortality, kidney cancer mortality. Lung cancer mortality. Brain cancer mortality., Cancer; Mortality- Circulatory disease mortality. Digestive disease mortality. Allergic, endocrine, metabolic, and nutritional disease mortality (combined). Non-malignant respiratory disease mortality. External causes mortality. Other and unknown causes of mortality., Non-cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disorders mortality., Non-cancer; Cardiovascular- Circulatory disease mortality., Non-cancer; Reproductive/Developmental- Prostate cancer mortality., Cancer; Reproductive/Developmental- Genitourinary disease mortality., Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality; esophageal cancer mortality; stomach cancer mortality; colorectal cancer mortality; pancreatic cancer mortality., Cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality., Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease mortality (combined)., Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality., Cancer; Lung/Respiratory- Lung cancer mortality., Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality., Non-cancer; Neurological/Behavioral- Brain cancer mortality., Cancer; External, other and unspecified causes of mortality.- External cause mortality; other and unknown causes of mortality., Non-cancer; Hepatic/Liver- Liver cancer mortality., Cancer; Renal/Kidney- Genitourinary disease mortality., Non-cancer; Thyroid- Allergic, endocrine, metabolic, and nutritional disease mortality (combined), Non-cancer; Immune/Hematological- Blood disorders mortality, Non-cancer

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 737525

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Outcomes, defined by ICD codes, were obtained from linkages to death certificate data. Underlying contributing causes of death were coded by a nosologist in the US and provided by the Statistica Canada for the Ontario plant. Leukemia, an outcome of primary interest, was analyzed both overall and as subtypes (lymphocytic, myelogenous, and acute vs chronic subtypes for both.). Subtype information was not available for 18 of the 65 cases due to changes in coding systems. The mean of 33 years of follow-up likely allowed for sufficient latency to analyze cancer mortality. Ascertainment was high: 3% of the sample was lost to follow-up, and another small group was presumed alive (<1000 workers terminated after 1979 who were not traced, see original report). The sample of over 17,000 workers was large, and there were increases in case numbers with the extended follow-up (ex. 20 additional leukemia deaths for a total of 71, Table 2). Nonetheless, numbers of cases were small for some outcomes (ex. specific leukemia subtypes).
	Metric 3B:	Selective Reporting	High	The authors reported results in keeping with their stated aim to evaluate "the mortality experience of 17 964 North American synthetic rubber industry workers during the period 1944 through 1991." SMRs were presented overall, stratified by hourly vs salaried worker status, and stratified by employment duration and follow-up time, as well as by type of work. The authors noted in the introduction that a companion paper would describe associations between specific chemical exposures and lympho-haematopoietic cancers and other diseases.

Domain 4: Potential Confounding / Variability Control

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Study Citation:	Delzell, E., Sathiakumar, N., Graff, J., Macaluso, M., Maldonado, G., Matthews, R., Health Effects Institute (2006). An updated study of mortality among North American synthetic rubber industry workers. Research Reports (Health Effects Institute) 62(132):1-63; discussion 65-74.
Health Outcome(s) Assessed:	Immune/Hematological- All lymphopoietic cancer (LHC) mortality. LHC mortality subtypes analyzed: leukemia (lymphocytic, myelogenous, other), non-Hodgkin's lymphoma, Hodgkins's disease, multiple myeloma,, Cancer; Cancer/Carcinogenesis- All cancers mortality, all benign neoplasm mortality. Lymphopoietic cancer mortality (leukemia, Hodgkin's disease, non-Hodgkin's disease, multiple myeloma), buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, prostate cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, other cancer mortality., Cancer; Mortality- All lymphopoietic cancer (LHC) mortality. LHC mortality subtypes analyzed: leukemia (lymphocytic, myelogenous, other), non-Hodgkin's lymphoma, Hodgkins's disease, multiple myeloma mortality. Prostate cancer mortality. Buccal cavity and pharynx cancer mortality; esophageal cancer mortality; stomach cancer mortality; colorectal cancer mortality; pancreatic cancer mortality. Pancreatic cancer mortality. Bladder cancer mortality, kidney cancer mortality. Lung cancer mortality. Brain cancer mortality., Cancer; Mortality- Circulatory disease mortality. Digestive disease mortality. Allergic, endocrine, metabolic, and nutritional disease mortality (combined). Non-malignant respiratory disease mortality. External causes mortality. Other and unknown causes of mortality., Non-cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disorders mortality., Non-cancer; Cardiovascular- Circulatory disease mortality., Non-cancer; Reproductive/Developmental- Prostate cancer mortality., Cancer; Reproductive/Developmental- Genitourinary disease mortality., Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality; esophageal cancer mortality; stomach cancer mortality; colorectal cancer mortality; pancreatic cancer mortality., Cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality., Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease mortality (combined)., Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality., Cancer; Lung/Respiratory- Lung cancer mortality., Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality., Non-cancer; Neurological/Behavioral- Brain cancer mortality., Cancer; External, other and unspecified causes of mortality.- External cause mortality; other and unknown causes of mortality., Non-cancer; Hepatic/Liver- Liver cancer mortality., Cancer; Renal/Kidney- Genitourinary disease mortality., Non-cancer; Thyroid- Allergic, endocrine, metabolic, and nutritional disease mortality (combined), Non-cancer; Immune/Hematological- Blood disorders mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	737525

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Standardized Mortality Ratios (SMRs) were estimated using standard methods accounting for age, sex and calendar period using appropriate referent populations. The authors did not incorporate indirect adjustments for potential confounders such as smoking.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The authors used standard approaches to calculate SMRs, accounting for age, calendar year, race and place of residence. SMRs were presented showing both observed and expected cases and included 95% confidence intervals. The reference populations came from the areas where plants were located (Texas, Kentucky, Louisiana, Ontario).
	Metric 5B:	Sensitivity	Medium	The sample size was large (>17,000 workers) and included 4,659 deaths. Case numbers and ability to detect associations varied for specific cancers, with fewer cases - as expected - for rare outcomes such as specific leukemia subtypes.

Additional Comments: This paper analyzed the mortality experience of more than 17,000 workers at 8 synthetic rubber plants and included over 15,000 workers employed in styrene-butadiene rubber production. Follow-up was extended to 1998 vs 1992 in earlier publications. Associations between cause-specific mortality and 1,3 butadiene (BD) was not analyzed using quantitative estimates of exposure. SMRs calculated using mortality rates from the general population suggested an increase in leukemia mortality among these workers; these SMRs were statistically significant only in the subset of hourly workers employed for 10+ years with 20-29 years since hire. Analyses of leukemia subtypes did not indicate a clear pattern of association, but Ns were small.Quantitative dose-response analyses using estimated cumulative exposure to butadiene were not included in this manuscript (HEROID 737525).

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Study Citation:	Delzell, E., Sathiakumar, N., Graff, J., Macaluso, M., Maldonado, G., Matthews, R., Health Effects Institute (2006). An updated study of mortality among North American synthetic rubber industry workers. Research Reports (Health Effects Institute) 62(132):1-63; discussion 65-74.
Health Outcome(s) Assessed:	Immune/Hematological- All lymphopoietic cancer (LHC) mortality. LHC mortality subtypes analyzed: leukemia (lymphocytic, myelogenous, other), non-Hodgkin's lymphoma, Hodgkins's disease, multiple myeloma,, Cancer; Cancer/Carcinogenesis- All cancers mortality, all benign neoplasm mortality. Lymphopoietic cancer mortality (leukemia, Hodgkin's disease, non-Hodgkin's disease, multiple myeloma), buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, prostate cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, other cancer mortality., Cancer; Mortality- All lymphopoietic cancer (LHC) mortality. LHC mortality subtypes analyzed: leukemia (lymphocytic, myelogenous, other), non-Hodgkin's lymphoma, Hodgkins's disease, multiple myeloma mortality. Prostate cancer mortality. Buccal cavity and pharynx cancer mortality; esophageal cancer mortality; stomach cancer mortality; colorectal cancer mortality; pancreatic cancer mortality. Pancreatic cancer mortality. Bladder cancer mortality, kidney cancer mortality. Lung cancer mortality. Brain cancer mortality., Cancer; Mortality- Circulatory disease mortality. Digestive disease mortality. Allergic, endocrine, metabolic, and nutritional disease mortality (combined). Non-malignant respiratory disease mortality. External causes mortality. Other and unknown causes of mortality., Non-cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disorders mortality., Non-cancer; Cardiovascular- Circulatory disease mortality., Non-cancer; Reproductive/Developmental- Prostate cancer mortality., Cancer; Reproductive/Developmental- Genitourinary disease mortality., Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality; esophageal cancer mortality; stomach cancer mortality; colorectal cancer mortality; pancreatic cancer mortality., Cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality., Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease mortality (combined)., Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality., Cancer; Lung/Respiratory- Lung cancer mortality., Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality., Non-cancer; Neurological/Behavioral- Brain cancer mortality., Cancer; External, other and unspecified causes of mortality.- External cause mortality; other and unknown causes of mortality., Non-cancer; Hepatic/Liver- Liver cancer mortality., Cancer; Renal/Kidney- Genitourinary disease mortality., Non-cancer; Thyroid- Allergic, endocrine, metabolic, and nutritional disease mortality (combined), Non-cancer; Immune/Hematological- Blood disorders mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	737525

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation:	Delzell, E., Sathiakumar, N., Hovinga, M., Macaluso, M., Julian, J., Larson, R., Cole, P., Muir, F., D.C. (1996). A follow-up study of synthetic rubber workers. Toxicology 113(1-3):182-189.
Health Outcome(s) Assessed:	Immune/Hematological- -Cancer mortality: All lymphopoietic cancer mortality. Leukemia mortality; leukemia subtype mortality [myelogenous leukemia (acute, chronic, unspecified), lymphocytic leukemia (acute, chronic unspecified), and unspecified leukemia (acute, chronic, unspecified)]; lymphosarcoma mortality; other lymphatic tissue cancer mortality. -Cancer incidence: Lymphopoietic cancer incidence (subtypes: Non-Hodgkins lymphoma, leukemia, multiple myeloma)., Cancer; Immune/Hematological- Blood disease mortality., Non-cancer; Cancer/Carcinogenesis- All cancers mortality, all benign neoplasm mortality. Lymphopoietic cancer mortality (leukemia, lymphosarcoma, other), central nervous system cancer mortality; prostate cancer mortality, buccal cavity and pharynx cancer mortality, digestive organ cancer mortality, esophageal cancer mortality, stomach cancer mortality, large intestine cancer mortality, rectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, bladder cancer mortality, kidney cancer mortality, lung cancer mortality, skin cancer mortality., Cancer; Cancer/Carcinogenesis- All cancer incidence. Incidence of cancer types: buccal cavity and pharynx cancer incidence, digestive organ cancer incidence (esophageal, stomach, large intestine, rectum, pancreas), larynx cancer incidence, lung cancer incidence, pleural cancer incidence, melanoma incidence, prostate cancer incidence, bladder cancer incidence, kidney cancer incidence, central nervous system cancer incidence, lymphopoietic cancer incidence (non-hodgkins lymphoma, leukemia, multiple myeloma). Note: cancer incidence was analyzed for Plant 8 (Ontario) only., Cancer; Mortality- (i) All causes of death. (ii) Non cancer mortality: blood disease mortality; mental, psychoneurotic and personality disorder mortality; nervous system disease mortality; circulatory disease mortality; genitourinary disease mortality; allergic, endocrine, metabolic, and nutritional disease mortality; digestive disease mortality; respiratory disease mortality; external cause mortality; other and unknown causes of mortality., Non-cancer; Mortality- Cancer mortality: all cancer mortality; all lymphopoietic cancer and subtype mortality (leukemia, leukemia subtypes, lymphosarcoma, other); central nervous system cancer mortality; prostate cancer mortality; buccal cavity and pharynx cancer mortality; digestive organ cancer mortality; esophageal cancer mortality; stomach cancer mortality; large intestine cancer mortality; rectal cancer mortality; liver cancer mortality; pancreatic cancer mortality; bladder cancer mortality; kidney cancer mortality; lung cancer mortality; skin cancer mortality., Cancer; Neurological/Behavioral- Central nervous system cancer mortality (all plants); central nervous system cancer incidence (plant 8, Canada)., Cancer; Neurological/Behavioral- Mental, psychoneurotic and personality disorder mortality; nervous system disease mortality., Non-cancer; Cardiovascular- Circulatory disease mortality., Non-cancer; Reproductive/Developmental- Prostate cancer mortality. Prostate cancer incidence (plant 8, Canada only)., Cancer; Reproductive/Developmental- Genitourinary disease mortality., Non-cancer; Gastrointestinal- -Mortality from cancers: Cancer of the buccal cavity and pharynx mortality; all digestive organ cancer mortality; esophageal cancer mortality; stomach cancer mortality; large intestine cancer mortality; rectal cancer mortality; pancreatic cancer mortality. -Incidence of cancers: Cancer of the buccal cavity and pharynx incidence; all digestive organ cancer incidence; esophageal cancer incidence; stomach cancer incidence; large intestine cancer incidence; rectal cancer incidence; pancreatic cancer incidence; larynx cancer incidence (cancer incidence analyzed for Plant 8, Ontario only)., Cancer; Gastrointestinal- Allergic, endocrine, metabolic, and nutritional disease mortality (combined); digestive disease mortality., Non-cancer; Musculoskeletal- Lymphosarcoma mortality, Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease mortality (combined), Non-cancer; Renal/Kidney- Cancer mortality: Bladder cancer mortality, kidney cancer mortality. Cancer incidence: bladder cancer incidence, kidney cancer incidence (cancer incidence analyzed for Plant 8, Ontario only)., Cancer; Lung/Respiratory- Lung cancer mortality. Lung cancer incidence (Plant 8, Ontario only)., Cancer; Lung/Respiratory- Respiratory disease mortality., Non-cancer; Skin/Connective Tissue- Skin cancer mortality. Melanoma incidence (Plant 8, Ontario only)., Cancer; External, unspecified, unknown causes- External cause mortality; other and unknown causes of mortality., Non-cancer; Hepatic/Liver- Liver cancer mortality., Cancer; Renal/Kidney- Genitourinary disease mortality., Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	51390 Linked HERO ID(s): 51390, 5554378

Domain	Metric	Rating	Comments
Domain 1: Study Participation			

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Study Citation:	Delzell, E., Sathiakumar, N., Hovinga, M., Macaluso, M., Julian, J., Larson, R., Cole, P., Muir, F., D.C. (1996). A follow-up study of synthetic rubber workers. Toxicology 113(1-3):182-189.
Health Outcome(s) Assessed:	Immune/Hematological- -Cancer mortality: All lymphopoietic cancer mortality. Leukemia mortality; leukemia subtype mortality [myelogenous leukemia (acute, chronic, unspecified), lymphocytic leukemia (acute, chronic unspecified), and unspecified leukemia (acute, chronic, unspecified)]; lymphosarcoma mortality; other lymphatic tissue cancer mortality. -Cancer incidence: Lymphopoietic cancer incidence (subtypes: Non-Hodgkins lymphoma, leukemia, multiple myeloma)., Cancer; Immune/Hematological- Blood disease mortality., Non-cancer; Cancer/Carcinogenesis- All cancers mortality, all benign neoplasm mortality. Lymphopoietic cancer mortality (leukemia, lymphosarcoma, other), central nervous system cancer mortality; prostate cancer mortality, buccal cavity and pharynx cancer mortality, digestive organ cancer mortality, esophageal cancer mortality, stomach cancer mortality, large intestine cancer mortality, rectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, bladder cancer mortality, kidney cancer mortality, lung cancer mortality, skin cancer mortality., Cancer; Cancer/Carcinogenesis- All cancer incidence. Incidence of cancer types: buccal cavity and pharynx cancer incidence, digestive organ cancer incidence (esophageal, stomach, large intestine, rectum, pancreas), larynx cancer incidence, lung cancer incidence, pleural cancer incidence, melanoma incidence, prostate cancer incidence, bladder cancer incidence, kidney cancer incidence, central nervous system cancer incidence, lymphopoietic cancer incidence (non-hodgkins lymphoma, leukemia, multiple myeloma). Note: cancer incidence was analyzed for Plant 8 (Ontario) only., Cancer; Mortality- (i) All causes of death. (ii) Non cancer mortality: blood disease mortality; mental, psychoneurotic and personality disorder mortality; nervous system disease mortality; circulatory disease mortality; genitourinary disease mortality; allergic, endocrine, metabolic, and nutritional disease mortality; digestive disease mortality; respiratory disease mortality; external cause mortality; other and unknown causes of mortality., Non-cancer; Mortality- Cancer mortality: all cancer mortality; all lymphopoietic cancer and subtype mortality (leukemia, leukemia subtypes, lymphosarcoma, other); central nervous system cancer mortality; prostate cancer mortality; buccal cavity and pharynx cancer mortality; digestive organ cancer mortality; esophageal cancer mortality; stomach cancer mortality; large intestine cancer mortality; rectal cancer mortality; liver cancer mortality; pancreatic cancer mortality; bladder cancer mortality; kidney cancer mortality; lung cancer mortality; skin cancer mortality., Cancer; Neurological/Behavioral- Central nervous system cancer mortality (all plants); central nervous system cancer incidence (plant 8, Canada)., Cancer; Neurological/Behavioral- Mental, psychoneurotic and personality disorder mortality; nervous system disease mortality., Non-cancer; Cardiovascular- Circulatory disease mortality., Non-cancer; Reproductive/Developmental- Prostate cancer mortality. Prostate cancer incidence (plant 8, Canada only)., Cancer; Reproductive/Developmental- Genitourinary disease mortality., Non-cancer; Gastrointestinal- -Mortality from cancers: Cancer of the buccal cavity and pharynx mortality; all digestive organ cancer mortality; esophageal cancer mortality; stomach cancer mortality; large intestine cancer mortality; rectal cancer mortality; pancreatic cancer mortality. -Incidence of cancers: Cancer of the buccal cavity and pharynx incidence; all digestive organ cancer incidence; esophageal cancer incidence; stomach cancer incidence; large intestine cancer incidence; rectal cancer incidence; pancreatic cancer incidence; larynx cancer incidence (cancer incidence analyzed for Plant 8, Ontario only)., Cancer; Gastrointestinal- Allergic, endocrine, metabolic, and nutritional disease mortality (combined); digestive disease mortality., Non-cancer; Musculoskeletal- Lymphosarcoma mortality, Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease mortality (combined), Non-cancer; Renal/Kidney- Cancer mortality: Bladder cancer mortality, kidney cancer mortality. Cancer incidence: bladder cancer incidence, kidney cancer incidence (cancer incidence analyzed for Plant 8, Ontario only)., Cancer; Lung/Respiratory- Lung cancer mortality. Lung cancer incidence (Plant 8, Ontario only)., Cancer; Lung/Respiratory- Respiratory disease mortality., Non-cancer; Skin/Connective Tissue- Skin cancer mortality. Melanoma incidence (Plant 8, Ontario only)., Cancer; External, unspecified, unknown causes- External cause mortality; other and unknown causes of mortality., Non-cancer; Hepatic/Liver- Liver cancer mortality., Cancer; Renal/Kidney- Genitourinary disease mortality., Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	51390 Linked HERO ID(s): 51390, 5554378

Domain	Metric	Rating	Comments
	Metric 1A: Participant Selection	Medium	The study population in TSCA report HEROID 5554378 included 17,964 men employed for at least one year at any of 8 synthetic rubber plants (7 in the US, 1 in Canada) at varying times between 1943 and 1991. Key results focusing on lymphopoietic cancers were published in HEROID 51390 (Delzell et al., 1996) and HEROID 51490 (Macaluso et al, 1996). Most analyses focused on 15,649 workers involved in styrene-butadiene rubber (SBR) production with mortality follow-up through 1992. Attrition from the eligible sample involved in SBR production was reported to be low: 10,939 (70%) were living or presumed alive, 3976 (25%) were deceased; a total of 734 (5%) workers who were terminated before 1979 and without current vital status information were considered lost to follow-up (p. 40). Because the sample was limited to workers employed for ≥1 year, employment duration in the analysis sample was long: 44% were employed >= 10 years (median 7.8 years) (p. 52). The primary concern is risk of healthy worker selection bias due to restricting eligibility to men employed for at least one year. The

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	51390 Linked HERO ID(s): 51390, 5554378

Domain	Metric	Rating	Comments
Domain 2: Exposure Characterization			

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	51390 Linked HERO ID(s): 51390, 5554378

Domain	Metric	Rating	Comments
	Metric 2A: Exposure Measurement	Medium	As described in TSCA report HEROID 5554378 and Macaluso et al 1996 (51490), 1,3 butadiene (BD) exposure was estimated by developing a job exposure matrix (JEM). The JEM was developed for each plant and each calendar year, taking historical changes in processes, equipment, tasks, and work areas into account. Expert opinion informed by records, visits and interviews was used to estimate exposure intensity using factors such as job task processes and durations, equipment, work area layout, distance from sources, and modeled ventilation patterns. 8,281 work area/job task combinations were combined into 308 “work area groups” with similar processes and jobs, for which time weighted 8h average exposures were calculated. Job histories, described as complete for 97% of included workers, were linked to the JEM to calculate cumulative BD ppm-years. Several variables were used as BD exposure indicators. Quantitative estimates (HEROID 5554378, Macaluso 51490) were categorized as 5 levels of cumulative BD ppm-years (0, <1, 1-19, 20-79, and 80+) for within-cohort analyses. Several analyses

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	51390 Linked HERO ID(s): 51390, 5554378

Domain	Metric	Rating	Comments
Domain 3: Outcome Assessment			

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	51390 Linked HERO ID(s): 51390, 5554378

Domain	Metric	Rating	Comments
	Metric 3A: Outcome Ascertainment	Medium	Outcome data came from sources likely to be valid, though they were not independently validated. Mortality data for HEROID 5554378 and related publications were obtained from the National Death Index, the Social Security death master file, the division of motor vehicles of three states, and the Canadian Mortality Data Base maintained by Statistics Canada. Causes were coded as or converted to ICD-8 values. Vital status was stated as ascertained for 95% of the SBR-exposed cohort, with 734 lost to follow-up. In addition, for the Canadian plant, cancer incidence data for the 1965-1992 period were obtained from the Ontario Cancer Registry; analyses of these data were limited to persons actively employed in 1965 or later. The number and nature of cancers diagnosed from 1943-1965 is uncertain. There was no evidence of bias due to incomplete or differential ascertainment of outcomes related to exposure. The mean of 25 years of follow-up likely allowed for sufficient latency to analyze cancer outcomes. The sample of over 15,000 workers was large. There were 3,853 deaths from known causes in the SBR-exposed group, including ~950 cancer deaths and 304 incident cancers. However

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	51390 Linked HERO ID(s): 51390, 5554378

Domain	Metric	Rating	Comments
	Metric 3B: Selective Reporting	High	Results were presented for analyses described as aims. The TSCA report (HEROID 5554378) included 71 tables with detailed results that included observed Ns for each cancer. Stratified and subgroup analyses highlighted results of particular interest, such as SMRs for employees with 10+ years worked and 20+ years since hire. Based on previous studies indicating a relationship between BD and leukemia, as well as BD and lymphosarcoma, these outcomes were of primary interest; cause-specific analyses focused on these outcomes.

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	51390 Linked HERO ID(s): 51390, 5554378

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	51390 Linked HERO ID(s): 51390, 5554378

Domain	Metric	Rating	Comments
	Metric 4A: Potential Confounding	Medium	Standardized mortality ratio (SMR) calculations accounted for age, race, calendar period and place of residence. Poisson models used for within-cohort analyses in HEROID 5554378 adjusted for age, race, years since hire, and calendar period; SBR plant was not a confounder and was excluded. Within-cohort analyses in Macaluso et al. 1996 adjusted within-cohort relative risks for age, race, and estimated styrene exposure. SES confounding was partly addressed by stratifying on ever vs never hourly work in some analyses. One concern is that styrene and BD were highly correlated. Analyses of outcomes of primary interest included adjustments for styrene as a potential confounder, or by presenting results stratified by both BD and styrene exposure levels. The authors justified not examining potential confounding by other co-exposures (e.g., toluene, hexane) as these were not established causes of lymphopoietic cancers, the outcomes of primary interest; confounding by these or other exposures including from other employment cannot be ascertained. An additional concern is that the authors were unable to address confounding by smoking as data were not available.

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	51390 Linked HERO ID(s): 51390, 5554378

Domain	Metric	Rating	Comments
Domain 5: Analysis			

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Chemical:	1,3-Butadiene- Parent compound
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Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Analysis methods were appropriate. SMRs with 95% confidence intervals were calculated using the US National and/or Ontario general population mortality rates. Tables included the numbers of observed cases. To assess dose response and potential confounding, SMRs of primary interest were stratified by quantitative and qualitative indicators of BD exposure, as well as by variables such as employment duration, years since hire, year of hire, hourly worker status, and race. For within-cohort analyses, Poisson regression, appropriate for these data, was used to fit multivariate models adjusting for confounders. Results of within-cohort analyses were presented as adjusted relative risks (RRs) for increasing categories of BD ppm-years with p-values; some but not all RRs included 95% confidence intervals. Several sensitivity analyses were included in HEROID 5554378. Varying exposure lags were also compared to address latency. The authors also examined alternative structural form specifications (e.g., polynomial transformations) to identify the best model fit, and evaluated potential interactions. Exposure group categories were selected to distribute leukemia cases adequately; results using alterna

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	51390 Linked HERO ID(s): 51390, 5554378

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	The sample size (>15,000 SBR workers) was large, and 3,976 deaths occurred during the 386,712 person-years of follow-up. However, numbers were small for the specific, rare cancers of primary interest such as leukemia (N ~ 48 in most analyses). Statistical power was limited for these outcomes, particularly for stratified analyses, or analyses of cancer subtypes.

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	51390 Linked HERO ID(s): 51390, 5554378

Domain	Metric	Rating	Comments
Additional Comments:	In this cohort of more than 15,000 styrene-butadiene rubber workers from up to 8 plants, overall mortality compared to the general population was low [SMR (95% CI) = 87 (85-90) for all-cause mortality and SMR = 93 (87-99) for cancer mortality). The TSCA report (HERO ID 5554378) and Macaluso et al. 1996 (51490) included within-cohort analyses in which relative risks for leukemia were calculated using quantitative estimates of cumulative BD exposure. Relative risks of leukemia were significantly elevated among workers with >80 ppm-years of estimated BD exposure, across all 3 categories of estimated styrene exposure. The report and Delzell et al. 1996 (51390) found that BD exposure was significantly associated with leukemia mortality among hourly workers, especially those employed for 10+ years with 20+ years since hire. Leukemia mortality was especially elevated in three work process groups thought to have relatively high BD exposure (polymerization, maintenance labor, laboratories), but was also significantly elevated in coagulation workers thought to have moderate styrene and low BD exposure. Healthy worker bias is an important concern as the sample was limited to workers employed for at least one year; the US plants had a high turnover rate for short-term employees. A large proportion of workers were also excluded from the Ontario plant as it was uncertain whether they had been employed in styrene-butadiene production. A second major concern is the lack of validation of any type for estimated BD exposure. The authors did not present any comparisons of calculated BD to objective measures. The extent of error and misclassification cannot be ascertained. Potential confounding by smoking, as well as by co-exposure to styrene (measures also unvalidated) are		

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Study Citation:	Delzell, E., Sathiakumar, N., Hovinga, M., Macaluso, M., Julian, J., Larson, R., Cole, P., Muir, F., D.C. (1996). A follow-up study of synthetic rubber workers. Toxicology 113(1-3):182-189.
Health Outcome(s) Assessed:	Immune/Hematological- -Cancer mortality: All lymphopoietic cancer mortality. Leukemia mortality; leukemia subtype mortality [myelogenous leukemia (acute, chronic, unspecified), lymphocytic leukemia (acute, chronic unspecified), and unspecified leukemia (acute, chronic, unspecified)]; lymphosarcoma mortality; other lymphatic tissue cancer mortality. -Cancer incidence: Lymphopoietic cancer incidence (subtypes: Non-Hodgkins lymphoma, leukemia, multiple myeloma)., Cancer; Immune/Hematological- Blood disease mortality., Non-cancer; Cancer/Carcinogenesis- All cancers mortality, all benign neoplasm mortality. Lymphopoietic cancer mortality (leukemia, lymphosarcoma, other), central nervous system cancer mortality; prostate cancer mortality, buccal cavity and pharynx cancer mortality, digestive organ cancer mortality, esophageal cancer mortality, stomach cancer mortality, large intestine cancer mortality, rectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, bladder cancer mortality, kidney cancer mortality, lung cancer mortality, skin cancer mortality., Cancer; Cancer/Carcinogenesis- All cancer incidence. Incidence of cancer types: buccal cavity and pharynx cancer incidence, digestive organ cancer incidence (esophageal, stomach, large intestine, rectum, pancreas), larynx cancer incidence, lung cancer incidence, pleural cancer incidence, melanoma incidence, prostate cancer incidence, bladder cancer incidence, kidney cancer incidence, central nervous system cancer incidence, lymphopoietic cancer incidence (non-hodgkins lymphoma, leukemia, multiple myeloma). Note: cancer incidence was analyzed for Plant 8 (Ontario) only., Cancer; Mortality- (i) All causes of death. (ii) Non cancer mortality: blood disease mortality; mental, psychoneurotic and personality disorder mortality; nervous system disease mortality; circulatory disease mortality; genitourinary disease mortality; allergic, endocrine, metabolic, and nutritional disease mortality; digestive disease mortality; respiratory disease mortality; external cause mortality; other and unknown causes of mortality., Non-cancer; Mortality- Cancer mortality: all cancer mortality; all lymphopoietic cancer and subtype mortality (leukemia, leukemia subtypes, lymphosarcoma, other); central nervous system cancer mortality; prostate cancer mortality; buccal cavity and pharynx cancer mortality; digestive organ cancer mortality; esophageal cancer mortality; stomach cancer mortality; large intestine cancer mortality; rectal cancer mortality; liver cancer mortality; pancreatic cancer mortality; bladder cancer mortality; kidney cancer mortality; lung cancer mortality; skin cancer mortality., Cancer; Neurological/Behavioral- Central nervous system cancer mortality (all plants); central nervous system cancer incidence (plant 8, Canada)., Cancer; Neurological/Behavioral- Mental, psychoneurotic and personality disorder mortality; nervous system disease mortality., Non-cancer; Cardiovascular- Circulatory disease mortality., Non-cancer; Reproductive/Developmental- Prostate cancer mortality. Prostate cancer incidence (plant 8, Canada only)., Cancer; Reproductive/Developmental- Genitourinary disease mortality., Non-cancer; Gastrointestinal- -Mortality from cancers: Cancer of the buccal cavity and pharynx mortality; all digestive organ cancer mortality; esophageal cancer mortality; stomach cancer mortality; large intestine cancer mortality; rectal cancer mortality; pancreatic cancer mortality. -Incidence of cancers: Cancer of the buccal cavity and pharynx incidence; all digestive organ cancer incidence; esophageal cancer incidence; stomach cancer incidence; large intestine cancer incidence; rectal cancer incidence; pancreatic cancer incidence; larynx cancer incidence (cancer incidence analyzed for Plant 8, Ontario only)., Cancer; Gastrointestinal- Allergic, endocrine, metabolic, and nutritional disease mortality (combined); digestive disease mortality., Non-cancer; Musculoskeletal- Lymphosarcoma mortality, Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease mortality (combined), Non-cancer; Renal/Kidney- Cancer mortality: Bladder cancer mortality, kidney cancer mortality. Cancer incidence: bladder cancer incidence, kidney cancer incidence (cancer incidence analyzed for Plant 8, Ontario only)., Cancer; Lung/Respiratory- Lung cancer mortality. Lung cancer incidence (Plant 8, Ontario only)., Cancer; Lung/Respiratory- Respiratory disease mortality., Non-cancer; Skin/Connective Tissue- Skin cancer mortality. Melanoma incidence (Plant 8, Ontario only)., Cancer; External, unspecified, unknown causes- External cause mortality; other and unknown causes of mortality., Non-cancer; Hepatic/Liver- Liver cancer mortality., Cancer; Renal/Kidney- Genitourinary disease mortality., Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	51390 Linked HERO ID(s): 51390, 5554378

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation:	Ehrenstein, von, O. S., Aralis, H., Cockburn, M., Ritz, B. (2014). In utero exposure to toxic air pollutants and risk of childhood autism. Epidemiology 25(6):851-858.
Health Outcome(s) Assessed:	Neurological/Behavioral- Autistic disorder, Non-cancer; Reproductive/Developmental- Autistic disorder, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	2453135

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	The authors examined risks for autistic disorder and impaired expressive language autistic disorder phenotypes in children in relation to in utero exposure to monitored ambient air toxics from urban emissions. The cohort consisted of children born in Los Angeles County, California between 1995 and 2006 to mothers who resided within in a 5km buffer around air-toxics monitoring stations during pregnancy (n=148,722). Children were assessed for the outcome between 1998 and 2009. At the time of outcome ascertainment the children were 36 to 71 months old.Of the 1,746,754 children who were born in Los Angeles County during the study period, the authors successfully geocoded birth addresses for 1,522,267 (87%). The authors do not report how many uncoded birth addresses were within versus outside the 5km buffer zone nor how many children with the outcomes of interest had uncoded addresses. Similarly, the authors excluded 1,436 records with missing or implausible gestational ages (< 21 weeks or > 46 weeks) or birth weights (< 500 g or > 6,800 g), and 492 deaths before age 6 years, but did not provide information on exposure or cases status for these children. Finally, children were excluded if they lack 50% of possible exposure measurements for each pregnancy month and the last 30 days of pregnancy. Again, it is not clear how many children with missing exposure data had the outcomes of interest. The missing information on children who were excluded leaves open the possibility of selection bias, although there is no direct evidence that such bias is present.
Domain 2: Exposure Characterization			

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Study Citation:	Ehrenstein, von, O. S., Aralis, H., Cockburn, M., Ritz, B. (2014). In utero exposure to toxic air pollutants and risk of childhood autism. Epidemiology 25(6):851-858.
Health Outcome(s) Assessed:	Neurological/Behavioral- Autistic disorder, Non-cancer; Reproductive/Developmental- Autistic disorder, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	2453135

Domain	Metric	Rating	Comments
	Metric 2A: Exposure Measurement	Medium	The authors initially evaluated data on 35 air toxics available from the California Air Resources Board that were previously associated with neurodevelopmental or neurotoxic effects. The authors ultimately only evaluated 24 of the 35 air toxics due to missing data. The chemicals evaluated included aromatic solvents, chlorinated solvents, volatile organics, total polycyclic aromatic hydrocarbons, and several metals. 1,3 - butadiene was one of the volatile organic compounds that was retained for analysis. Geocoded birth addresses were linked to air toxics data from the California Air Resources Board. The methods that the Board uses to measure ambient air toxics at 4 monitoring stations in Los Angeles County are reported in detail on their website. The stations collect 24-hour integrated samples every 12 days at each monitoring site. Children were assigned pollutant exposure values based upon the measurements at the nearest monitor. All geocoded addresses within <5km (~3.1 miles) of a monitoring station in the Los Angeles Basin were included. The exclusion based on distance of 5km or greater was selected to balance exposure misclassification against sample size limitations as distance from a station increased. In sensitivity analyses, the buffer size was restricted to <3.5km (~2.2miles). Exposure measures were created for the entire in utero period and for the first (first day of the last menstrual period to day 92), second (days 93–185) and third (day 186 to birth) trimesters, based on birth dates and gestational ages. Monthly average exposures for each chemical were calculated for each month of pregnancy, then monthly averages were used to calculate averages across each trimester. Children were excluded from the exposure assessment if fewer than 50% of possible readings for each pregnancy month and the last 30 days of pregnancy were missing, One weakness of this study is that it lacks personal exposure measurements for mothers and biomarkers of exposure at birth for children, which leaves open the possibility of some degree of exposure misclassification.

Domain 3: Outcome Assessment

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Study Citation:	Ehrenstein, von, O. S., Aralis, H., Cockburn, M., Ritz, B. (2014). In utero exposure to toxic air pollutants and risk of childhood autism. Epidemiology 25(6):851-858.
Health Outcome(s) Assessed:	Neurological/Behavioral- Autistic disorder, Non-cancer; Reproductive/Developmental- Autistic disorder, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	2453135

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Children with autistic disorder were identified through records maintained by the California Department of Developmental Services, which contracts with seven regional centers in Los Angeles County. The authors report that services at these centers are available to children regardless of citizenship or financial status, which means services are available to all families that seek them. Cases were defined by a primary diagnosis of autistic disorder, the most severe form among autism spectrum disorders. Cases (n=768) were ascertained between 1998 and 2009, when the children were between the ages of 36–71 months old. By those ages, the majority of autistic disorder cases would be clinically apparent, making outcome misclassification due to age unlikely for the most severe form of the disorder. The diagnosis of autism disorder was based on criteria in the Diagnostic and Statistical Manual of Mental Disorders (code 299.00). The diagnostic code was reported on a Client Development Evaluation Report used by service centers throughout the study period. The authors cite a validation study established the reliability and validity of the Client Development Evaluation Report in California. The authors also cite a paper their efforts to link 10,821 Department of Developmental Services autistic disorder records to birth records in Los Angeles County based on child identifiers, which resulted in 8,600 successfully linked records (80% of all cases).They report that they excluded 41 children whose mothers did not reside in Los Angeles County during pregnancy, 508 children with missing or implausible gestational ages or birth weights, 448 children who did not have a primary diagnosis of autistic disorder, and 768 children whose mothers did not reside in the 5km buffer around air monitoring stations at the time of birth. When the same exclusions were applied to the 3.5km buffer zone, the 380 cases and 69,415 non-cases were identified. The authors also assessed a secondary outcome related to phenotypic severity among 5-year-old children (n=419). The phenotype of ”impaired” expressive language was defined as ”child does not use words, uses simple words only, or uses two-word sentences”. The phenotype of ”less impaired” expressive language was defined as ”child uses sentences of 3 words or more, or can engage at least in basic conversation”. The authors did not account for intelligence quotient because this information was not universally available. The case ascertainment approach in this study has several strengths, including a definition that is limited to severe cases, an established clinical case definition, and validated methods for case diagnosis. However, the authors’ inability to link 20% of cases from service center records to birth records raises concern about primary outcome misclassification. Other less concerning potential causes of outcome misclassification include exclusion of children with missing and implausible gestational ages or birth weights, children with a secondary diagnosis of autistic disorder, and children who died prior to the age of 6. Finally, it is possible that children with autistic disorder were misclassified as not having the condition because their parents did not seek care or because they were diagnosed outside the service centers that took part in the study.
	Metric 3B:	Selective Reporting	Medium	The authors provide results for primary and secondary analyses described in the methods section, and they provide justification for secondary analyses and sensitivity analyses. Results are reported as effect estimates and 95% confidence intervals.

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Study Citation:	Ehrenstein, von, O. S., Aralis, H., Cockburn, M., Ritz, B. (2014). In utero exposure to toxic air pollutants and risk of childhood autism. Epidemiology 25(6):851-858.
Health Outcome(s) Assessed:	Neurological/Behavioral- Autistic disorder, Non-cancer; Reproductive/Developmental- Autistic disorder, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	2453135

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Medium	The authors provide information on the characteristics of cases and non-cases, and they provide justification for selection of confounders and for sensitivity analyses. All models were adjusted for birth year. Other models were further adjusted for potential confounders selected a priori, including maternal age, race/ethnicity, place of birth (US vs. non-US), education, parity, type of insurance, and offspring sex. The authors also considered paternal age and education, pregnancy complications, birth weight, and type of birth (caesarean/vaginal), but these were not ultimately included because they did not change the estimates of interest by more than 5%. Chemicals with the strongest associations with the outcome were included in two- and three-pollutant models; 1,3-butadiene models were additionally adjusted for formaldehyde, meta/para-xylene, and both meta/para-xylene and lead.
Domain 5: Analysis			
	Metric 5A: Analysis	Medium	The authors provide plots that display trends in exposure measurements overtime and by station. They also provide a correlation matrix with Pearson's correlation coefficients that demonstrates the level of collinearity between exposure measures, and they also used factor analysis with varimax rotation to further examine the correlation structure of exposures further. Information is provided to demonstrate the relationship between potential cofounders, exposures, and outcomes. Models were adjusted for potential confounders, and sensitivity analyses were also conducted (stratification by sex, by expressive language abilities (restricted to 5-year-olds), and by regional center catchment area, as well as restricted to term births). The authors analyzed the associations between air toxicant exposures in utero and autistic disorder and expressive language impairments between age 3 and 6 using unconditional logistic regression and provide odds ratios (ORs) per IQR increase in pregnancy exposures for each toxic. The authors also conducted and reported on adjusted 2- and 3-pollutant models. The models included pollutants having the strongest associations with autistic disorder and that "loaded either on the same or on different factors or did not load on any factor".
	Metric 5B: Sensitivity	Medium	The duration and range of exposure levels of exposure in the study population was sufficient to examine the hypothesis. The exposures were measured during the entire in utero period. The analysis accounted for lag time between exposure in utero and the development of clinically apparent autistic disorder later in childhood (3 to 6 years). The sample size was large (n = 148,722) with 768 cases of autistic disorder.

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Study Citation:	Ehrenstein, von, O. S., Aralis, H., Cockburn, M., Ritz, B. (2014). In utero exposure to toxic air pollutants and risk of childhood autism. Epidemiology 25(6):851-858.
Health Outcome(s) Assessed:	Neurological/Behavioral- Autistic disorder, Non-cancer; Reproductive/Developmental- Autistic disorder, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	2453135

Domain	Metric	Rating	Comments
Additional Comments:	The authors examined risks for autistic disorder in children in relation to in utero exposure to monitored ambient air toxics (including 1,3-butadiene) from urban emissions. The study used adequate exposure assessment, outcome assessment, and analysis methods. Concerns include the limited information provided on some aspects of participant selection procedures and the potential for residual confounding due to co-exposure to other ambient air toxics. In single pollutant models, 1,3-butadiene was positively associated with autistic disorder (participants within 5km of an air monitor: OR = 1.59 (1.18, 2.15), participants within 3.5km of an air monitor: OR = 1.70 (1.12, 2.57)). Results were attenuated to non-significance in 2- and 3-pollutant models.		

Overall Quality Determination Medium

Study Citation:	Ehrenstein, Von, O. S., Heck, J. E., Park, A. S., Cockburn, M., Escobedo, L., Ritz, B. (2016). In utero and early-life exposure to ambient air toxics and childhood brain tumors: a population-based case-control study in California, USA. Environmental Health Perspectives 124(7):1093-1099.
Health Outcome(s) Assessed:	Neurological/Behavioral- primitive neuroectodermal tumor (PNET), medulloblastoma, astrocytoma, Cancer; Cancer/Carcinogenesis- primitive neuroectodermal tumor (PNET), medulloblastoma, astrocytoma, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5684085

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Cases of childhood brain cancer, including cases of primitive neuroectodermal tumor (PNET), medulloblastoma, astrocytoma, in this case-control study were selected from the California Cancer Registry. Cases were selected before age 6 and diagnosed in 1990-2007. Cases were then matched to California birth certificates from the California Department of Public Health's Office of Vital Records using first and last names as well as birth dates; matching was successful in 89% of cases. Controls without a cancer diagnosis before age 6 were randomly selected from California birth rolls and frequency matched to all childhood cancer cases during the same period at a ratio of 20 controls per case. Subjects were excluded if they had a missing gestational age from birth certificates (n=74 cases and n=12,035 controls), if they did not have at least one air toxics reading for each full month of pregnancy and within the last 30 days of pregnancy, if they did not live within <5 miles from a California Air Resources Board monitor, or if their gestational ages or birth weights were considered non-viable (viable gestational ages were considered to be 146-323 days, viable birth weights were considered to be 500-6,800 g). 719 controls were also excluded due do ying before 6 years of age after matching to California death records. The final sample size included n=183 cases and n=30,569 controls. There is no direct evidence of selection bias as the study attempted to draw cases and controls from the same eligible population, and none of the selection criteria are expected to disproportionately affected by exposure or outcome.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Low	Exposure to 1,3-butadience was assessed based on participants geocoded residential addresses listed on birth certificates. From 1990 to 1997, only a ZIP code was listed on the birth certificate, and the ZIP code centroid were used for exposure measurement. 1,3-butadiene exposure was measured via air toxics monitors set up by the California Air Resources Board, which collects 24-hour integrated samples of ambient air concentrations every 12 days (n=31 monitors) at locations expected to representative of the area. The distance from each monitor to geocoded addresses was calculated and addresses more than 5 miles away from the nearest monitor were excluded as exposure estimates may be less accurate at greater distances. Exposure was characterized as averages for each trimester, the entire pregnancy period, and the first year of life to ensure temporality. The exposure assessment methodology is likely reliable given the use of public data, but the potential discrepancy between listed address on birth certificate and actual residence is also a limitation. The study estimated that up to 9% to 30% of families may move during pregnancy, thus there are concerns over non-differential misclassification bias.
Domain 3: Outcome Assessment				

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Study Citation:	Ehrenstein, Von, O. S., Heck, J. E., Park, A. S., Cockburn, M., Escobedo, L., Ritz, B. (2016). In utero and early-life exposure to ambient air toxics and childhood brain tumors: a population-based case-control study in California, USA. Environmental Health Perspectives 124(7):1093-1099.
Health Outcome(s) Assessed:	Neurological/Behavioral- primitive neuroectodermal tumor (PNET), medulloblastoma, astrocytoma, Cancer; Cancer/Carcinogenesis- primitive neuroectodermal tumor (PNET), medulloblastoma, astrocytoma, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5684085

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The International Classification of Disease Oncology (ICD-O) codes were used to characterize PNET (ICD-O code 9473) and medulloblastoma (ICD-O code 9470), while the International Classification of Childhood Cancer was used to characterize astrocytoma (ICC-3 code 032). Cases were pulled from the California Cancer Registry. Controls were stated to be "without a cancer diagnosis", which may have been checked via linkage of birth certificates with the California Cancer Registry, although this is not explicitly stated by the paper. However, there is no evidence of outcome misclassification.
	Metric 3B:	Selective Reporting	Medium	The results on all analyses outlined in the Methods section were reported in the results.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Potential confounders were selected based on previous knowledge and previous examination of demographic and perinatal factors related to cancer status in the data. Included covariates were birth year (matching variable), maternal age and education, race/ethnicity, and place of birth (United States vs. non-United States). Other variables that were also considered but not included in the final models were types of insurance (socio-economic status measure), rural/urban residence, parity, offspring sex, preterm birth. No information was included on the collection of covariate data, for example, whether the information was self-reported by parents or collected through public records. Exposure to other air toxics was also measured, and correlations across pollutants were presented. No adjustment was made for c-pollutants.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Logistic regression was used to estimate odds ratios per interquartile-range increase in pregnancy exposures during each trimester, the entire pregnancy, and the first 12 months of life for each outcome. Descriptive information is provided regarding exposure levels, specifically the IQR increase of 1,3-butadiene is specified to be 0.257 ppbV. Numbers of cases/controls are presented for each analysis. Effect estimates are presented with 95% confidence intervals. Sensitivity analyses were performed adding additional potential confounders and restricted to participants with term birth.
	Metric 5B:	Sensitivity	Medium	The sample size was like adequately large (n of cases = 183, and n of controls = 30,569), especially given the rarity of childhood brain cancer. The smallest number of cases was for medulloblastoma (n=34), but this size is still likely large enough to detect an effect. The IQR of 0.257 ppbV is likely wide enough to provide sufficient exposure contrast.

Additional Comments: This case-control study on the association between 1,3-butadiene and childhood brain cancer had an adequate sample size based on public records from 1990-2007, which was a strength due to the rarity of outcome. There is minimal concern over selection bias. The main limitation of the study is the exposure measurement based on air monitor readings. There is concern over misclassification bias due to discrepancy between registered and actual residential address, even though the bias is non-differential between cases and controls. However, significant positive associations were reported for exposure to 1,3-butadiene and the odds of developing primitive neuroectodermal tumors in children by six years of age.

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Study Citation:	Ehrenstein, Von, O. S., Heck, J. E., Park, A. S., Cockburn, M., Escobedo, L., Ritz, B. (2016). In utero and early-life exposure to ambient air toxics and childhood brain tumors: a population-based case-control study in California, USA. Environmental Health Perspectives 124(7):1093-1099.
Health Outcome(s) Assessed:	Neurological/Behavioral- primitive neuroectodermal tumor (PNET), medulloblastoma, astrocytoma, Cancer; Cancer/Carcinogenesis- primitive neuroectodermal tumor (PNET), medulloblastoma, astrocytoma, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5684085

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation:	Graff, J. J., Sathiakumar, N., Macaluso, M., Maldonado, G., Matthews, R., Delzell, E. (2009). The Effect of Uncertainty in Exposure Estimation on the Exposure-Response Relation between 1,3-Butadiene and Leukemia. International Journal of Environmental Research and Public Health 6(9):2436-2455.
Health Outcome(s) Assessed:	Mortality- Leukemia mortality, Cancer; Immune/Hematological- Leukemia mortality, Cancer; Cancer/Carcinogenesis- Leukemia mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	2950774

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This paper used data from a retrospective cohort of North American butadiene-styrene rubber workers to analyze the association between 1,3 butadiene (BD) exposure and leukemia, taking the uncertainty of exposure estimation into account. The cohort is described here as including 500,174 person years and 81 decedents with leukemia. Elsewhere (e.g. see TSCA report HEROID 5554378 and the main analysis of these data reported Graff et al 2005 HEROID 737523), the cohort has been characterized as including over 16,500 adult men employed for at least one year in any of 8 facilities between 1943 and 1991. One primary concern is risk of healthy worker selection bias due to restricting eligibility to men employed for at least one year. However, there is no direct evidence of bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Exposure estimation was detailed elsewhere (Macaluso et al, 2004 HEROID 646914). Briefly, a job exposure matrix (JEM) was developed for different job tasks and time periods based on expert opinion, using plant records, facility visits, and interviews. The JEM was used to estimate cumulative BD exposure based on worker job histories. To address uncertainty, for each calendar period, each work area and job task within each calendar period was assigned a distribution of exposure estimates with lower and upper bounds. These estimates had a wide (e.g., 8h time-weighted exposure for tank farm operators had estimates ranging from 2 to 113 ppm). Industrial hygiene data were described as sparse, limiting the ability to validate exposure estimates. However, exposure measurements collected in select areas at one or two of the facilities in the 1970s and 1980s were shown to overlap with estimated exposure distributions. Nonetheless, an important limitation is that the validity of using a mean or midpoint to reflect exposure for each job task was uncertain. This paper addressed this uncertainty by estimating a distribution of 1,000 sets of potential exposure values by randomly selecting a percentile from their possible range of exposure based on each worker's area/job group and year. The 1000 JEMs were then used to estimate 1000 datasets with varied exposure values for each worker. Within each dataset, exposure was categorized into four categories of approximate quartiles (>0–<33.7, 33.7–<184.7, 184.7–<425.0, and 425.0+ ppm-years), compared to none. The distribution of RRs resulting from analyzing the 1000 datasets was then evaluated.
Domain 3: Outcome Assessment				

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Study Citation:	Graff, J. J., Sathiakumar, N., Macaluso, M., Maldonado, G., Matthews, R., Delzell, E. (2009). The Effect of Uncertainty in Exposure Estimation on the Exposure-Response Relation between 1,3-Butadiene and Leukemia. International Journal of Environmental Research and Public Health 6(9):2436-2455.
Health Outcome(s) Assessed:	Mortality- Leukemia mortality, Cancer; Immune/Hematological- Leukemia mortality, Cancer; Cancer/Carcinogenesis- Leukemia mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	2950774

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Vital status was ascertained by linkage to the US National Death Index (NDI), the Social Security death master file, the division of motor vehicles of three states, and the Canadian Mortality Data Base maintained by Statistics Canada. The authors stated that death certificate information was sought for individuals who died before 1979, the NDI start date (no further details; no evidence that cases were missed). The authors attempted to obtain medical records for all subjects whose death certificate mentioned leukemia; this analysis was limited to subjects whose medical records confirmed a leukemia diagnosis and subjects whose death certificate indicated leukemia was an underlying or contributing cause of death. Use of ICD codes was mentioned in the main analysis, along with follow-up through 1998 (Graff et al. 2005, HEROID 737523), which likely allowed for sufficient latency to analyze cancer outcomes.
	Metric 3B:	Selective Reporting	Medium	Results were presented for analyses described as aims.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	Models were adjusted for the same variables as in the main analysis, age, years since hire, and estimated occupational co-exposure to other agents (styrene and dimethyldithiocarbamate (DMDTC). Residual confounding by other variables such as smoking, typically not available in retrospective occupational cohorts, cannot be ruled out.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Analysis methods were appropriate. Poisson regression was used to estimate the association between increasing categories of cumulative exposure to butadiene and leukemia, adjusting for confounding (details in the main analysis paper). Confidence intervals were reported for the primary RRs from the main analysis (Graff et al. 2005, HEROID 737523). In this paper, the distribution of relative rates for each BD cumulative exposure category derived from the multiple uncertainty datasets was reported, along with the proportion of results that suggested a non-monotonic dose-response relationship.
	Metric 5B:	Sensitivity	Medium	The sample size (>16,000 workers) was large. Cumulative BD exposure categories ranged from none to ≥425 ppm-years. The cohort included 81 leukemia deaths. Although the number of cases was not large, there was no evidence of inadequate sensitivity.

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Study Citation:	Graff, J. J., Sathiakumar, N., Macaluso, M., Maldonado, G., Matthews, R., Delzell, E. (2009). The Effect of Uncertainty in Exposure Estimation on the Exposure-Response Relation between 1,3-Butadiene and Leukemia. International Journal of Environmental Research and Public Health 6(9):2436-2455.
Health Outcome(s) Assessed:	Mortality- Leukemia mortality, Cancer; Immune/Hematological- Leukemia mortality, Cancer; Cancer/Carcinogenesis- Leukemia mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	2950774

Domain	Metric	Rating	Comments
Additional Comments:	This study analyzed the association between butadiene exposure and leukemia mortality in a cohort of more than 16,000 male styrene-butadiene rubber workers employed for at least one year between 1943 and 1991 at 8 North American facilities. There were 81 leukemia cases identified in follow-up through 1998. This study was a complementary analysis to Graff et al., 2005 HEROID 737523 (the main results paper). The focus of this paper was to evaluate the potential impact on allowing for uncertainty in the estimated exposure, by analyzing the relative risks obtained in 1,000 alternative datasets of exposure estimates. The distribution of relative risks obtained in datasets were compared to those in the main analysis that analyzed a single primary exposure estimate, using the same exposure quartiles vs. a referent unexposed group: 1 (>0–<33.7 ppm-years), 2 (33.7–<184.7 ppm-years) 3 (184.7–<425.0 ppm-years, RR=2.9), and 4 (425.0+ ppm-years). RRs for categories 1, 3 and 4 were very close to those in the main analysis. However, the RR for exposure category two – which was lower than the RR for category 1 in the main analysis – 99% of the RRs in the uncertainty analysis were higher. This uncertainty analysis provided support for a positive association between BD exposure and leukemia, and for a monotonic dose-response relationship. Healthy worker effect bias cannot be ruled out due to having limited the cohort to men with a one-year minimum employment. However, there is no direct evidence of such bias.		

Overall Quality Determination **Medium**

Study Citation:	Graff, J. J., Sathiakumar, N., Macaluso, M., Maldonado, G., Matthews, R., Delzell, E. (2005). Chemical exposures in the synthetic rubber industry and lymphohematopoietic cancer mortality. Journal of Occupational and Environmental Medicine 47(9):916-932.
Health Outcome(s) Assessed:	Immune/Hematological- Lymphohematopoietic cancer mortality, Cancer; Cancer/Carcinogenesis- Lymphohematopoietic cancer mortality, Cancer; Mortality- Lymphohematopoietic cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	737523

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This cohort study evaluated associations between occupational exposure to 1,3-butadiene and lymphohematopoietic cancer mortality among workers at 6 North American rubber plants. Study participants (n=16,579) were men who had worked at any of the study sites "for at least 1 year by the end of 1991 and who were actively working as of a calendar year that varied by plant from 1943 to 1950, depending on availability of employment records." Individuals were excluded if they died or who were lost to follow-up prior to reaching 40 years of age or 10 years since hire (Delzell et al., 2001, HERO ID 737524). Outcome assessment was based on linkage to mortality databases and loss to follow-up was minimal (3%). Comparisons are made among workers with varying exposure levels within the cohort as well as to the general population; bias arising from the healthy worker effect is possible among the latter set of comparisons. For within-cohort comparisons, it is not clear whether bias could have arisen due to healthier workers remaining employed in exposed jobs for longer; however, the available information does not raise serious concerns regarding selection bias for analyses that do not use the general population as the reference group.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Exposure to 1,3-butadiene was assessed using a job exposure matrix (JEM) developed for the rubber plants included in this study based on job histories and expert assessment. Industrial hygiene measurements were not incorporated into the JEM or used to inform validation. JEM estimates did appear to incorporate the use of personal protective equipment (Macaluso et al., 2004 HERO ID 646914). Estimation of exposure was based only on each subject's time working at the study sites, rather than based on lifetime occupational exposure. Some degree of exposure misclassification is likely, but this is unlikely to significantly alter effect estimates.
Domain 3: Outcome Assessment				

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Study Citation:	Graff, J. J., Sathiakumar, N., Macaluso, M., Maldonado, G., Matthews, R., Delzell, E. (2005). Chemical exposures in the synthetic rubber industry and lymphohematopoietic cancer mortality. Journal of Occupational and Environmental Medicine 47(9):916-932.
Health Outcome(s) Assessed:	Immune/Hematological- Lymphohematopoietic cancer mortality, Cancer; Cancer/Carcinogenesis- Lymphohematopoietic cancer mortality, Cancer; Mortality- Lymphohematopoietic cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	737523

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The outcome of interest was mortality due to several forms of lymphohematopoietic cancer: all lymphohematopoietic cancer, non-Hodgkin's lymphoma, multiple myeloma, Hodgkin's disease, all leukemia, chronic lymphocytic leukemia, acute myelogenous leukemia, and "other forms of leukemia." Outcomes were assessed using cause of death codes on death certificates. An attempt was made to obtain medical records for all subjects with underlying or contributing cause of death codes for lymphohematopoietic cancer. Both individuals whose medical records confirmed they had lymphohematopoietic cancer, as well as those who had cause of death codes for lymphohematopoietic cancer but did not have available medical records were included in analyses. There is some concern for outcome misclassification due to differences in coding practices over time, as well as to the use of medical records to define the outcome for only some participants.
	Metric 3B:	Selective Reporting	Medium	The authors described their primary and secondary analyses in the methods section, and results for all primary analyses were included in the results section. Results are consistently reported for the main exposure variable (cumulative exposure in ppm-years), but less consistently reported across outcome types for alternate characterizations of the exposure variable.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	All analyses were restricted to men only. For analyses comparing workers to the general population, standardized mortality ratios were computed using age, calendar period, and race-specific rates among US male populations, and age and calendar-period specific rates among Ontario male populations. For analyses comparing outcomes among workers with varying exposure levels, the following confounders were considered for inclusion: age, years since hire, calendar period, and race. No information was provided on how potential confounders were identified. Potential confounding by non-occupational factors was not evaluated. No measure of education or socioeconomic status was considered. Ultimately, only age and years since hire were included in models due to other potential confounders "having little impact on agent-specific RRs." Multi-pollutant models including two other occupational exposures (styrene and dimethyldithiocarbamate) were constructed. However, the introduction mentions a number of additional potential co-exposures in rubber plants that are not addressed in this analysis. There is some concern for bias due to residual confounding.
Domain 5: Analysis				

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Health Outcome(s) Assessed:	Immune/Hematological- Lymphohematopoietic cancer mortality, Cancer; Cancer/Carcinogenesis- Lymphohematopoietic cancer mortality, Cancer; Mortality- Lymphohematopoietic cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	737523

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Poisson regression was used to estimate relative rates of lymphohematopoietic cancers associated with 1,3-butadiene exposure among workers adjusted for confounders and two occupational co-exposures. The exposure variable was categorized in all analyses. Separate analyses examined the exposure quantified as ppm-years, ppm-years due to exposure intensities <= 100 ppm, ppm-years due to exposure intensities >100 ppm, and total exposures peaks (>100 ppm). Sensitivity analyses included examination of exposure lagged by 10 years. In addition to analyses examining within-cohort associations, standardized mortality ratios were calculated using the general population as a reference. All results were reported with 95% confidence intervals.
	Metric 5B:	Sensitivity	Medium	The sample size was large (n= 15,579). No additional concerns regarding study sensitivity were identified.

Additional Comments: This occupational cohort study of male rubber plant workers examined the association between exposure to 1,3-butadiene and mortality due to various forms of lymphohematopoietic cancer using adequate methods and a large sample size. There is some concern for exposure misclassification due to the use of a job exposure matrix that did not incorporate and was not validated against workplace measurements, as well as for bias due to potential residual confounding by other workplace exposures and/or non-occupational factors. Cumulative exposure to 1,3-butadiene was associated increased risk of leukemia mortality in single agent models. Associations were largely positive but attenuated to non-significance in models including adjustment for exposure to styrene and dimethyldithiocarbamate.

Overall Quality Determination Medium

Study Citation:	Hall, C., Heck, J. E., Ritz, B., Cockburn, M., Escobedo, L. A., Ehrenstein, von, O. S. (2019). Prenatal Exposure to Air Toxics and Malignant Germ Cell Tumors in Young Children. Journal of Occupational and Environmental Medicine 61(6):529-534.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- germ cell tumors (all germ cell tumors, yolk sac tumors, teratomas), Cancer; Reproductive/Developmental- germ cell tumors (all germ cell tumors, yolk sac tumors, teratomas), Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5641117

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This population-based case control study examined the association between exposure to air toxics (i.e., 1,3-butadiene) during pregnancy and malignant germ cell tumors (GCTs) diagnosed before age 6 in California from 1988-2013. Cases (3km buffer analyses: n = 243; 4 km buffer analyses: n = 99 (yolk sac tumors) and teratoma (n = 125)) were obtained from the California Cancer Registry and cancer-free controls (3km buffer analyses: n = 147,100; 4km buffer analyses: n = 155,191) were randomly selected from California birth records and frequency matched to cases by birth year. Children were included if there was at least one air toxics exposure reading for each full month of pregnancy and if they were born after 1984 and lived within a specific radius of air monitoring stations. Cases and controls were selected from the same eligible population using robust population-based records, minimizing concern for selection bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Exposure to 1,3-butadiene during pregnancy was measured using data California Air Resources Board (CARB) Air Toxics Program data. The program collects 24 hour samples every 12 days from monitors around the state. Distance from air monitors to participant homes or zip code centroids was assessed. Zip code centroids were used before 1998 and residential addresses at birth were geocoded from 1998 onward. Different buffers were used and analyzed in the study (3km and 4km from monitors). Exposure levels were assessed for each trimester. Pregnancy timing was assessed using date of birth and gestational ages determined by date of last menstrual period.Exposure misclassification was possible due to variation in 1,3-butadiene concentrations within buffers as well as due to changes in residential address during pregnancy (addresses at birth were used for exposure assessment). However, misclassification is not expected to vary by case/control status. Thus, concern for misclassification bias is minimal.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	High	Cancer cases diagnosed before age 6 were identified from the California Cancer Registry records (1988-2013) using International Classification of Childhood Cancer, Version 3 (ICCC-3) codes 101-105. Histological subtypes were identified using International Classification of Diseases for Oncology, Version 3 (ICD-O-3) codes (yolk sac tumors: code 9071; malignant teratomas: codes 9080-9084 with malignant behavior codes). Some cases (n=54) were not coded for these subtypes (i.e., mixed germ cell tumors, germinomas, other). State cancer registries are a valid approach to identifying clinical cancer cases. Although there is some potential that a small number of cases were missed (i.e., those that were not clinically diagnosed), the likelihood of this occurring and introducing substantial bias is minimal.

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Health Outcome(s) Assessed:	Cancer/Carcinogenesis- germ cell tumors (all germ cell tumors, yolk sac tumors, teratomas), Cancer; Reproductive/Developmental- germ cell tumors (all germ cell tumors, yolk sac tumors, teratomas), Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5641117

Domain	Metric		Rating	Comments
	Metric 3B:	Selective Reporting	Medium	Results are reported for all anticipated analyses outlined in the methods.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Potential confounders were selected using information in the literature and previous studies. One known risk factor for GCTs, cryptorchidism, was not accounted for as data were not available for the study population, preventing a ”good” rating. Birth year was controlled for via matching of cases and controls. Models adjusted for maternal age, maternal race/ethnicity, and neighborhood SES index (5-levels). Additional potential confounders considered but not included in models were maternal years of education and source or payment for prenatal care. Authors also explored adjustment for race/ethnicity using increasingly detailed indicator variables (i.e., additional groups). Ultimately, the detailed race/ethnicity variables were not included in models (did not alter effect estimates by 10% or more). No discussion of child’s sex as a potential confounder; however, it is not clear that this variable would be associated with prenatal exposure to 1,3-butadiene.Distributions are provided for all confounders, along with information those with missing confounding variable data.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	Associations between GCT risk and 1,3-butadiene exposure during pregnancy were assessed using unconditional logistic regression. Effect estimates and 95% CI are reported for the first two trimesters of pregnancy and for the entire pregnancy, along with case and control numbers for each analysis. Primary analyses assessed those children who lived within 3km buffer of an air monitoring station during pregnancy, and analyses of GCT by histological subtype used children who lived within a 4km buffer to increase sample size. Because air pollutants were expected to be highly correlated, a factor analysis with principal component extraction was conducted. Analyses were presented by these exposure factor groups. Exposure distribution information is provided.
	Metric 5B:	Sensitivity	Low	Although the overall sample size is adequate (243 cases and 147,100 controls) analyses for 1,3-butadiene had smaller sample sizes (10 cases and 21,770 controls) and particularly few cases, which may have impacted the study’s sensitivity. The exposure distributions are adequate to detect an effect. Additionally, exposures measured during pregnancy likely represent an etiologically relevant time period and allow for sufficient latency.

Additional Comments: This population-based case control study examined risk of germ cell tumor development before age 6 and maternal exposure to 1,3-butadiene during pregnancy in California. Overall, the study design was adequate and there are minimal concerns regarding substantial bias due to participant selection, outcome ascertainment, and analytical approaches. Although there was potential for exposure misclassification, this would be expected to be non-differential. One key confounder, cryptorchidism, was not accounted for in analyses. However, the study remains of medium confidence.

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Health Outcome(s) Assessed:	Cancer/Carcinogenesis- germ cell tumors (all germ cell tumors, yolk sac tumors, teratomas), Cancer; Reproductive/Developmental- germ cell tumors (all germ cell tumors, yolk sac tumors, teratomas), Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5641117

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation:	Hayes, R. B., Zhang, L., Yin, S., Swenberg, J. A., Xi, L., Wiencke, J., Bechtold, W. E., Yao, M., Rothman, N., Haas, R., O'Neill, J. P., Zhang, D., Wiemels, J., Dosemeci, M., Li, G., Smith, M. T. (2000). Genotoxic markers among butadiene polymer workers in China. Carcinogenesis 21(1):55-62.
Health Outcome(s) Assessed:	Immune/Hematological- White blood cell count, granulocytes, lymphocytes, lymphocyte %, erythrocytes, platelets, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5586518

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This occupational study examined the association between multiple measures of 1,3-butadiene exposure and hematologic parameters among workers at a polybutadiene rubber production facility in Yanshan, China. Participants were recruited from a group of 42 workers with high potential exposure to 1,3-butadiene identified based on job type (DMF process analysts, polymer process analysts, and process operators); of these 42 workers, 41 agreed to participate in the study. A second set of unexposed participants were recruited from work unites where 1,3-butadiene exposure was not expected to occur. 40 unexposed workers were identified, of which 2 were excluded due to past exposure to 1,3-butadiene. The final study population consisted of 41 exposed and 38 unexposed workers (n=79). Unexposed workers were matched "in groups" to exposed workers based on age (within 5 years) and sex. No further inclusion or exclusion criteria were provided. No information was provided on the type of work performed by unexposed workers. While some details of participant selection were not provided, the available information does not raise serious concerns regarding selection bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Exposure to 1,3-butadiene and its metabolites was assessed via four methods. First, as described under the participant selection domain, a binary measure of exposure (exposed versus unexposed) was assessed based on job type. Second, exposure to 1,3-butadiene in air was assessed for workers during a 6-hour shift using personal air samplers at the breathing zone. Samples were analyzed using "GC/FID" (acronym not spelled out but presumably gas chromatography-flame ionization detection). LOD estimated to be 1-2 ppb. The study also states that multiple grab samples during shifts and that canister samples were taken at 5 locations, although it is not clear that these samples were used in analysis of health outcomes. Third, the 1,3-butadiene metabolite mercapturic acid butanediol (M-1) was measured in urine samples collected during shifts at 0-3 hours and 4-6 hours using GC/GC/MS. It is unclear if urine samples taken at different timepoints were combined. Values were creatinine-standardized. LOD for M-1 in urine was not reported. A second metabolite (mercapturic acid butenol, or M-2) was also measured but not detected. Air and urine monitoring appear to have been conducted for all exposed workers and for a subset of unexposed workers (n=14). Fourth, THBVal hemoglobin adducts, a biomarker of 1-3,butadiene exposure, were measured in blood samples collected post-shift. While some details of exposure assessment are not provided, the use of multiple measures is a strength. Additionally, monitoring of air and urine samples among a subset of unexposed workers confirmed no to low exposure among this group. However, it is unclear whether monitoring of exposure during a shift immediately prior to outcome assessment reflects the etiologically relevant time window.

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Study Citation:	Hayes, R. B., Zhang, L., Yin, S., Swenberg, J. A., Xi, L., Wiencke, J., Bechtold, W. E., Yao, M., Rothman, N., Haas, R., O'Neill, J. P., Zhang, D., Wiemels, J., Dosemeci, M., Li, G., Smith, M. T. (2000). Genotoxic markers among butadiene polymer workers in China. Carcinogenesis 21(1):55-62.
Health Outcome(s) Assessed:	Immune/Hematological- White blood cell count, granulocytes, lymphocytes, lymphocyte %, erythrocytes, platelets, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5586518

Domain	Metric		Rating	Comments
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Post-shift blood samples were collected and were fractioned and stored. Lymphocytes were stimulated with phytohemagglutinin and harvested at 72 hours after culture initiation. A differential blood count was carried out with a Coulter blood counter on fresh whole blood within 2 hours of collection and numbers of granulocytes and lymphocytes and platelet counts were derived from total leukocyte count and lymphocyte percentage. In addition to hematologic parameters, a set of genotoxicity measures were also assessed, but these are not the focus of this evaluation.
	Metric 3B:	Selective Reporting	Medium	Analyses described in the methods were reported in the results.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	Unexposed workers were matched to exposed workers "in groups" based on age and sex. No other potential confounders were discussed or analyzed. There is some concern that results could be due to bias from residual confounding. This concern is particularly acute for analyses limited to exposed workers only, as these analyses did not benefit from age and sex matching.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The analytic approach was adequate, although largely limited to bivariate tests. Outcomes were compared among exposed versus unexposed workers using the Wilcoxon test. Among exposed workers, quantitative measures of exposure (air samples, urine samples, and adducts) were examined in relation to outcomes using Spearman correlation. The study also mentions linear regression analyses using log-transformed values but details are not provided and results from these analyses are only described briefly in the text.
	Metric 5B:	Sensitivity	Low	The small sample size was small (n = 79) limiting the ability to detect associations especially for analyses conducted only among exposed workers (n=41). The exposure range measured in air was adequate (DMF analysts median BD = 54 ppm, range 0-3090; polymerization analysts median BD = 6.5 ppm, range 0-1078; recovery operators median BD = 7.0 ppm, range 0->12,000). No other concerns regarding study sensitivity were identified.

Additional Comments: This occupational study assessed the association between hematologic parameters and measures of 1,3-butadiene and/or its metabolites measured by job type, in air, in urine, and in blood. Major concerns include the potential for residual confounding and the small sample size. Minor concerns include a lack of information some aspects of participant selection and exposure assessment methods. The study found that exposed workers had higher lymphocyte counts and higher lymphocyte percentages of total white blood cell count than unexposed workers. The study also found that 1,3-butadiene exposure measured in personal air samples was significantly positively correlated with lymphocyte counts and lymphocyte percentages among exposed workers.

Overall Quality Determination Low

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Health Outcome(s) Assessed:	Immune/Hematological- White blood cell count, granulocytes, lymphocytes, lymphocyte %, erythrocytes, platelets, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5586518

Domain	Metric	Rating	Comments

Study Citation:	Heck, J. E., He, D., Wing, S. E., Ritz, B., Carey, C. D., Yang, J., Stram, D. O., Marchand, Le, L., Park, S. L., Cheng, I., Wu, A. H. (2024). Exposure to outdoor ambient air toxics and risk of breast cancer: The multiethnic cohort. International Journal of Hygiene and Environmental Health 259:114362.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Breast cancer, Cancer; Reproductive/Developmental- Breast cancer, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	11438289

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	This study used data from the prospective population-based Multiethnic Cohort (MEC) study, which recruited participants residing in Hawaii and California from 1993-1996. This analysis of air toxic exposure estimates and breast cancer incidence was limited to MEC participants who were female and residents of California. Eligible women did not have a breast cancer diagnosis prior to entering the cohort, completed the 26-page mailed baseline questionnaire, and had geocoded addresses (n=57,999). Of these, the study excluded women whose breast cancer occurred within 5 years of baseline (n=7,630), who had no National Air Toxics Assessment (NATA) exposure estimates during the relevant exposure window from 1998-2003, and women whose geocoded address were out of range or on the boundary of census tracts during the follow up period (n=1,646), and Native Hawaiian participants (n=58). The study included a total of 48,665 women who were followed from 1998 until the earliest breast cancer incidence, death, or the end of the study (December 31, 2013). Deaths were ascertained using state death certificates and the National Death Index. The study did not provide details on initial participation rates or comparisons of included vs. excluded participants. However, there was no evidence of selection bias.
Domain 2: Exposure Characterization			

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Study Citation:	Heck, J. E., He, D., Wing, S. E., Ritz, B., Carey, C. D., Yang, J., Stram, D. O., Marchand, Le, L., Park, S. L., Cheng, I., Wu, A. H. (2024). Exposure to outdoor ambient air toxics and risk of breast cancer: The multiethnic cohort. International Journal of Hygiene and Environmental Health 259:114362.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Breast cancer, Cancer; Reproductive/Developmental- Breast cancer, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	11438289

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Data from the National Air Toxics Assessment's (NATA) Hazardous Air Pollutant Exposure Model (HAPEM) and Assessment System for Population Exposure Nationwide (ASPEN) models were used together to estimate exposure to 1,3-butadiene and 14 other chemicals during a 1998-2003 window. Measures are based on a national inventory of toxic air pollutant emission sources compiled every three years, with ambient concentrations estimated using weather information (ASPEN model) used as input to for human exposure models (HAPEM). HAPEM models generate an expected inhalation exposure concentration using inputs that include human activity patterns, ambient air quality, and indoor/outdoor concentrations. The authors noted that there has been previous concern in combining NATA data across years as the methods have shifted and improved over time. The authors confirmed the compatibility of the NATA 1999 and 2002 data with HAPEM5 to model the exposure assessment. Monthly exposure estimates at the census tract level were computed and assigned to month and year values linked to each residence with a geocoded address. Residential addresses collected at baseline were updated by periodic mailings to participants, and by linkages to administrative data and registries. Addresses for 1998-2002 and 2001-2003 were linked to the 1999 and 2002 NATA models, respectively, using 2000 census tracts. Changes in exposure estimates between 1999 and 2002 were not described, and subsequent exposure estimates were not discussed. Follow-up for breast cancer incidence included the period 2003 to 2013, allowing for a 5-year lag from the 1998 baseline. The EPA overall confidence rating for 1,3 butadiene was reported by the authors as "lower" for both the 1999 and 2002 NATA data; several other air toxics analyzed were rated as medium or higher confidence. Some misclassification of individual exposure is likely, but there was no evidence of bias.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Cases were defined as incident invasive breast cancers using ICD codes C500-C509 (revision not specified), excluding ICD-O-3 equal to 9050–9055, 9140, or 9590–9992. Ductal carcinoma in situ was not included. Cases were ascertained through linkage with the California Cancer Registry, which has been certified as having >95% case ascertainment. Analyses examined associations with all cases, as well as separately with hormone receptor negative (i.e., negative for both estrogen receptor [ER] and progesterone receptor [PR] status) and hormone receptor positive (ER+ or PR+) cancers.
	Metric 3B:	Selective Reporting	Medium	There are no concerns for selective reporting. Authors described their analyses in the methods and results sections.
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Heck, J. E., He, D., Wing, S. E., Ritz, B., Carey, C. D., Yang, J., Stram, D. O., Marchand, Le, L., Park, S. L., Cheng, I., Wu, A. H. (2024). Exposure to outdoor ambient air toxics and risk of breast cancer: The multiethnic cohort. International Journal of Hygiene and Environmental Health 259:114362.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Breast cancer, Cancer; Reproductive/Developmental- Breast cancer, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	11438289

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Confounders were selected a priori. All models were adjusted for: age (used as the time scale), census tract clustering, race and ethnicity, BMI, family history of breast cancer, age at first live birth, age at menarche, number of children, menopausal status at baseline, self-reported hormone replacement therapy, physical activity, energy intake, alcohol use, smoking history, educational attainment, and a census block group neighborhood socioeconomic status index (baseline and current). Pearson correlations between 1,3-butadiene and other traffic-related air toxics analyzed in this study were >0.70; correlations with industry-related air toxics were 0.02 to 0.29. A sensitivity model adjusted for traffic pollution using NOx concentrations; findings were very similar to models without this adjustment. The authors did not discuss examining other potential co-exposure confounding, but there was no evidence of bias.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Descriptive data on participant characteristics, as well as distributions of each air toxic analyzed, were shown overall and stratified by race/ethnicity. Descriptive data on outcomes were not shown. Cox proportional hazard models were used to analyze associations per IQR increase in time-dependent air toxics exposure and breast cancer incidence, lagged by 5 years. The authors stated that they tested for adequate linearity in dose-response prior to conducting analyses; the method used was not described. Hazard ratios and 95% confidence intervals were reported for both crude and multivariate-adjusted models, and the number of cases was provided. Primary results came from a complete case analysis; results were very similar using multiple imputation in a sensitivity analyses. Other supplemental analyses included stratifying by race/ethnicity, restricting the sample to non-smokers, and mover/non-mover status, with similar findings. There was no evidence for important concerns with respect to analysis.
	Metric 5B:	Sensitivity	Medium	Sample size (>40,000 women) and the number of cases (1,520 and 1,261 in crude and adjusted models, respectively) were large. The study population was aged 45 to 75 years at baseline (90% postmenopausal at baseline). There was variability in estimated 1,3-butadiene exposure (mean 0.0508 ug/m3, range 0.0006 to 0.3738). Models included a 5-year exposure lag. A potential limitation is that, according to the authors, case numbers were too sparse to incorporate 10- or 15-year lags to address potentially longer breast cancer latency.

Additional Comments: This study used a population-based prospective cohort (MEC) to analyze the association between 1,3-butadiene and 14 other air toxics and invasive breast cancer incidence among more than 48,000 women residing in California. Women were recruited in 1993-1996, exposure was estimated for 1998 to 2003, and participants were followed up for breast cancer incidence from 2003 to 2013, allowing for a 5-year lag. The analysis included more than 1,500 incident cases. Exposure to 1,3-butadiene was estimated based on National Air Toxics Assessment (NATA) models and assigned to residential addresses at the census tract level. A significantly increased risk of breast cancer was found for exposure to 1,3-butadiene [HR per IQR increase = 1.18 (95% CI: 1.13, 1.23). Results were similar in crude and adjusted models, and in numerous sensitivity analyses. Though the precision of modeled exposure estimates is uncertain, the large size, prospective design, and robustness of findings were strengths of this study.

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Study Citation:	Heck, J. E., He, D., Wing, S. E., Ritz, B., Carey, C. D., Yang, J., Stram, D. O., Marchand, Le, L., Park, S. L., Cheng, I., Wu, A. H. (2024). Exposure to outdoor ambient air toxics and risk of breast cancer: The multiethnic cohort. International Journal of Hygiene and Environmental Health 259:114362.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Breast cancer, Cancer; Reproductive/Developmental- Breast cancer, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	11438289

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation:	Heck, J. E., Park, A. S., Qiu, J., Cockburn, M., Ritz, B. (2014). Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood. International Journal of Hygiene and Environmental Health 217(6):662-668.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Acute lymphoblastic leukemia (ALL), Cancer; Immune/Hematological- Acute lymphoblastic leukemia (ALL), Cancer; Cancer/Carcinogenesis- Acute myeloid leukemia (AML), Cancer; Immune/Hematological- Acute myeloid leukemia (AML), Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	2345720

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	This case-control study evaluated associations between air measurements of 1,3-butadiene and two forms of cancer (acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) among a subset of participants in the population-based Air Pollution and Childhood Cancer Study (APCC). In the APCC study, cases were children younger than age six included in the California Cancer Registry from 1990-2007 and matched to birth certificates on name, date of birth, and social security number (89% matched to birth records). Controls were randomly selected from among California birth certificates and were frequency-matched to cases on year of birth (20:1 matching). Exclusion criteria were: death due to other causes before age 6 (controls), missing information on gestational age on birth certificates, "likely non-viable births" among controls (birth weight <500 g or <20 weeks gestational age), and home addresses listed as outside of California. For the current study, cases and controls were further limited to those living within 2 km (for ALL) or 6 km (for AML) radius of an air monitoring station. This resulted in the exclusion of 2,584 ALL cases, 394 AML cases, and 142,188 controls. Cases and controls were further limited to participants who had at least one air monitor reading during each full month of pregnancy and at least one reading during the last 30 days of pregnancy. The remaining analytic sample sizes were ALL: 66 cases, 2,626 controls; AML: 41 cases, 17,296 controls). The available information does not raise serious concerns regarding selection bias.
Domain 2: Exposure Characterization			
	Metric 2A: Exposure Measurement	Medium	Exposure measurements were sourced from the California community based environmental air toxics monitoring, which collect 24hr samples every 12 days. Authors report utilizing 39 different site monitors, but note that not every monitor had measurements for all the included air toxics for the study; the impact specifically on 1,3-butadiene measurements is not provided. For ALL and AML, participants were restricted to those whose birth address was within 2 km and 6 km of a monitor, respectively; participants were assigned values from that monitor. Exposure averages during each pregnancy trimester, the entire pregnancy, and the child's first year of life were calculated using available measurements from the assigned monitor. There is some concern for exposure misclassification due to use of the birth address only to estimate exposures throughout pregnancy and into infancy. The authors also note that 1,3-butadiene is relatively unstable in ambient air, potentially also contributing to misclassification.
Domain 3: Outcome Assessment			

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Study Citation:	Heck, J. E., Park, A. S., Qiu, J., Cockburn, M., Ritz, B. (2014). Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood. International Journal of Hygiene and Environmental Health 217(6):662-668.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Acute lymphoblastic leukemia (ALL), Cancer; Immune/Hematological- Acute lymphoblastic leukemia (ALL), Cancer; Cancer/Carcinogenesis- Acute myeloid leukemia (AML), Cancer; Immune/Hematological- Acute myeloid leukemia (AML), Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	2345720

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The outcomes of interest were acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Individuals with ALL and AML were identified using the California Cancer Registry. A cited reference (Heck et al. 2013, HERO ID 2093110) indicates that cancer types are listed in the registry using ICD codes; however, the specific codes used to identify ALL and AML were not provided in this study. While some details were not provided, outcome misclassification is not anticipated to be a major concern.
	Metric 3B:	Selective Reporting	Medium	Authors described the analyses in the methods section and reported results.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	The following potential confounding variables were included in regression models based on previously reported associations with the outcomes and/or with exposure to air pollution: birth year, maternal race/ethnicity, mother's birth place (US/foreign), parity, and neighborhood socioeconomic index. Child sex, rural/urban area of residence, and maternal age were also evaluated as potential confounding variables but were ultimately not included in models as the resulted in changes in effect estimates of less than 5%. There is some potential for residual confounding by other air toxics in the study, which were stated to be correlated with each other.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Authors conducted unconditional logistic regression and reported effect estimates and confidence limits. Additional sensitivity analyses were conducted to compare the influence of zip codes on risk of AML or ALL instead of home addresses. Sensitivity analyses included adjustment for alternate measures of socioeconomic status (maternal educational attainment, health insurance type) and use of zip code centroid instead of home address to assign exposures. Missing data were not described.
	Metric 5B:	Sensitivity	Medium	The sample size was adequate for both outcome. Additionally, the population was relevant and included children under 6 (sensitive life stage) with or without AML/ALL. There is some uncertainty regarding exposure levels and contrast, as information on the distribution of exposures was not provided.

Additional Comments: This case-control study examined the association between 1,3-butadiene levels in ambient air and two forms of leukemia among children under the age of 6 in California. Minor concerns include the potential for exposure misclassification due to exposure assignment based on birth address and limited information on some aspects of the analysis (e.g., missing data) and study aspects related to sensitivity (e.g., no information provided on the exposure distribution in this subset of the overall study population). 1,3-butadiene exposure during the 3rd trimester and across the entire pregnancy was associated with increased odds of acute lymphoblastic leukemia (3rd trimester OR [95% CI]: 1.54 [1.19, 1.99], entire pregnancy OR [95% CI]: 1.76 [1.09, 2.86]). 1,3-butadiene exposure during the child's first year of life was associated with increased odds of acute myeloid leukemia (OR [95% CI]: 2.35 [1.02, 5.39]).

Overall Quality Determination Medium

Study Citation:	Heck, J. E., Park, A. S., Qiu, J., Cockburn, M., Ritz, B. (2013). Retinoblastoma and ambient exposure to air toxics in the perinatal period. Journal of Exposure Science and Environmental Epidemiology 25(2):182-186.
Health Outcome(s) Assessed:	Ocular/Sensory- Retinoblastoma, Cancer; Cancer/Carcinogenesis- Retinoblastoma, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	2369182

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	The study analyzed retinoblastoma risk among children younger than age 6 in California as a part of the Air Pollution and Childhood Cancer (APCC) study, which is a large case–control investigation of air pollution exposure among California children. Cases were ascertained from California Cancer Registry records of cancer diagnoses between 1990 and 2007 among children younger than age 6. Population-based controls were selected at random from California birth records for the same time period, and frequency matched to all childhood cancer cases by birth year. Controls had no cancer diagnosis listed in the California Cancer Registry before age 6. Authors linked participants to California death records in order to exclude them from 1550 controls who had died of other causes in early childhood (< age 6). Children with missing information on gestational age (20 cases, 9219 controls) were excluded from analyses. 30,704 children (103 cases, 30,601 controls) were included in analyses because they were living within 5 miles of a monitor and had sufficient values recorded for at least one pollutant. The 131,314 additional children who were excluded from the present study because they were not living within 5 miles of any monitor were much more likely to be residing in a rural county (21% vs 6%). There was no direct evidence of selection bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Exposure to 1,3-Butadiene was assessed via linking participant addresses to values reported from the California Air Resources Board (CARB)"s Air Toxics Program. CARB monitors report data beginning in 1990 and measure ambient concentrations of 1,3-butadiene by collecting "24-h integrated samples every 12 from each monitor." Monitors are located across the state of California, but are most frequently located in high-traffic urban areas, industrial neighborhoods, or agriculturally intense rural regions. The distance from each monitor to a participant home was assessed and participants were assigned 1,3-butadiene levels corresponding to the measurements from the nearest monitor. The study reported that they also attempted to use kriging to assign values but did not find significant differences from their original analysis (data not provided). Measurements were averaged across 3 months pre-conception, each trimester, the whole period of pregnancy, and the first year of life in order to account for latency. While the exposure assessment does not account for metereologic factors or individual behaviors, these are not expected to differentially affect cases relative to controls; thus there is no evidence of significant bias.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	The outcome of interest in this study was retinoblastoma. Cases were reported from the California Cancer Registry records. They included cases with International Classification of Childhood Cancer, Third edition (ICCC-3) code 050.

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Study Citation:	Heck, J. E., Park, A. S., Qiu, J., Cockburn, M., Ritz, B. (2013). Retinoblastoma and ambient exposure to air toxics in the perinatal period. Journal of Exposure Science and Environmental Epidemiology 25(2):182-186.
Health Outcome(s) Assessed:	Ocular/Sensory- Retinoblastoma, Cancer; Cancer/Carcinogenesis- Retinoblastoma, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	2369182

Domain	Metric		Rating	Comments
	Metric 3B:	Selective Reporting	Medium	The authors described their primary analyses in the methods section and results were reported for all primary analyses. No concerns for selective reporting
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Considered covariates included maternal race/ethnicity and nativity, paternal age, year of birth, and the method of payment for prenatal care (private health insurance vs. Medi-Cal/other government-sponsored health insurance/self=pay) as a proxy for socioeconomic status. These covariates were puled from birth certificates, and were chosen due to the study authors' previous work on retinoblastoma. The study explains that that race, Latino ethnicity, and socioeconomic status are related to air pollution exposures. Co-exposure to a wide variety of other air toxics reported by CARB were also considered. In general, there is no evidence of residual confounding.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Analysis methods were appropriate. Descriptive data presented mean pollutant values and interquartile ranges, as well as numbers of cases and controls. Logistic regression analyses were conducted for each pollutant separately, with adjustment for potential confounding variables. Odds ratios and 95% confidence intervals for associations between pollutants and retinoblastoma were presented, per IQR increase in 1,3-butadiene. Sensitivity analyses were described, including stratified by region, time period, and whether retinoblastoma was bilateral or unilateral.
	Metric 5B:	Sensitivity	Medium	The number of participants (n-103 cases, n=30,601) is likely large enough to detect an effect. The reported IQR for 1,3-Butadiene is 0.26 ppbV, which indicates that there is likely enough exposure contrast to detect an effect.

Additional Comments: This case-control study used data from the Air Pollution and Childhood Cancer study to examine the association between ambient 1,3-butadiene levels and retinoblastoma incidence among children. There were no significant concerns for bias across the study, although there are potential concerns for exposure misclassification due to the lack of consideration for individual behaviors that may influence exposure. The study reported significantly higher probability of retinoblastoma in participants exposed to higher levels of 1,3-butadiene during pregnancy.

Overall Quality Determination Medium

Study Citation:	IISRP, (2000). Support: Lymphohematopoietic cancer among workers exposed to 1,3-butadiene, styrene and dimethyldithiocarbamate in the synthetic rubber industry, with cover letter dated 012600.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- lymphohematopoietic cancer (leukemias, non-Hodgkin's lymphomas, multiple myelomas, Hodgkin's disease), Cancer; Immune/Hematological- lymphohematopoietic cancer (leukemias, non-Hodgkin's lymphomas, multiple myelomas, Hodgkin's disease), Cancer; Mortality- lymphohematopoietic cancer (leukemias, non-Hodgkin's lymphomas, multiple myelomas, Hodgkin's disease), Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5664525

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This occupational cohort study examined the association between 1,3-butadiene exposure and leukemia mortality in an occupational population from 1944 through 1991. Male workers (n=17,694) who worked in synthetic rubber plants for at least one year were identified using plant records. Eight rubber plants were included (7 in the United States, 1 in Canada). The final study population included 13, 130 men. Men were excluded from the study if they worked at two plants, as the records lacked information on work area/job assignment information (used to estimate exposure levels). 12 duplicate records capturing men who worked at more than one plant in the study period were also excluded. 3,468 men were excluded because they died or follow-up ended before 40 years of age or before 10 years since hire. There is no comparison of those included and excluded from the study population. However, a high percentage of the eligible population was included in the study with minimal loss to follow-up, which minimizes concern for selection bias.The primary concern is risk of healthy worker selection bias due to restricting eligibility to men employed for at least one year. Overall, it cannot be ascertained to what extent excluded workers may have differed from those included in terms of 1,3 butadiene exposure and cancer mortality. However, selection bias due to excluding short term workers is an important concern and cannot be ruled out.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Exposure to 1,3-butadiene was assessed by reviewing the job-exposure matrix approach used to estimate exposure from previous studies and updating accordingly. During the review, experts (i.e., industrial hygienists and chemical engineers) visited the six synthetic rubber plants to obtain additional information on work practices, operations, and engineering controls, and additional data on air speeds throughout each plant. The JEM incorporated measures of time, task- and plant-specific information, and detailed job histories, although data validating the JEM is not provided. Although there is potential for exposure misclassification, this is expected to be nondifferential.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Leukemia mortality data were obtained from plant records and data from individual tracing and record linkages with national and private agencies. Death certificates provided information on cause of death. For those with leukemia or another blood disorder listed as the attributed cause of death, medical records or pathology data were obtained to confirm the diagnosis (n = 49 out of 59 cases). Personnel, medical, and death certificate records are expected to be reliable measures of leukemia deaths. However, measures of solely deaths due to leukemia do not capture those with incident leukemia. Misclassification is expected to be minimal.

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Study Citation:	IISRP, (2000). Support: Lymphohematopoietic cancer among workers exposed to 1,3-butadiene, styrene and dimethyldithiocarbamate in the synthetic rubber industry, with cover letter dated 012600.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- lymphohematopoietic cancer (leukemias, non-Hodgkin's lymphomas, multiple myelomas, Hodgkin's disease), Cancer; Immune/Hematological- lymphohematopoietic cancer (leukemias, non-Hodgkin's lymphomas, multiple myelomas, Hodgkin's disease), Cancer; Mortality- lymphohematopoietic cancer (leukemias, non-Hodgkin's lymphomas, multiple myelomas, Hodgkin's disease), Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5664525

Domain	Metric		Rating	Comments
	Metric 3B:	Selective Reporting	Medium	Results are reported for all analyses described in the methods.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	Age and years since hire were included in models as confounders. Additionally, the study was restricted to male workers, effectively controlling for sex. Styrene and sodium dimethyldithiocarbamate (DMDTC) were included in multiple pollutant models. Key confounders including smoking status, other co-exposures encountered in the occupational environment that are associated with leukemia, race, and SES, were not included in analyses, meriting a low/deficient rating.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The association between leukemia mortality and occupational 1,3-butadiene exposure was analyzed via Poisson regression models. Effect estimates and 95% CI are reported for all analyses, along with p for trend (where applicable). Analyses used tertiles of exposure (among exposed leukemia decedents), quartiles, or quintiles of exposure in analyses. Median exposure levels among cases are provided.Both single-pollutant and multiple pollutant models were used to assess associations. Additionally, a 5- or 10-year lag was applied in some analyses to assess cumulative exposures to account for the latency of leukemia disease.
	Metric 5B:	Sensitivity	Medium	The sample size was likely adequate (n = 13,130 men) to detect an effect, although the number of cases was fairly low due to the rare nature of leukemia (n = 59). The follow-up period was appropriate to detect the disease given the expected latency of leukemia. No other concerns related to study sensitivity.

Additional Comments: This occupational cohort study examined the association between leukemia mortality and 1,3-butadiene exposure in a population of male synthetic rubber plant workers (n = 13,130). The approaches to participant selection, outcome ascertainment, and statistical analyses were adequate and not expected to introduce substantial bias. There was some potential of exposure misclassification due to the exposure estimation approach (i.e., incorporating information on job history and plant/task/temporal data); however, such misclassification would not be expected to be differential by outcome status. Additionally, some key confounders (including smoking status, other occupational coexposures, race, and SES) were not considered or incorporated in analyses. Overall, concerns about major sources of residual bias are minimal.

Overall Quality Determination Medium

Study Citation:	Luo, J., Hendryx, M., Ducatman, A. (2011). Association between six environmental chemicals and lung cancer incidence in the United States. Journal of Environmental and Public Health 2011:463701.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lung cancer incidence rate (county-level, United States), Cancer; Lung/Respiratory- Lung cancer incidence rate (county-level, United States), Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1021648

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	This ecological study analyzed the association between county-level age-adjusted cancer incidence rates in the United States in 1992-2007 (n=215 counties) and industrial toxic emissions data on 1,3-butadiene from the Toxic Releases Inventory (TRI) database covering the same counties from 1988 to 1990. The authors utilized the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute to obtain information on lung cancer incidence. As the authors detail, at the time of publication, SEER collected information on cancer incidence from 17 population-based registries covering approximately 26% of the US population. The counties included in the analyses provided lung cancer incidence information obtained from 13 of the registries (including Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, and Alaska). Of the 225 counties included, 215 (95.5%) could be linked to the TRI database. Given the ecological nature of this study, the methods for participant selection were appropriate, with no major concerns for bias.
Domain 2: Exposure Characterization			
	Metric 2A: Exposure Measurement	Low	Estimated county-level 1,3 butadiene exposure was obtained from the Toxics Releases Inventory (TRI). TRI data are limited to industrial emissions reported by facilities meeting requirements that include manufacturing or processing over 25,000 pounds annually or otherwise using more than 10,000 pounds of any chemical on the TRI list. The authors obtained total TRI on-site releases for six chemicals from 1988-1990, excluding 1987 because it was the first year of reporting and data may have been incomplete. Exposure estimates preceded cancer incidence by 2 to 17 years. Exposure to individual chemicals was analyzed as any non-zero release (dichotomous) and as natural log-transformed estimated pounds/year (continuous). Of the 215 counties, only 12 (5.5%) were characterized as having non-zero release of 1,3 butadiene. An important oversight is that the authors did not state whether 94.5% of counties assigned zero values for BD releases were excluded from analyses using the continuous exposure variable vs. included by assigning them a low non-zero value (equivalent to approaches used for values below detection limits). A second concern is that because TRI data exclude major sources of 1,3-butadiene such as vehicle exhaust, wood smoke, and cigarette smoke, along with industrial emissions from small facilities not meeting reporting requirements, county-level exposure is likely inadequately characterized in the counties classified as having zero BD releases. This concern is especially elevated given that so few counties (5.5%) had non-zero TRI emissions for BD. A third concern is misclassification of personal exposure due not only to use of county-level data, but also to factors such as the lack of information on the duration of county residence and proximity to point sources among cases. Multiple concerns make the utility of exposure estimates uncertain.

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Study Citation:	Luo, J., Hendryx, M., Ducatman, A. (2011). Association between six environmental chemicals and lung cancer incidence in the United States. Journal of Environmental and Public Health 2011:463701.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lung cancer incidence rate (county-level, United States), Cancer; Lung/Respiratory- Lung cancer incidence rate (county-level, United States), Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1021648

Domain	Metric		Rating	Comments
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Lung cancer incidence is the outcome of interest for this study, and information was obtained from the SEER database. Age-adjusted lung cancer rates were obtained from the database for years 1992-2007 from 13 of the 17 SEER registries. These were chosen because they had been participating in the SEER program prior to the year 2000 and had data available for the time period of interest. The use of SEER data lends confidence to appropriate outcome classification. While validation was not discussed, this does not raise any major concerns as the data is sourced from various population-based cancer registries which likely utilize appropriate techniques for classifying cancer outcomes. It should be noted that outcome data were available for selected areas. However, there was no evidence that counties for which outcome data were not available differed from those included.
	Metric 3B:	Selective Reporting	Medium	The results reported within the study align with the analyses described in the methods section.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	County attributes data on potential confounders was obtained from the SEER database, derived using the 1990 census or from the 2003 and 2006 Behavioral Risk Factor Surveillance System (BRFSS) surveys supplemented with health department smoking data. Multivariate models adjusted for the 1990 data on the proportion of the county population that was nonwhite, male, had a college degree or higher education, and families below poverty level, as well as the prevalence of smoking in 2003–2006, and the proportion of metro and non-metro areas based on USDA Urban Continuum codes. Two other variables considered, unemployment rate and the percent of the population without a high school education, were excluded due to their high correlation with each other and the poverty rate. Though the authors did not provide a rationale for selecting these confounders but there was no evidence that these adjustments were inappropriate. There were several other potential concerns. A justification for combining data from 1990 and 2003-2006 was not provided, and changes in confounding variables over time (e.g. smoking rates) were not discussed. Confounding by co-exposures to other TRI release variables analyzed was not evaluated, although the total amount of releases for all 6 chemicals was analyzed. More importantly, confounding by non-industrial sources of BD exposure, such as vehicle emissions, was not discussed. Confounding or modification by exposure to other BD sources cannot be ruled out.
Domain 5: Analysis				

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Study Citation:	Luo, J., Hendryx, M., Ducatman, A. (2011). Association between six environmental chemicals and lung cancer incidence in the United States. Journal of Environmental and Public Health 2011:463701.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lung cancer incidence rate (county-level, United States), Cancer; Lung/Respiratory- Lung cancer incidence rate (county-level, United States), Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1021648

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Low	Analyses estimated associations between county-level BD releases and county lung cancer rates using linear regression. Results of univariate and multivariate models were shown using BD release exposure characterized using both a dichotomous (any vs none) and a log-transformed continuous variable. As noted earlier, it was unclear how the continuous BD exposure variable addressed zero release values. Missing data for both exposure variables and covariates was not discussed. Furthermore, despite the extremely large proportion of zero BD release values, model diagnostics and sensitivity analyses were not discussed to ensure that use of the continuous exposure variable was appropriate. Effect estimates were presented as coefficients and p-values; confidence intervals were not provided despite the sparseness of BD exposure data and potential imprecision of effect estimates. Along with overall associations, results were presented stratified by gender and by metro/non-metro (rural vs. urban) area; counts of the number of counties with BD releases included in each stratum were not shown. The extent to which analyses conducted treated the sparse exposure data appropriately is a concern.
	Metric 5B:	Sensitivity	Low	There are some concerns pertaining to study sensitivity for their analysis of 1,3-butadiene. Out of the 215 counties examined in the author's analyses, only 12 of them had nonzero releases of this chemical. In the discussions section of the study, the authors highlight that, due to the low number of counties with nonzero releases, "we may have little statistical power to detect effects that may be present."

Additional Comments: This ecological study analyzed associations between lung cancer incidence rates and industrial emissions exposure information that included 1,3 butadiene for 215 counties throughout the United States. Exposure data came reflected releases reported to the EPA's TRI in 1988-1990; outcome data came from the SEER databases, which represented 26% of the US population, for 1992-2007. A potentially important limitation is uncertainty of the extent to which variability in exposure to 1,3 butadiene was captured, given that only 12 of the 215 counties had nonzero emissions levels. TRI data are limited to facilities manufacturing or processing over 25,000 pounds annually or otherwise using more than 10,000 pounds of any chemical on the TRI list. Variability in exposure to 1,3 butadiene from smaller facilities, as well as from sources such as vehicle emissions and wood or cigarette smoke, was not reflected in the TRI measure. Thus, the extent to which county-level BD exposure was captured for 94.5% of the counties included in the analysis is uncertain.

Overall Quality Determination Low

Study Citation:	Niehoff, N. M., Gammon, M. D., Keil, A. P., Nichols, H. B., Engel, L. S., Sandler, D. P., White, A. J. (2019). Airborne mammary carcinogens and breast cancer risk in the Sister Study. Environment International 130:104897.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- ER + invasive breast cancer, Cancer; Cancer/Carcinogenesis- ER - invasive breast cancer, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5440630

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This cohort study of airborne carcinogens and breast cancer risk used data from a large previously established cohort, the Sister Study. Recruitment details, inclusion/exclusion criteria, and response rates over the course of follow up (>91%) were reported elsewhere (Sandler et al. 2017, HEROID 7213712; NIEHS web). The cohort enrolled women from 2003 to 2009, and breast cancers incident after a mean 8.4 years of follow-up were analyzed. Women eligible for participation had a sister who had been diagnosed with breast cancer but no prior breast cancer diagnosis themselves. Of the 50,884 women enrolled in, this analysis excluded the following: 163 women diagnosed with breast cancer before completing enrollment or without follow-up information; 1003 whose addresses could not be geocoded; 882 residents of Puerto Rico; and 46 women residing in areas not included in this study, resulting in a sample of 49,718 women. Included and excluded participants had similar characteristics. Sample size was large, there was sufficient description of participants, and there was no evidence that initial participation or attrition were associated with exposure to 1,3-butadiene or any of the other airborne carcinogens under study.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	This study used air toxics concentrations from the EPA's 2005 National Air Toxics Assessment (NATA) database) to assign participant residential addresses to census-tract level estimates of several air toxics, including 1,3-butadiene. NATA includes emissions data from point sources, non-point sources, and from on-road and non-road mobile sources (e.g. factories, prescribed burns, cars, boats). Data are used as inputs to air dispersion models that incorporate parameters such as meteorological factors to estimate ambient concentrations at the census tract level. Measures represent one-year averages. 94% of participants were enrolled in 2005 or later, and thus the 2005 exposure estimates primarily predated enrollment for the majority of participants. The authors also reported that the population has been stable, with 80% remaining at same address throughout follow-up. Misclassification of individual exposure due to factors such as variability within census tracts, variability in time spent outdoors, and variability in exposure levels over time. Though misclassification is likely, there was no evidence of important bias.
Domain 3: Outcome Assessment				

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Study Citation:	Niehoff, N. M., Gammon, M. D., Keil, A. P., Nichols, H. B., Engel, L. S., Sandler, D. P., White, A. J. (2019). Airborne mammary carcinogens and breast cancer risk in the Sister Study. Environment International 130:104897.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- ER + invasive breast cancer, Cancer; Cancer/Carcinogenesis- ER - invasive breast cancer, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5440630

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	High	Incident breast cancer diagnosis was self-reported in annual health updates or follow-up questionnaires and corroborated with medical records. Records were obtained for 81% of diagnosed cases. Self-report was used for those without medical records, but authors report that agreement was high between self-report and record (PPV >99%). Medical records or self-reported data were used to characterize tumors by stage, histology and estrogen receptor status. Outcome characterization is likely to be highly sensitive and specific, with minimal misclassification.
	Metric 3B:	Selective Reporting	High	The results reported within this study are consistent with the analyses outlined in the methodology and statistical analysis section. Results presented for each analysis, both significant and non-significant.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	This study assessed an array of potential confounders based on review of a priori considerations and published literature. Confounders were selected using a DAG provided in the supplemental figures. Age was used as the time scale, and of 11 variables considered, confounders included in the final models were race, residence type (urbanicity), highest level of education and cigarette smoking. Socioeconomic indicators other than education were not discussed. This study also evaluated potential effect modification by BMI and physical activity, and co-exposure to multiple air toxics was assessed using classification and regression tree analysis. There was no evidence of important residual confounding.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	This study used appropriate statistical analyses to examine the association between exposure to air pollutants and breast cancer, estimating Hazard Ratios and 95% CI using Cox proportional hazards models. The authors reported evaluating the proportional hazards assumption. Values for the 26 air pollutants were 100% complete for the entire study population. 1,3-butadiene and other air toxics were modeled using quintiles of exposure. The study estimated associations between air toxic quintiles and all breast cancers, as well as with estrogen receptor (ER) positive invasive cancers. Analyses included single pollutant associations for the full population, as well as sensitivity analyses restricting the sample to non-Hispanic whites (85% of the population), women who remained at the baseline address for >10 years, women enrolled in 2005 or later, cases confirmed by medical records, and additionally adjusting for region. To assess potential effect modification by BMI and physical activity, the authors examined both additive and multiplicative interactions. The study also included multi-pollutant analysis using Classification and Regression Tree (CART) models. There was no evidence of deficiencies in the analyses.

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Study Citation:	Niehoff, N. M., Gammon, M. D., Keil, A. P., Nichols, H. B., Engel, L. S., Sandler, D. P., White, A. J. (2019). Airborne mammary carcinogens and breast cancer risk in the Sister Study. Environment International 130:104897.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- ER + invasive breast cancer, Cancer; Cancer/Carcinogenesis- ER - invasive breast cancer, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5440630

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Low	Sample size was large. However, low levels of exposure and the use of census tract-based estimates were limitations. Quintiles of exposure (ug/m3) were as follows: 0–0.03 ug/m3, >0.03–0.05 ug/m3, >0.05–0.07 ug/m3, and >0.07–0.09 ug/m3. In addition to uncertainty that the estimated concentrations were in a range at which risk of breast cancer might be increased, it is likely that the available data had limited ability to adequately rank participants with respect to differences in chronic exposure to 1,3-butadiene.

Additional Comments: This is a large, well-designed prospective cohort study of air pollutants and breast cancer risk which used appropriate methods. Analyses included nearly 50,000 women in the Sister Study cohort, with exposure to 1,3-butadiene estimated using the EPA's NATA emissions estimates for 2005. Associations between incident breast cancer and 1,3-butadiene exposure did not reach statistical significance. However, given the combination of census-tract estimates and low concentrations across the entire population, the study may not have had sufficient sensitivity to detect an effect of 1,3-butadiene on breast cancer risk. Estimated 1,3-butadiene exposure levels in the lowest and highest quintiles were 0–0.03 ug/m3 and >0.07–0.09 ug/m3 respectively.

Overall Quality Determination Medium

Study Citation:	Sathiakumar, N., Bolaji, B. E., Brill, I., Chen, L., Tipre, M., Leader, M., Arora, T., Delzell, E. (2021). 1,3-Butadiene, styrene and lymphohaematopoietic cancers among North American synthetic rubber polymer workers: exposure-response analyses. Occupational and Environmental Medicine 78(12):859-868.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Mortality from all leukemia, leukemia subtypes (lymphoid leukemia, myeloid leukemia, acute myeloid leukemia (AML)).Mortality from non-Hodgkin's lymphoma (NHL), multiple myeloma, and all B-cell malignancies (includes lymphoid leukemia, NHL and multiple myeloma)., Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	10192219

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This study analyzed associations between occupational exposure to 1,3-butadiene and lympho-haematopoietic cancer (LHC) mortality in a cohort of styrene-butadiene rubber (SBR) workers employed at six North American facilities between 1943 and 1991. This analysis included 21,087 workers (16,579 male, 4,508 female) employed at any time between 1943 and 1991. Vital status was ascertained for 99% of the cohort through 2009. At the end of this follow-up period, the median time since hire was 40 years. The lengthy follow-up and large size are strengths of the cohort. Inclusion criteria were a potential limitation. Women were included in the cohort if they were employed for at least one day before January 1, 1992. However, inclusion was limited to men who had been employed for at least one year. This criterion may have induced some risk of healthy worker bias given the high turnover during the first year of employment. However, there was no evidence that eligibility criteria led to any bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Estimation of occupational exposure to BD was summarized by the authors and described in detail elsewhere (Macaluso et al., 2004 HEROID 646914). Estimates were developed by investigators blinded to outcomes. Quantitative estimates of 1,3-butadiene (BD) exposure were derived retrospectively based on job-exposure matrices (JEMs) that captured work areas and job tasks, along with historical information on changes in operations. This study analyzed cumulative estimates of occupational exposure to BD through 1991 using exposure quartiles and continuous variables. The median (IQR) cumulative BD exposure was 48 (11-167) ppm-years. This analysis did not examine associations with exposure intensity variables, which were highly correlated with cumulative exposure (Spearman r 0.86 for cumulative BD and number of high-intensity tasks). There were several potential limitations of exposure estimates. First, validity is uncertain because few objective measures were available for comparison with estimated concentrations. However, a limited evaluation of validity indicated that the 90% uncertainty intervals for JEM concentration estimates overlapped with ranges of reported measurements that were collected in select years (see Macaluso et al). Second, cumulative exposure was estimated using job histories through 1991, at which time 4,079 workers in the cohort remained actively employed. The authors stated that exposure concentrations were low for the 46% of these workers exposed to monomers at that time (1.1 ppm for BD). While the additional cumulative exposure among these workers is uncertain, Macaluso et al reported higher mean BD exposure intensities (range 4 to 720 ppm) for historical job task groups through 1990. Although the validity and precision of exposure estimates is uncertain, there was no evidence of important error or bias.

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Study Citation:	Sathiakumar, N., Bolaji, B. E., Brill, I., Chen, L., Tipre, M., Leader, M., Arora, T., Delzell, E. (2021). 1,3-Butadiene, styrene and lymphohaematopoietic cancers among North American synthetic rubber polymer workers: exposure-response analyses. Occupational and Environmental Medicine 78(12):859-868.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Mortality from all leukemia, leukemia subtypes (lymphoid leukemia, myeloid leukemia, acute myeloid leukemia (AML)).Mortality from non-Hodgkin's lymphoma (NHL), multiple myeloma, and all B-cell malignancies (includes lymphoid leukemia, NHL and multiple myeloma)., Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	10192219

Domain	Metric	Rating	Comments
Domain 3: Outcome Assessment			
	Metric 3A: Outcome Ascertainment	Medium	The outcomes analyzed in this study were mortality from all leukaemia, leukemia subtypes (lymphoid leukaemia, myeloid leukaemia, acute myeloid leukemia [AML]), non-Hodgkin's lymphoma (NHL), multiple myeloma and all B-cell malignancies (including lymphoid leukaemia, NHL and multiple myeloma). The authors notes that B-cell malignancy cases may have included a few T-cell neoplasms (NHL and lymphoid leukemias). Vital status through 2009 was ascertained for 99% of the cohort. Previous publications noted that outcomes were ascertained via linkage to sources including the National Death Index, the Social Security death master file, state motor vehicle records, and the Canadian Mortality Data Base maintained by Statistics Canada, using ICD codes to identify underlying and contributing causes of death (Sathiakumar et al 2021 HEROID 9038746). In a previous update, causes of death were validated based on medical records retrieved for more than 86% of leukemias, and over 80% for other selected outcomes. Diagnoses were confirmed for 100% of leukemias. At the end of follow up, the median time since hire was 40 years, the median age was 69 years, and 46% of the cohort was deceased. The use of reliable sources, lengthy follow up and select validation are strengths of this study. The analysis of mortality vs incidence was a potential limitation; some cancers analyzed can have relatively long survival. However, the length of follow-up was likely adequate for analyzing mortality in a majority of the cohort.
	Metric 3B: Selective Reporting	High	Study reported results described in methodology.
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Medium	Primary models were adjusted for age at hire, year of hire, race, sex, plant, and ever hourly status (an indicator related to socioeconomic status). Covariates were selected a priori and based on previous studies of the cohort. Supplementary models for leukemia also analyzed the association between cumulative BD exposure and outcomes stratified by the median (among leukemia cases) cumulative co-exposure to styrene (Spearman's r for BD and styrene >0.80 among decedents). The lack of information on lifestyle factors such as smoking habits was a potential limitation. However, there was no evidence of important residual confounding by such factors.
Domain 5: Analysis			

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Study Citation:	Sathiakumar, N., Bolaji, B. E., Brill, I., Chen, L., Tipre, M., Leader, M., Arora, T., Delzell, E. (2021). 1,3-Butadiene, styrene and lymphohaematopoietic cancers among North American synthetic rubber polymer workers: exposure-response analyses. Occupational and Environmental Medicine 78(12):859-868.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Mortality from all leukemia, leukemia subtypes (lymphoid leukemia, myeloid leukemia, acute myeloid leukemia (AML)).Mortality from non-Hodgkin's lymphoma (NHL), multiple myeloma, and all B-cell malignancies (includes lymphoid leukemia, NHL and multiple myeloma)., Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	10192219

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	Analysis methods were appropriate. Descriptive data were provided. Cox proportional hazards models were used to estimate relative risks with 95% confidence intervals. Exposure was modeled using quartiles of the exposure distribution among cases to analyze the shape of dose-response relationships, as well as using continuous exposure variables. Case counts were shown for all analyses. Dose-response patterns for leukemia were further analyzed using restricted cubic splines, which supported positive associations. To reduce the influence of potential exposure outliers or errors, sensitivity analyses with continuous exposure variables used "trimmed" BD exposure variables that excluded workers who were unexposed and/or above the 95th percentile of exposure. Additional sensitivity analyses found little meaningful impact of using reduced sets of covariates or including 10- or 20-year exposure lags. The authors also confirmed the absence of significant sex differences in associations. Minor potential limitations include that details on missing data were not discussed, and transformations to better approximate non-linearities were not explored. There was no evidence of important errors or deficiencies in the analysis approach.
	Metric 5B:	Sensitivity	Medium	The sample size of over 20,000 workers was large, follow up ranged from 18 to 66 years, and there was variability in exposure, with mean (SD) cumulative BD exposure of 187 (517) ppm-years. The number of cases was as follows: all leukemia n=132 (n=52, 67 and 41 for lymphoid, myeloid and AML, respectively); NHL n=110, multiple myeloma n=60, and all B-cell malignancies n=213. There was no indication of inadequate sensitivity.

Additional Comments: This study analyzed associations between exposure to 1,3-butadiene and risk of mortality from leukemia and other LHCs in a retrospective cohort of 21,087 male and female styrene-butadiene rubber workers employed between 1943 and 1991. In this follow-up through 2009, this study found significant associations between cumulative 1,3-butadiene exposure and risk of all leukemia and lymphoid leukemia; associations did not reach significance for other leukemia subtypes examined. Associations with NHL, multiple myeloma, and all B-cell malignancies were null and non-significant. Strengths included the large cohort size, lengthy follow-up, 99% vital status ascertainment, and appropriate analysis methods. Potential limitations include uncertain validity of exposure estimates, that analysis was limited to mortality outcomes, and the exclusion of male workers employed for less than one year. Given high turnover among short-term workers, this exclusion may have induced some health worker effect bias.

Overall Quality Determination Medium

Study Citation:	Sathiakumar, N., Bolaji, B., Brill, I., Chen, L., Tipre, M., Leader, M., Arora, T., Delzell, E. (2021). 1,3-Butadiene, styrene and selected outcomes among synthetic rubber polymer workers: Updated exposure-response analyses. Chemico-Biological Interactions 347:109600.
Health Outcome(s) Assessed:	Lung/Respiratory- lung cancer mortality, Cancer; Cancer/Carcinogenesis- lung cancer mortality, Cancer; Mortality- lung cancer mortality, Cancer; Renal/Kidney- kidney cancer mortality, Cancer; Cancer/Carcinogenesis- kidney cancer mortality, Cancer; Mortality- kidney cancer mortality, Cancer; Gastrointestinal- esophagus cancer mortality, Cancer; Cancer/Carcinogenesis- esophagus cancer mortality, Cancer; Mortality- esophagus cancer mortality, Cancer; Gastrointestinal- pancreas cancer mortality, Cancer; Cancer/Carcinogenesis- pancreas cancer mortality, Cancer; Mortality- pancreas cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	9038746

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	This occupational cohort study evaluated associations between cumulative exposure to 1,3-butadiene (and styrene) and a number of cancer- and respiratory-related mortality outcomes among synthetic rubber polymer workers.The larger cohort study of mortality was comprised of workers employed at eight North American synthetic rubber polymer plants, including 17,924 men classified as having worked, between 1943 and January 1, 1992, for at least one year and 4861 women classified as having worked for at least one day during the same time period at any of the plants. The updated cohort extended the follow up to 2009. The present study is restricted to the six plants for which quantitative butadiene and styrene monomer exposure estimates were developed. The present study included 16,579 men and 4508 women from the cohort. The complete inclusion/exclusion criteria for the cohort are not described in this article, but in previous studies (HERO IDs: 51490, 737525, 6592911, 51390) however some details are not presented. There is some concern regarding the ”healthy worker effect” among male participants as inclusion into the cohort required one year of employment which may impact sensitive populations, however this concern is not present among female participants as inclusion required one day of employment.
Domain 2: Exposure Characterization			

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Study Citation:	Sathiakumar, N., Bolaji, B., Brill, I., Chen, L., Tipre, M., Leader, M., Arora, T., Delzell, E. (2021). 1,3-Butadiene, styrene and selected outcomes among synthetic rubber polymer workers: Updated exposure-response analyses. Chemico-Biological Interactions 347:109600.
Health Outcome(s) Assessed:	Lung/Respiratory- lung cancer mortality, Cancer; Cancer/Carcinogenesis- lung cancer mortality, Cancer; Mortality- lung cancer mortality, Cancer; Renal/Kidney- kidney cancer mortality, Cancer; Cancer/Carcinogenesis- kidney cancer mortality, Cancer; Mortality- kidney cancer mortality, Cancer; Gastrointestinal- esophagus cancer mortality, Cancer; Cancer/Carcinogenesis- esophagus cancer mortality, Cancer; Mortality- esophagus cancer mortality, Cancer; Gastrointestinal- pancreas cancer mortality, Cancer; Cancer/Carcinogenesis- pancreas cancer mortality, Cancer; Mortality- pancreas cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	9038746

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Exposure estimates were developed from work histories, including "identifying for each plant-specific work area/job combination its component tasks that involved exposure and documenting historical changes in those tasks; calculating plant-, work area/job-, and time-specific average exposure indices (8-hour timeweighted average concentration in parts per million, ppm) and compiling these into job-exposure matrices (JEMs); and linking the time- and work area/job-specific exposure estimates in the JEMs with each employee's work history to obtain cumulative exposure estimates, as well as dates of first exposure to BD and styrene" (Sathiakumar et al., 2021).Historical estimation of exposure to 1,3-butadiene, styrene is detailed in another article (HERO ID: 646914). Briefly, researchers "conducted in-depth walk-through surveys of each plant, reviewed plant records, and carried out over 200 interviews of managers and long-term employees" (Macaluso et al., 2010; HERO ID: 646914) however "personnel records did not always characterize job assignments with precision" (Macaluso et al., 2010; HERO ID: 646914). Additional air sampling was done at one time point for a subset of jobs, and exposures were estimated over the entire study duration. An update of exposure estimates quantify the uncertainty with an average error margin of ±400% (median: ±100%).Exposure misclassification may exist but is not expected to greatly change the effect estimates.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Mortality data for all cancer-related outcomes were obtained for 99% of the cohort for the full study follow-up period (through 2009) "using information from the Social Security Administration, Pension Benefits Inc. and the National Death Index (NDI) for US workers and from the national Canadian Mortality Data Base (CMDB) for Canadian workers" (Sathiakumar et al., 2021). Though some uncertainty with respect to misclassification is inherent to vital certificates, it is not expected to greatly impact the effect estimate.
	Metric 3B:	Selective Reporting	Medium	Authors described the analyses in the methods section and presented results for all primary analyses and secondary analyses except for "reduced" models which were summarized in the text noting "the reduced models did not identify statistically significant results" (Sathiakumar et al., 2021).
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Models (using person-day records) adjusted for covariates associated with cancer-related mortality outcomes, and/or exposure to 1,3-butadiene and styrene: age at hire, year of hire, race, sex(except when analyzing men and women separately), plant and ever hourly status.Key confounders are considered appropriately, it is possible that residual confounding could explain part of the observed effect however concern is minimal.

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Study Citation:	Sathiakumar, N., Bolaji, B., Brill, I., Chen, L., Tipre, M., Leader, M., Arora, T., Delzell, E. (2021). 1,3-Butadiene, styrene and selected outcomes among synthetic rubber polymer workers: Updated exposure-response analyses. Chemico-Biological Interactions 347:109600.
Health Outcome(s) Assessed:	Lung/Respiratory- lung cancer mortality, Cancer; Cancer/Carcinogenesis- lung cancer mortality, Cancer; Mortality- lung cancer mortality, Cancer; Renal/Kidney- kidney cancer mortality, Cancer; Cancer/Carcinogenesis- kidney cancer mortality, Cancer; Mortality- kidney cancer mortality, Cancer; Gastrointestinal- esophagus cancer mortality, Cancer; Cancer/Carcinogenesis- esophagus cancer mortality, Cancer; Mortality- esophagus cancer mortality, Cancer; Gastrointestinal- pancreas cancer mortality, Cancer; Cancer/Carcinogenesis- pancreas cancer mortality, Cancer; Mortality- pancreas cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	9038746

Domain	Metric		Rating	Comments
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Authors conducted multivariable Cox regression to estimate hazard ratios and exposure-response trends, and reported effect estimates, confidence limits, and p-values. Descriptive information about outcome and exposure were provided. Sensitivity analyses were conducted to minimize differences in uncontrolled factors by excluding person-day records having zero cumulative exposure, as well as "to investigate the influence of data at extreme exposure values" by analyzing "exposure-response trends using "trimmed" data that excluded all unexposed person-time and all person-time with ppm-years values above the 95th percentile of the exposure distribution of outcome-specific decedents" (Sathiakumar et al., 2021).
	Metric 5B:	Sensitivity	Medium	This study provided a relatively large sample size, with a cohort spanning decades, which is appropriate given the expected latency of outcome development and the use of mortality measures. The estimated exposure range provides adequate variability.

Additional Comments: Overall, this occupational cohort study used a large cohort of synthetic rubber polymer workers to evaluate relationships between 1,3 butadiene and styrene and selected diseases. Notably, the study included a relatively robust analysis. Other than the limitations inherent to occupational cohort studies, the study did not have substantial flaws. Of the cancer mortality outcomes, "a consistent positive exposure-response relationship was evident only for bladder cancer" (Sathiakumar et al., 2021).

Overall Quality Determination Medium

Study Citation:	Sathiakumar, N., Bolaji, B., Brill, I., Chen, L., Tipre, M., Leader, M., Arora, T., Delzell, E. (2021). 1,3-Butadiene, styrene and selected outcomes among synthetic rubber polymer workers: Updated exposure-response analyses. Chemico-Biological Interactions 347:109600.
Health Outcome(s) Assessed:	Lung/Respiratory- Non-cancer respiratory mortality: nonmalignant respiratory disease (NMRD), chronic obstructive pulmonary disease (COPD) and pneumonia, Non-cancer; Mortality- Non-cancer respiratory mortality: nonmalignant respiratory disease (NMRD), chronic obstructive pulmonary disease (COPD) and pneumonia, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	9038746

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This occupational cohort study evaluated associations between cumulative exposure to 1,3-butadiene (and styrene) and a number of cancer- and respiratory-related mortality outcomes among synthetic rubber polymer workers.The larger cohort study of mortality was comprised of workers employed at eight North American synthetic rubber polymer plants, including 17,924 men classified as having worked, between 1943 and January 1, 1992, for at least one year and 4861 women classified as having worked for at least one day during the same time period at any of the plants. The updated cohort extended the follow up to 2009. The present study is restricted to the six plants for which quantitative butadiene and styrene monomer exposure estimates were developed. The present study included 16,579 men and 4508 women from the cohort. The complete inclusion/exclusion criteria for the cohort are not described in this article, but in previous studies (HERO IDs: 51490, 737525, 6592911, 51390) however some details are not presented. There is some concern regarding the ”healthy worker effect” among male participants as inclusion into the cohort required one year of employment which may impact sensitive populations, however this concern is not present among female participants as inclusion required one day of employment.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Exposure estimates were developed from work histories, including “identifying for each plant-specific work area/job combination its component tasks that involved exposure and documenting historical changes in those tasks; calculating plant-, work area/job-, and time-specific average exposure indices (8-hour timeweighted average concentration in parts per million, ppm) and compiling these into job-exposure matrices (JEMs); and linking the time- and work area/job-specific exposure estimates in the JEMs with each employee’s work history to obtain cumulative exposure estimates, as well as dates of first exposure to BD and styrene” (Sathiakumar et al., 2021).Historical estimation of exposure to 1,3-butadiene, styrene is detailed in another article (HERO ID: 646914). Briefly, researchers “conducted in-depth walk-through surveys of each plant, reviewed plant records, and carried out over 200 interviews of managers and long-term employees” (Macaluso et al., 2010; HERO ID: 646914) however ”personnel records did not always characterize job assignments with precision” (Macaluso et al., 2010; HERO ID: 646914). Additional air sampling was done at one time point for a subset of jobs, and exposures were estimated over the entire study duration. An update of exposure estimates quantify the uncertainty with an average error margin of ±400% (median: ±100%).Exposure misclassification may exist but is not expected to greatly change the effect estimates.
Domain 3: Outcome Assessment				

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Study Citation:	Sathiakumar, N., Bolaji, B., Brill, I., Chen, L., Tipre, M., Leader, M., Arora, T., Delzell, E. (2021). 1,3-Butadiene, styrene and selected outcomes among synthetic rubber polymer workers: Updated exposure-response analyses. Chemico-Biological Interactions 347:109600.
Health Outcome(s) Assessed:	Lung/Respiratory- Non-cancer respiratory mortality: nonmalignant respiratory disease (NMRD), chronic obstructive pulmonary disease (COPD) and pneumonia, Non-cancer; Mortality- Non-cancer respiratory mortality: nonmalignant respiratory disease (NMRD), chronic obstructive pulmonary disease (COPD) and pneumonia, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	9038746

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Mortality data for all cancer-related outcomes were obtained for 99% of the cohort for the full study follow-up period (through 2009) "using information from the Social Security Administration, Pension Benefits Inc. and the National Death Index (NDI) for US workers and from the national Canadian Mortality Data Base (CMDB) for Canadian workers" (Sathiakumar et al., 2021). Though some uncertainty with respect to misclassification is inherent to vital certificates, it is not expected to greatly impact the effect estimate.
	Metric 3B:	Selective Reporting	Medium	Authors described the analyses in the methods section and presented results for all primary analyses and secondary analyses except for "reduced" models which were summarized in the text noting "the reduced models did not identify statistically significant results" (Sathiakumar et al., 2021).
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Models (using person-day records) adjusted for covariates associated with cancer-related mortality outcomes, and/or exposure to 1,3-butadiene and styrene: age at hire, year of hire, race, sex(except when analyzing men and women separately), plant and ever hourly status.Key confounders are considered appropriately, it is possible that residual confounding could explain part of the observed effect however concern is minimal.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Authors conducted multivariable Cox regression to estimate hazard ratios and exposure-response trends, and reported effect estimates, confidence limits, and p-values. Descriptive information about outcome and exposure were provided. Sensitivity analyses were conducted to minimize differences in uncontrolled factors by excluding person-day records having zero cumulative exposure, as well as "to investigate the influence of data at extreme exposure values" by analyzing "exposure-response trends using "trimmed" data that excluded all unexposed person-time and all person-time with ppm-years values above the 95th percentile of the exposure distribution of outcome-specific decedents" (Sathiakumar et al., 2021).
	Metric 5B:	Sensitivity	Medium	This study provided a relatively large sample size, with a cohort spanning decades, which is appropriate given the expected latency of outcome development and the use of mortality measures. The estimated exposure range provides adequate variability.

Additional Comments: Overall, this occupational cohort study used a large cohort of synthetic rubber polymer workers to evaluate relationships between 1,3 butadiene and styrene and selected diseases. Notably, the study included a relatively robust analysis. Other than the limitations inherent to occupational cohort studies, the study did not have substantial flaws. Of the cancer mortality outcomes, "a consistent positive exposure-response relationship was evident only for bladder cancer" (Sathiakumar et al., 2021).

Overall Quality Determination — Medium

Study Citation:	Sathiakumar, N., Bolaji, B., Brill, I., Chen, L., Tipre, M., Leader, M., Arora, T., Delzell, E. (2021). 1,3-Butadiene, styrene and selected outcomes among synthetic rubber polymer workers: Updated exposure-response analyses. Chemico-Biological Interactions 347:109600.
Health Outcome(s) Assessed:	Renal/Kidney- bladder cancer mortality, Cancer; Cancer/Carcinogenesis- bladder cancer mortality, Cancer; Mortality- bladder cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	9038746

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This occupational cohort study evaluated associations between cumulative exposure to 1,3-butadiene (and styrene) and a number of cancer- and respiratory-related mortality outcomes among synthetic rubber polymer workers.The larger cohort study of mortality was comprised of workers employed at eight North American synthetic rubber polymer plants, including 17,924 men classified as having worked, between 1943 and January 1, 1992, for at least one year and 4861 women classified as having worked for at least one day during the same time period at any of the plants. The updated cohort extended the follow up to 2009. The present study is restricted to the six plants for which quantitative butadiene and styrene monomer exposure estimates were developed. The present study included 16,579 men and 4508 women from the cohort. The complete inclusion/exclusion criteria for the cohort are not described in this article, but in previous studies (HERO IDs: 51490, 737525, 6592911, 51390) however some details are not presented. There is some concern regarding the ”healthy worker effect” among male participants as inclusion into the cohort required one year of employment which may impact sensitive populations, however this concern is not present among female participants as inclusion required one day of employment.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Exposure estimates were developed from work histories, including “identifying for each plant-specific work area/job combination its component tasks that involved exposure and documenting historical changes in those tasks; calculating plant-, work area/job-, and time-specific average exposure indices (8-hour timeweighted average concentration in parts per million, ppm) and compiling these into job-exposure matrices (JEMs); and linking the time- and work area/job-specific exposure estimates in the JEMs with each employee’s work history to obtain cumulative exposure estimates, as well as dates of first exposure to BD and styrene” (Sathiakumar et al., 2021).Historical estimation of exposure to 1,3-butadiene, styrene is detailed in another article (HERO ID: 646914). Briefly, researchers “conducted in-depth walk-through surveys of each plant, reviewed plant records, and carried out over 200 interviews of managers and long-term employees” (Macaluso et al., 2010; HERO ID: 646914) however ”personnel records did not always characterize job assignments with precision” (Macaluso et al., 2010; HERO ID: 646914). Additional air sampling was done at one time point for a subset of jobs, and exposures were estimated over the entire study duration. An update of exposure estimates quantify the uncertainty with an average error margin of ±400% (median: ±100%).Exposure misclassification may exist but is not expected to greatly change the effect estimates.
Domain 3: Outcome Assessment				

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Study Citation:	Sathiakumar, N., Bolaji, B., Brill, I., Chen, L., Tipre, M., Leader, M., Arora, T., Delzell, E. (2021). 1,3-Butadiene, styrene and selected outcomes among synthetic rubber polymer workers: Updated exposure-response analyses. Chemico-Biological Interactions 347:109600.
Health Outcome(s) Assessed:	Renal/Kidney- bladder cancer mortality, Cancer; Cancer/Carcinogenesis- bladder cancer mortality, Cancer; Mortality- bladder cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	9038746

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Mortality data for all cancer-related outcomes were obtained for 99% of the cohort for the full study follow-up period (through 2009) “using information from the Social Security Administration, Pension Benefits Inc. and the National Death Index (NDI) for US workers and from the national Canadian Mortality Data Base (CMDB) for Canadian workers” (Sathiakumar et al., 2021). Though some uncertainty with respect to misclassification is inherent to vital certificates, it is not expected to greatly impact the effect estimate.
	Metric 3B:	Selective Reporting	Medium	Authors described the analyses in the methods section and presented results for all primary analyses and secondary analyses except for “reduced” models which were summarized in the text noting ”the reduced models did not identify statistically significant results” (Sathiakumar et al., 2021).
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Models (using person-day records) adjusted for covariates associated with cancer-related mortality outcomes, and/or exposure to 1,3-butadiene and styrene: age at hire, year of hire, race, sex(except when analyzing men and women separately), plant and ever hourly status.Key confounders are considered appropriately, it is possible that residual confounding could explain part of the observed effect however concern is minimal.
Domain 5: Analysis				
	Metric 5A:	Analysis	High	Authors conducted multivariable Cox regression to estimate hazard ratios and exposure-response trends, and reported effect estimates, confidence limits, and p-values. “For bladder cancer, we used restricted cubic spline (RCS) Cox regression models to further describe monomer exposure-response curves and to explore the possibility of nonlinear associations” (Sathiakumar et al., 2021).Descriptive information about outcome and exposure were provided. Sensitivity analyses were conducted to minimize differences in uncontrolled factors by excluding person-day records having zero cumulative exposure, as well as “to investigate the influence of data at extreme exposure values” by analyzing “exposure-response trends using “trimmed” data that excluded all unexposed person-time and all person-time with ppm-years values above the 95th percentile of the exposure distribution of outcome-specific decedents” (Sathiakumar et al., 2021).Additional sensitivity analyses were performed for bladder cancer only: including styrene co-exposure, underlying cause of death data only (as opposed to both underlying and contributing cause of death data), categorical variables for age at hire and year of hire, restricted to person-time 1960 and later (since there was no bladder cancer death before 1960), and withdrawing employees from follow up after 1991.
	Metric 5B:	Sensitivity	Medium	This study provided a relatively large sample size, with a cohort spanning decades, which is appropriate given the expected latency of outcome development and the use of mortality measures. The estimated exposure range provides adequate variability.

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Study Citation:	Sathiakumar, N., Bolaji, B., Brill, I., Chen, L., Tipre, M., Leader, M., Arora, T., Delzell, E. (2021). 1,3-Butadiene, styrene and selected outcomes among synthetic rubber polymer workers: Updated exposure-response analyses. Chemico-Biological Interactions 347:109600.
Health Outcome(s) Assessed:	Renal/Kidney- bladder cancer mortality, Cancer; Cancer/Carcinogenesis- bladder cancer mortality, Cancer; Mortality- bladder cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	9038746

Domain	Metric	Rating	Comments
Additional Comments:	Overall, this occupational cohort study used a large cohort of synthetic rubber polymer workers to evaluate relationships between 1,3 butadiene and styrene and selected diseases. Notably, the study included a relatively robust analysis for bladder cancer. Other than the limitations inherent to occupational cohort studies, the study did not have substantial flaws. Of the cancer mortality outcomes, “a consistent positive exposure-response relationship was evident only for bladder cancer” (Sathiakumar et al., 2021).		

Overall Quality Determination Medium

Study Citation:	Sathiakumar, N., Brill, I., Delzell, E. (2009). 1,3-butadiene, styrene and lung cancer among synthetic rubber industry workers. Journal of Occupational and Environmental Medicine 51(11):1326-1332.
Health Outcome(s) Assessed:	Lung/Respiratory- Lung cancer mortality, Cancer; Cancer/Carcinogenesis- Lung cancer mortality, Cancer; Mortality- Lung cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1600222

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	The study included 20,059 rubber industry workers (4101 women and 15,958 men) from a larger occupational cohort drawn from 8 facilities. The authors provide references to earlier manuscripts that describe how participants were selected. Previous studies indicated that the study included workers employed between 1943 and 1991(Delzell et al. 2006, HEROID 737525; Sathiakumar et al 2009 HEROID 1330953). This study analyzed mortality through 1998 for men and 2002 for women. The paper indicates that 1,697 workers from two factories were excluded because detailed work histories and historical exposure information were not available. The exclusion of workers from these factories could introduce selection bias if their exposure-outcome relationships were substantially different. The authors also indicate that 1,031 (410 women, 621 men) workers were excluded because they dropped out of mortality follow-up at ages younger than the youngest lung cancer decedent. The authors do not provide information to help assess the bias associated with loss to follow up. A prior paper indicated that male participants were excluded if they worked less than a year (Delzell et al. 2006, HEROID 737525). Selection bias associated with the exclusion of short-term workers (risk of healthy worker effect) is possible.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	The authors provide references to prior manuscripts that provide exposure assessment methods and summarize the methods in brief. Quantitative exposure estimates were assigned using a job-exposure matrix (JEM) that accounted for variation in exposure by plant location, work area/job group, and time periods of work. The JEM was used to estimate 8-hour time-weighted exposure based on job histories. The paper does not provide enough methodological detail to directly assess error or bias associated with exposure misclassifications. Validation of exposure estimates was not discussed. The authors do note the possibility of random misclassification of exposure for never hourly workers because their job assignments tended to be less specific than those of hourly workers.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Lung cancer mortality and vital status was ascertained through linkages with several national databases. Vital status ascertainment was about 97% complete for both women and men. Use of ICD codes or nosologist review was not mentioned. Lung cancer deaths were ascertained for 104 female and 551 male workers, including deaths where lung cancer was identified as the underlying or contributing cause of death. No information is provided about the exposures of participants lost to mortality follow-up. Mean years since hire were 31 years in men and 39-40 years in women; follow-up time for analyses of lung cancer mortality was likely adequate for a majority of the sample.

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Study Citation:	Sathiakumar, N., Brill, I., Delzell, E. (2009). 1,3-butadiene, styrene and lung cancer among synthetic rubber industry workers. Journal of Occupational and Environmental Medicine 51(11):1326-1332.
Health Outcome(s) Assessed:	Lung/Respiratory- Lung cancer mortality, Cancer; Cancer/Carcinogenesis- Lung cancer mortality, Cancer; Mortality- Lung cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1600222

Domain	Metric	Rating	Comments
	Metric 3B: Selective Reporting	Medium	The authors report their analysis plan in the methods section and provide justification for sensitivity analyses. Results are provided for all analyses described in the methods section.
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Medium	Models adjusted for age, year of birth, race, years since hire, plant and pay status (ever vs never hourly) and were stratified by gender. The influence of adjusting for styrene co-exposure was also examined. The authors provide information on the distribution of potential confounders in relation to lung cancer outcomes, and they provide justification for selecting the confounders to include in their models. One limitation of the paper is that the authors did not have access to smoking data, so residual confounding based on smoking is possible.
Domain 5: Analysis			
	Metric 5A: Analysis	Medium	Cox proportional hazard models were used to analyze associations between butadiene exposure and lung cancer. Effect estimates from models were presented as rate ratios or beta coefficients with measures of variability and p-values. Age was used as the time variable; the authors checked the proportional hazard assumption using age-exposure interaction terms. The paper compared multiple analytic approaches to estimate the robustness of associations between butadiene exposure lung cancer and explained the benefit of each approach, including sensitivity analyses. The comparative analyses included using BD as continuous untransformed, natural log transformed, and as deciles; analyzing ever vs never exposure among hourly and among never-hourly workers; incorporating exposure lags to exclude inadequate follow-up time; and evaluating the influence of using very low vs no exposure as the referent. The amount of missing data on exposures, and confounders is not presented in this paper, nor are any methods for imputing data.
	Metric 5B: Sensitivity	Medium	The duration and range of exposure levels of exposure in the study population was sufficient to examine the hypothesis. The authors accounted for lag time between exposure and outcome in sensitivity analyses. The overall sample size was large, and the study included 551 lung cancer deaths in men and 104 in women. The authors recognized that an apparent increased risk of lung cancer in some female subgroups may be due to small sample size, however case Ns were not provided for subgroup analyses.

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Study Citation:	Sathiakumar, N., Brill, I., Delzell, E. (2009). 1,3-butadiene, styrene and lung cancer among synthetic rubber industry workers. Journal of Occupational and Environmental Medicine 51(11):1326-1332.
Health Outcome(s) Assessed:	Lung/Respiratory- Lung cancer mortality, Cancer; Cancer/Carcinogenesis- Lung cancer mortality, Cancer; Mortality- Lung cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1600222

Domain	Metric	Rating	Comments
Additional Comments:	This study analyzed the association between occupational exposure to butadiene and lung cancer mortality in a cohort of 4101 women and 15,958 men employed at 8 styrene-butadiene rubber plants. Mean follow-up time was 31 years in men and 39-40 years in women; there were 551 lung cancer deaths in men and 104 in women. The authors conducted a series of analyses to evaluate the robustness of previous results in this cohort suggesting that butadiene exposure may be to be associated with lung cancer mortality among women; there were no associations observed in analyses of men, among whom exposures were higher. Inconsistencies in results did not persuasively support a causal association among women. There was no dose-response relationship using deciles or in analyses that excluded never-exposed women. Evidence of a relationship was limited to a significant increase in lung cancer mortality associated with ever vs. never exposure to butadiene among women that was most notable among hourly workers. The authors speculated that this association might be attributable to factors such as an unidentified exposure, confounding by smoking, or confounding by another unidentified variable.		

Overall Quality Determination Medium

Study Citation:	Sathiakumar, N., Brill, I., Leader, M., Delzell, E. (2015). 1,3-Butadiene, styrene and lymphohematopoietic cancer among male synthetic rubber industry workers–Preliminary exposure-response analyses. Chemico-Biological Interactions 241:40-49.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Leukemia mortality, Non-Hodgkin's Lymphoma mortality, Multiple Myeloma mortality, Cancer; Immune/Hematological- Leukemia mortality, Non-Hodgkin's Lymphoma mortality, Multiple Myeloma mortality, Cancer; Mortality- Leukemia mortality, Non-Hodgkin's Lymphoma mortality, Multiple Myeloma mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	4659248

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	This retrospective cohort study analyzed mortality patterns among 16,579 men employed before January 1, 1992, who had worked for at least one year at any of 6 synthetic rubber plants located in the US and Canada. The study included workers for whom detailed work histories were available. Details on exclusions based on work history information or employment duration were not included in this publication. Employment at these styrene-butadiene rubber (SBR) plants began as early as 1944, the mean year of hire was 1954 among cases and 1960 among non-cases. The study included mortality follow-up through 2009; previous studies of this cohort included follow-up through 1999. Vital status ascertainment was described as 99% complete at the time of this analysis. Loss to follow-up varied by outcome. Specifically, participants with unknown vital status were excluded from outcome-specific analyses if they were lost to follow-up at ages below the youngest age at which there was a known death from that outcome: 168 for leukemia (lost before age 32 years; 1% of the initial sample), 372 for non-Hodgkin's lymphoma (lost before age 41 years), and 1144 for multiple myeloma (lost before age 49 years; 6.7% of the initial sample). There was no evidence that attrition from analysis samples was biased. Having limited the study to men employed for at least one year is a concern: excluding short-term workers might induce a healthy worker effect bias as the most vulnerable workers may have had a high turnover. However, there was no direct evidence of such bias.
Domain 2: Exposure Characterization			

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Study Citation:	Sathiakumar, N., Brill, I., Leader, M., Delzell, E. (2015). 1,3-Butadiene, styrene and lymphohematopoietic cancer among male synthetic rubber industry workers–Preliminary exposure-response analyses. Chemico-Biological Interactions 241:40-49.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Leukemia mortality, Non-Hodgkin's Lymphoma mortality, Multiple Myeloma mortality, Cancer; Immune/Hematological- Leukemia mortality, Non-Hodgkin's Lymphoma mortality, Multiple Myeloma mortality, Cancer; Mortality- Leukemia mortality, Non-Hodgkin's Lymphoma mortality, Multiple Myeloma mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	4659248

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Cumulative exposure to 1,3-butadiene (BD) during employment was estimated based on job titles, tasks and work areas, which were characterized using detailed work histories. Estimates were calculated using a plant- and calendar-year specific job exposure matrix (JEM) developed with expert input as described elsewhere (Macaluso et al, HEROID 646914). There was insufficient industrial hygiene monitoring data to construct or validate BD estimates. However, in a limited validation at one of the 8 plants, "the correlation between estimated and measured BD ppm was moderate overall (Spearman's r=0.45)", with a higher correlation for a subset of high-exposure SBR-specific jobs (r=0.81). The validity of exposure estimates at all other plants was not evaluated. An additional source of error is that cumulative butadiene exposure was estimated through 1991: subsequent exposure among the 21% of participants still employed after that date was excluded. The authors stated that the impact of this limitation on cumulative exposure was likely small, given the lower exposure intensities after 1991. Despite limitations, there was no evidence of exposure misclassification that was differential, or of a magnitude that would notably change effect estimates. Reverse causation was not a concern: occupational butadiene exposure began well before the mortality outcomes analyzed in this study. The long follow-up also allowed for adequate latency: the mean duration from hire to mortality was 34-38 years among mortality subgroups and workers who were not cases. The examined the dose-response relationship using deciles of estimated exposure (defined based on distributions among cases for each analysis) as well as continuous variables.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	The outcomes analyzed in this study were mortality from leukemia (n=114), Non-Hodgkin's lymphoma (n=89), or multiple myeloma (n=48), identified as either an underlying or contributing cause of death. Cause of death information was identified from death certificates, the United States (US) National Death Index and the Canadian Mortality Data Base using data linkages. Other studies of this cohort mention the use of ICD codes to identify cause of death (e.g. Sathiakumar et al 2019, HEROID 6592911). Participants were employed in 1944-1991: with vital status ascertained through 2009, there was a period of about 18 to 65 years since hire to the end of follow-up, sufficient for an analysis of cancer mortality in the majority of the cohort. A limitation of this study, common to mortality studies, is the lack of data on the extent to which any prevalent health outcomes were included in the comparison group. It is uncertain whether or to what extent this limitation might have affected results.
	Metric 3B:	Selective Reporting	Medium	The authors described their primary and secondary analyses in the methods section and results were reported for all analyses in the manuscript or supplement. No concerns for selective reporting.
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Sathiakumar, N., Brill, I., Leader, M., Delzell, E. (2015). 1,3-Butadiene, styrene and lymphohematopoietic cancer among male synthetic rubber industry workers–Preliminary exposure-response analyses. Chemico-Biological Interactions 241:40-49.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Leukemia mortality, Non-Hodgkin's Lymphoma mortality, Multiple Myeloma mortality, Cancer; Immune/Hematological- Leukemia mortality, Non-Hodgkin's Lymphoma mortality, Multiple Myeloma mortality, Cancer; Mortality- Leukemia mortality, Non-Hodgkin's Lymphoma mortality, Multiple Myeloma mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	4659248

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	The authors examined potential confounding by age, race, plant (facility), years since hire (employment duration), year of birth, payroll status (ever vs never hourly), and year of initial hire. Confounders were examined independently and jointly; final models adjusted for year of birth, plant, race and age. Plant was included as a surrogate for unmeasured workforce characteristics. Criteria for determining which confounders to include in final models were not specified. Potential confounding by smoking history was not discussed. Co-exposure confounding by styrene was not examined: butadiene and styrene were highly correlated among leukemia decedents (Pearson's r = 0.90, p < 0.0001), and like butadiene, styrene exposure was associated with leukemia and with non-Hodgkin's lymphoma. Confounding is a concern, but there was no direct evidence of important residual bias.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Analysis methods were appropriate. Descriptive data presented distributions of key variables in cases and non-cases (e.g. BD and styrene exposure, age, race, years since hire). Cox regression was used to estimate the association between BD exposure and each outcome adjusting for age (used as the time variable), as well as adjusting for the final set of confounders. Associations were reported as relative risks or beta coefficients with 95% confidence intervals. Exposure and covariates were included as time-dependent variables. The authors compared results of analyses using alternative forms of the exposure variable to evaluate the pattern of dose-response. These included outcome-specific decile categories (i.e., based on distributions among cases), ordinal mean-scored deciles, continuous untransformed BD, and continuous BD variables with natural log, log-10, and square root transformations. Zero values were imputed as 1-ppm for transformations. Model fit was compared using Akaike's information criteria. The authors tested age-exposure interaction terms to assess the proportional hazards assumption. Sensitivity analyses to examine robustness included evaluating associations among men hired before vs after 1960 when there were important declines in exposure in the industry, as well as using a series of lagged exposure variables (5, 10, 15, 20 years) to exclude exposure occurring close in time to death. A minor concern is that the comparison group of non-cases included any diagnosed and still living cases along with decedents from other related cancers; however, the comparator group was large. There was no evidence of important error or bias in the analyses.
	Metric 5B:	Sensitivity	Medium	There was substantial variability in cumulative BD exposure: median (IQR) exposure was 124 (337.1) ppm-years in leukemia decedents and 54 (164.7) ppm-years in the remaining cohort. Despite the large N of more than 16,000 men, sensitivity is a concern due to the small number of cases, in particular for multiple myeloma (n=48) as well as for stratified analyses.

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Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Leukemia mortality, Non-Hodgkin's Lymphoma mortality, Multiple Myeloma mortality, Cancer; Immune/Hematological- Leukemia mortality, Non-Hodgkin's Lymphoma mortality, Multiple Myeloma mortality, Cancer; Mortality- Leukemia mortality, Non-Hodgkin's Lymphoma mortality, Multiple Myeloma mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	4659248

Domain	Metric	Rating	Comments
Additional Comments:	This retrospective occupational cohort study of more than 16,000 male workers at 6 styrene-butadiene rubber plants in the US and Canada analyzed the relationship between estimated butadiene exposure and mortality from three outcomes: leukemia (n=114), non-Hodgkin's lymphoma (n=89), and multiple myeloma (n=48). Cox models were used to analyze the association between job exposure matrix-estimated BD exposure and each outcome adjusted for age, race, plant, and year of birth. Results suggested that BD exposure was associated with leukemia using multiple functional forms of the exposure variable. Associations were not significant in the sample hired after 1960 when BD exposure levels were reduced, but this may be due in part to the smaller number (n=21) of leukemia decedents. Upper deciles of BD exposure were also associated with non-Hodgkin's lymphoma mortality, but the magnitude and significance declined in the highest decile. Associations between cumulative BD exposure and NHL did not reach significance using continuous variables. BD exposure was not significantly associated with myeloma in this study; sensitivity was likely lower for this outcome given the small number of myeloma deaths. Potential limitations include that it was only possible to evaluate BD exposure estimates against environmental measures at one facility during a limited period, that the study included only workers employed for at least one year (risk of healthy worker bias), that outcomes were limited to mortality (uncertain whether any prevalent cases were included as comparators), and that the number of cases for these rare outcomes was modest. Exposure accrued after 1991 in 21% of the cohort was excluded from exposure variables; however, exposure in this period was also accrued at low intensity. Residual confounding by smoking and by styrene co-exposure cannot be ruled out. Despite concerns, the study has important strengths including large sample size, lengthy follow-up, and extensive analyses; there was no direct evidence of important bias.		

Overall Quality Determination Medium

Study Citation:	Sathiakumar, N., Delzell, E. (2009). A follow-up study of mortality among women in the North American synthetic rubber industry. Journal of Occupational and Environmental Medicine 51(11):1314-1325.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- All cancers mortality, all benign neoplasm mortality, buccal cavity and pharynx cancer mortality, , esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality., Cancer; Mortality- Blood disorders mortality; mental disorders mortality; allergic, endocrine, metabolic, and nutritional disease combined mortality; nervous system disease mortality; circulatory disease mortality; non-malignant respiratory disease mortality; digestive disease mortality; genitourinary disease mortality; external causes mortality; other known and unknown causes mortality., Non-cancer; Mortality- All cancers mortality, all benign neoplasm mortality, buccal cavity and pharynx cancer mortality, , esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality., Cancer; Lung/Respiratory- Lung cancer mortality, Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality, Non-cancer; Immune/Hematological- Lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality., Cancer; Immune/Hematological- Blood disorders mortality., Non-cancer; Neurological/Behavioral- Brain cancer mortality., Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality., Non-cancer; Cardiovascular- Circulatory disease mortality., Non-cancer; Reproductive/Developmental- Breast cancer mortality, uterine cancer mortality, ovarian cancer mortality., Cancer; Reproductive/Developmental- Genitourinary disease mortality., Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality,., Cancer; Gastrointestinal- Allergic, endocrine, metabolic, and nutritional disease combined mortality, digestive disease mortality., Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality., Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease combined mortality., Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality., Cancer; Renal/Kidney- Genitourinary disease mortality., Non-cancer; External, other, and unknown causes- External causes mortality; other known and unknown causes mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1330953 Linked HERO ID(s): 1330953, 646914, 6592911

Domain	Metric	Rating	Comments
Domain 1: Study Participation			

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1330953 Linked HERO ID(s): 1330953, 646914, 6592911

Domain	Metric		Rating	Comments
	Metric 1A:	Participant Selection	Medium	Thie study (HEROID 1330953) analyzed the mortality experience of 4,863 women employed in 8 North American synthetic rubber manufacturing plants (4,498 white, 365 non-white) in the US (7 plants) and Canada. All women hired from start of operations (varying dates from 1943 to 1965) who worked for at least 1 day before 1991 (the close of cohort ascertainment in a companion cohort of male workers) were eligible, with mortality ascertainment follow-up through 2002. The median duration of employment through 1991 was 1.6 years. Particularly given the high turnover, including women regardless of work duration reduced the likelihood of healthy worker selection bias. 70% of women were aged 60 or older at the end of follow-up. The median follow-up since hire was 39 years, likely sufficient for analyses of cancer mortality. Attrition was low, with only 134 (3%) of women whose vital status was unknown. Although women hired after 1991 were not included, the 10-year follow-up of these employees is unlikely to have contributed importantly to mortality. There is no evidence to suggest potential selection bias. However, while the manuscript states that "the study included 4863 women who were employed for at least 1 day before the close of cohort ascertainment", it does not explicitly state that these 4863 women represented the total number of women employees.

Domain 2: Exposure Characterization

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Health Outcome(s) Assessed:	Cancer/Carcinogenesis- All cancers mortality, all benign neoplasm mortality, buccal cavity and pharynx cancer mortality, , esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality., Cancer; Mortality- Blood disorders mortality; mental disorders mortality; allergic, endocrine, metabolic, and nutritional disease combined mortality; nervous system disease mortality; circulatory disease mortality; non-malignant respiratory disease mortality; digestive disease mortality; genitourinary disease mortality; external causes mortality; other known and unknown causes mortality., Non-cancer; Mortality- All cancers mortality, all benign neoplasm mortality, buccal cavity and pharynx cancer mortality, , esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality., Cancer; Lung/Respiratory- Lung cancer mortality, Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality, Non-cancer; Immune/Hematological- Lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality., Cancer; Immune/Hematological- Blood disorders mortality., Non-cancer; Neurological/Behavioral- Brain cancer mortality., Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality., Non-cancer; Cardiovascular- Circulatory disease mortality., Non-cancer; Reproductive/Developmental- Breast cancer mortality, uterine cancer mortality, ovarian cancer mortality., Cancer; Reproductive/Developmental- Genitourinary disease mortality., Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality,., Cancer; Gastrointestinal- Allergic, endocrine, metabolic, and nutritional disease combined mortality, digestive disease mortality., Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality., Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease combined mortality., Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality., Cancer; Renal/Kidney- Genitourinary disease mortality., Non-cancer; External, other, and unknown causes- External causes mortality; other known and unknown causes mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1330953 Linked HERO ID(s): 1330953, 646914, 6592911

Domain	Metric	Rating	Comments
	Metric 2A: Exposure Measurement	Medium	Most analyses used qualitative characteristics related to exposure to evaluate mortality patterns; only associations with breast and lung cancer used quantitative estimates of cumulative BD exposure. Methods used to quantitatively estimate BD exposure were described in HEROID 5554378 (a TSCA report). Briefly, estimates were derived for 6 plants where work histories included sufficient details on job tasks and work areas. Time-weighted average BD exposure was estimated for different jobs based on calculations informed by factors such as job tasks, task durations, work area characteristics including air flow, equipment, distance from point sources, estimated leakage, and background estimates in various areas. Calculations were specific for each job process, work area, plant, and calendar year, taking historic changes into account. Estimates were not validated, and comparisons with the limited BD measures available were not described. These estimates were applied to within-cohort analyses relating exposure to two mortality outcomes: 5 categories of BD ppm-years were used for lung cancer, and 3 categories for breast cancer. In addition, SMRs were stratified by work area, and for ever-vs never-hourly workers, groups with varying probabilities of BD exposure. (i) Work area analyses. SMRs were stratified by work area: 34% of women [61% ever-hourly] had worked styrene-butadiene rubber (SBR) operations; 50% had worked in administration [2% ever-hourly], and 27% [34% ever-hourly] in residual operations (ex. general services, safety, design - uncertain BD exposure). (ii) Ever vs. never-hourly workers. Hourly workers were more likely to have had BD exposure.

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Study Citation:	Sathiakumar, N., Delzell, E. (2009). A follow-up study of mortality among women in the North American synthetic rubber industry. Journal of Occupational and Environmental Medicine 51(11):1314-1325.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- All cancers mortality, all benign neoplasm mortality, buccal cavity and pharynx cancer mortality, , esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality., Cancer; Mortality- Blood disorders mortality; mental disorders mortality; allergic, endocrine, metabolic, and nutritional disease combined mortality; nervous system disease mortality; circulatory disease mortality; non-malignant respiratory disease mortality; digestive disease mortality; genitourinary disease mortality; external causes mortality; other known and unknown causes mortality., Non-cancer; Mortality- All cancers mortality, all benign neoplasm mortality, buccal cavity and pharynx cancer mortality, , esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality., Cancer; Lung/Respiratory- Lung cancer mortality, Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality, Non-cancer; Immune/Hematological- Lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality., Cancer; Immune/Hematological- Blood disorders mortality., Non-cancer; Neurological/Behavioral- Brain cancer mortality., Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality., Non-cancer; Cardiovascular- Circulatory disease mortality., Non-cancer; Reproductive/Developmental- Breast cancer mortality, uterine cancer mortality, ovarian cancer mortality., Cancer; Reproductive/Developmental- Genitourinary disease mortality., Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality,., Cancer; Gastrointestinal- Allergic, endocrine, metabolic, and nutritional disease combined mortality, digestive disease mortality., Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality., Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease combined mortality., Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality., Cancer; Renal/Kidney- Genitourinary disease mortality., Non-cancer; External, other, and unknown causes- External causes mortality; other known and unknown causes mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1330953 Linked HERO ID(s): 1330953, 646914, 6592911

Domain	Metric		Rating	Comments
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Outcomes, defined by ICD codes, were obtained from linkages to death certificate data. Underlying contributing causes of death were independently coded by two nosologists in the US and provided by the Statistica Canada for the Ontario plant. Validation of death certificates vs. medical records was not mentioned. The median of 39 years of follow-up since first hire allowed for sufficient latency to analyze cancer mortality. Ascertainment of mortality status was high: vital status was not ascertained for only 3% of the sample (N=134 of 4,863 women). Case numbers were small for rare cancers of particular interest (e.g., N=10 leukemias).
	Metric 3B:	Selective Reporting	Low	Overall SMRs were calculated for 33 outcome variables. Stratified SMRs were presented for select outcomes; it is unclear how these were selected (text stated these "were limited to categories with at least 250 subjects and at least 50 deaths", but data were shown for bladder cancer n=8, and not for circulatory disease). Similarly, few SMRs were presented - and only in the text - comparing women with ever/never BD exposure. The rationale for this was unclear. Only breast and lung cancer were analyzed in within-cohort analyses using quantitative estimates of cumulative BD exposure; this decision was justified as based on limiting analyses to cancers with at least 10 exposed cases.
Domain 4: Potential Confounding / Variability Control				

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Study Citation: Sathiakumar, N., Delzell, E. (2009). A follow-up study of mortality among women in the North American synthetic rubber industry. Journal of Occupational and Environmental Medicine 51(11):1314-1325.

Health Outcome(s) Assessed: Cancer/Carcinogenesis- All cancers mortality, all benign neoplasm mortality, buccal cavity and pharynx cancer mortality, , esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality., Cancer; Mortality- Blood disorders mortality; mental disorders mortality; allergic, endocrine, metabolic, and nutritional disease combined mortality; nervous system disease mortality; circulatory disease mortality; non-malignant respiratory disease mortality; digestive disease mortality; genitourinary disease mortality; external causes mortality; other known and unknown causes mortality., Non-cancer; Mortality- All cancers mortality, all benign neoplasm mortality, buccal cavity and pharynx cancer mortality, , esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality., Cancer; Lung/Respiratory- Lung cancer mortality, Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality, Non-cancer; Immune/Hematological- Lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality., Cancer; Immune/Hematological- Blood disorders mortality., Non-cancer; Neurological/Behavioral- Brain cancer mortality., Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality., Non-cancer; Cardiovascular- Circulatory disease mortality., Non-cancer; Reproductive/Developmental- Breast cancer mortality, uterine cancer mortality, ovarian cancer mortality., Cancer; Reproductive/Developmental- Genitourinary disease mortality., Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality,., Cancer; Gastrointestinal- Allergic, endocrine, metabolic, and nutritional disease combined mortality, digestive disease mortality., Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality., Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease combined mortality., Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality., Cancer; Renal/Kidney- Genitourinary disease mortality., Non-cancer; External, other, and unknown causes- External causes mortality; other known and unknown causes mortality, Non-cancer

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 1330953 Linked HERO ID(s): 1330953, 646914, 6592911

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Standardized Mortality Ratios (SMRs) were estimated using standard methods accounting for age, sex and calendar period using appropriate referent populations. In addition, for lung cancer, the authors incorporated an indirect adjustment for smoking. However, there was no adjustment for co-exposures to both BD and styrene.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The authors used standard approaches to calculate SMRs, accounting for age, calendar year, race and place of residence. SMRs were presented showing both observed and expected cases and included 95% confidence intervals. SMRs were compared using state-specific vs. regional reference populations. For lung cancer, the authors estimated the potential impact of smoking on SMRs using a published method of indirect adjustment. Within-cohort analyses using Poisson regression to estimate associations between cumulative BD exposure and for the 2 selected cancers were adjusted for age, years since hire, and ever-hourly status. Results for most outcomes utilized SMRs, which are limited by the potential influence of healthy worker effect.
	Metric 5B:	Sensitivity	Medium	The sample included nearly 5,000 women with 181,831 person-years of follow-up. However, numbers of cases for many outcomes was small (<20), limiting statistical power.

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Health Outcome(s) Assessed:	Cancer/Carcinogenesis- All cancers mortality, all benign neoplasm mortality, buccal cavity and pharynx cancer mortality, , esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality., Cancer; Mortality- Blood disorders mortality; mental disorders mortality; allergic, endocrine, metabolic, and nutritional disease combined mortality; nervous system disease mortality; circulatory disease mortality; non-malignant respiratory disease mortality; digestive disease mortality; genitourinary disease mortality; external causes mortality; other known and unknown causes mortality., Non-cancer; Mortality- All cancers mortality, all benign neoplasm mortality, buccal cavity and pharynx cancer mortality, , esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality., Cancer; Lung/Respiratory- Lung cancer mortality, Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality, Non-cancer; Immune/Hematological- Lymphopoietic cancer mortality, non-Hodgkin's lymphoma mortality, Hodgkin's lymphoma mortality, leukemia mortality, multiple myeloma mortality., Cancer; Immune/Hematological- Blood disorders mortality., Non-cancer; Neurological/Behavioral- Brain cancer mortality., Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality., Non-cancer; Cardiovascular- Circulatory disease mortality., Non-cancer; Reproductive/Developmental- Breast cancer mortality, uterine cancer mortality, ovarian cancer mortality., Cancer; Reproductive/Developmental- Genitourinary disease mortality., Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality,., Cancer; Gastrointestinal- Allergic, endocrine, metabolic, and nutritional disease combined mortality, digestive disease mortality., Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality., Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease combined mortality., Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality., Cancer; Renal/Kidney- Genitourinary disease mortality., Non-cancer; External, other, and unknown causes- External causes mortality; other known and unknown causes mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1330953 Linked HERO ID(s): 1330953, 646914, 6592911

Domain	Metric	Rating	Comments
Additional Comments:	This study examined women employed at 8 North American styrene-butadiene rubber plants., primarily focused on examining cancers of lymphohematopoietic tissues, breast, and ovary. Strengths in this study include the minimal concern for selection bias due to their transparent description of methods and accounting for potential healthy worker survivor bias; however there is some concern for selective reporting due to a lack of clarity as to why certain results were presented while others were not. Significant relationships were only observed among ever-hourly workers for lung and bladder cancers.		

Overall Quality Determination Medium

Study Citation:	Sathiakumar, N., Tipre, M., Leader, M., Brill, I., Delzell, E. (2019). Mortality among men and women in the North American synthetic rubber industry, 1943 to 2009. Journal of Occupational and Environmental Medicine 61(11):887-897.
Health Outcome(s) Assessed:	Immune/Hematological- Leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, Cancer; Cancer/Carcinogenesis- All cancers mortality, benign neoplasms mortality, leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, other cancers mortality, Cancer; Mortality- All cancers mortality, benign neoplasms mortality. Leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, other cancer mortality, Cancer; Mortality- Blood disorders mortality; mental disorders mortality; allergic, endocrine, and metabolic disease combined mortality; nervous system disease mortality; circulatory disease mortality; non-malignant respiratory disease mortality; digestive disease mortality; genitourinary disease mortality; external causes mortality; other known and unknown causes mortality; all cause mortality, Non-cancer; Immune/Hematological- Blood disorders mortality; allergic, endocrine, and metabolic disease combined mortality, Non-cancer; Neurological/Behavioral- Brain cancer mortality, Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality, Non-cancer; Cardiovascular- Circulatory disease mortality, Non-cancer; Reproductive/Developmental- Prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, Cancer; Reproductive/Developmental- Genitourinary disease mortality, Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, Cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality, Non-cancer; Nutritional/Metabolic- Allergic, endocrine, and metabolic disease combined mortality, Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality, Cancer; Lung/Respiratory- Lung cancer mortality, Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality, Non-cancer; External causes, other causes, unknown causes, all cause mortality- External causes mortality, other causes mortality, unknown causes mortality, all cause mortality, Non-cancer; Hepatic/Liver- Liver cancer mortality, Cancer; Renal/Kidney- Genitourinary disease mortality, Non-cancer; Thyroid- Allergic, endocrine, and metabolic disease combined mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6592911 Linked HERO ID(s): 1330953, 646914, 6592911

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	HEROID 6592911 analyzed mortality patterns in 22,785 men (N=17,294) and women (N=4,861) employed at 8 synthetic rubber plants (7 in the US, 1 in Canada) at varying times between 1943 and 1991. Overall, 14,009 (66%) workers were classified as ever exposed to 1,3 butadiene (BD). Men were eligible for inclusion if employed for at least one year, women if employed for at least one day. Additional details were provided in HEROID 5554378 for men (hereafter original report) and in HEROID 1330953 for women. This study extended mortality follow-up to 2009 (previously through 1998 in men, 2002 in women). Median times since initial hire at this follow-up was 39 years in men and 44 years in women. Attrition was low, with only 286 subjects (1%) whose vital status was unknown (N=11,882 or 52% alive; 10,617 or 47% deceased). Healthy worker bias is a potential concern among men, whose eligibility was limited to workers employed for at least 1 year (the original report noted that there was high turnover at $<$ 1 year). Median employment duration through 1991 was 11.4 years in men, and 1.6 years in women.

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Study Citation:	Sathiakumar, N., Tipre, M., Leader, M., Brill, I., Delzell, E. (2019). Mortality among men and women in the North American synthetic rubber industry, 1943 to 2009. Journal of Occupational and Environmental Medicine 61(11):887-897.
Health Outcome(s) Assessed:	Immune/Hematological- Leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, Cancer; Cancer/Carcinogenesis- All cancers mortality, benign neoplasms mortality, leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, other cancers mortality, Cancer; Mortality- All cancers mortality, benign neoplasms mortality. Leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, other cancer mortality, Cancer; Mortality- Blood disorders mortality; mental disorders mortality; allergic, endocrine, and metabolic disease combined mortality; nervous system disease mortality; circulatory disease mortality; non-malignant respiratory disease mortality; digestive disease mortality; genitourinary disease mortality; external causes mortality; other known and unknown causes mortality; all cause mortality, Non-cancer; Immune/Hematological- Blood disorders mortality; allergic, endocrine, and metabolic disease combined mortality, Non-cancer; Neurological/Behavioral- Brain cancer mortality, Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality, Non-cancer; Cardiovascular- Circulatory disease mortality, Non-cancer; Reproductive/Developmental- Prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, Cancer; Reproductive/Developmental- Genitourinary disease mortality, Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, Cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality, Non-cancer; Nutritional/Metabolic- Allergic, endocrine, and metabolic disease combined mortality, Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality, Cancer; Lung/Respiratory- Lung cancer mortality, Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality, Non-cancer; External causes, other causes, unknown causes, all cause mortality- External causes mortality, other causes mortality, unknown causes mortality, all cause mortality, Non-cancer; Hepatic/Liver- Liver cancer mortality, Cancer; Renal/Kidney- Genitourinary disease mortality, Non-cancer; Thyroid- Allergic, endocrine, and metabolic disease combined mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6592911 Linked HERO ID(s): 1330953, 646914, 6592911

Domain	Metric	Rating	Comments
Domain 2: Exposure Characterization			

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Study Citation:	Sathiakumar, N., Tipre, M., Leader, M., Brill, I., Delzell, E. (2019). Mortality among men and women in the North American synthetic rubber industry, 1943 to 2009. Journal of Occupational and Environmental Medicine 61(11):887-897.
Health Outcome(s) Assessed:	Immune/Hematological- Leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, Cancer; Cancer/Carcinogenesis- All cancers mortality, benign neoplasms mortality, leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, other cancers mortality, Cancer; Mortality- All cancers mortality, benign neoplasms mortality. Leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, other cancer mortality, Cancer; Mortality- Blood disorders mortality; mental disorders mortality; allergic, endocrine, and metabolic disease combined mortality; nervous system disease mortality; circulatory disease mortality; non-malignant respiratory disease mortality; digestive disease mortality; genitourinary disease mortality; external causes mortality; other known and unknown causes mortality; all cause mortality, Non-cancer; Immune/Hematological- Blood disorders mortality; allergic, endocrine, and metabolic disease combined mortality, Non-cancer; Neurological/Behavioral- Brain cancer mortality, Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality, Non-cancer; Cardiovascular- Circulatory disease mortality, Non-cancer; Reproductive/Developmental- Prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, Cancer; Reproductive/Developmental- Genitourinary disease mortality, Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, Cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality, Non-cancer; Nutritional/Metabolic- Allergic, endocrine, and metabolic disease combined mortality, Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality, Cancer; Lung/Respiratory- Lung cancer mortality, Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality, Non-cancer; External causes, other causes, unknown causes, all cause mortality- External causes mortality, other causes mortality, unknown causes mortality, all cause mortality, Non-cancer; Hepatic/Liver- Liver cancer mortality, Cancer; Renal/Kidney- Genitourinary disease mortality, Non-cancer; Thyroid- Allergic, endocrine, and metabolic disease combined mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6592911 Linked HERO ID(s): 1330953, 646914, 6592911

Domain	Metric	Rating	Comments
	Metric 2A: Exposure Measurement	Medium	Qualitative and quantitative indicators of exposure are discussed separately. (A). Qualitative exposure evaluation. Analyses in this paper examined differences in mortality stratified by any vs no exposure to butadiene, as well as by duration worked ($<$ vs $\geq$ 10 years, an indicator related to accumulated exposure) and time since hire ($<$ vs $\geq$ 20 years). (B) Methods used to quantify BD. The paper presented distributions of estimated cumulative BD exposure at 6 plants with sufficient records to construct these estimates, as well as p-values from analyses relating cumulative BD exposure to some outcomes. BD estimates were calculated using a plant- and calendar-year specific job exposure matrix (JEM) that was updated as described in HEROID 646914. Briefly, estimates were improved with input from an industrial hygienist, a chemical engineer, and plant technical staff who provided new information and verified the validity of updated assumptions used to compute estimates. As before, job-group specific exposure estimates were estimated based on task activities and durations. For this update, exposure estimates were developed for new, more refined job tasks which were previously combined. Additional quantitative information was collected from each plant to refine estimation model inputs over previously more generalized assumptions (e.g., verification of work surface areas, improved estimates of vessel content in reactor areas, systematic review of all production and maintenance tasks during plant visits). In addition, as part of the update, the team collected 170 independent short-term air-speed measurements (22-36 per plant) to improve estimates of airflow at the physical locations where tasks were conducted. Finally, 90% uncertainty intervals were estimated for exposure for the first time. (C) Evaluation/validation of updated BD estimates. Macaluso et al (HEROID 646914) showed for estimates compared with quantitative BD measures for the first time. The refinements they used led to higher BD cumulative exposure estimates than those obtained

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6592911 Linked HERO ID(s): 1330953, 646914, 6592911

Domain	Metric		Rating	Comments
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Outcomes, defined by ICD codes, were obtained from linkages to death certificate data. Underlying contributing causes of death were coded by a nosologist in the US and provided by the Statistica Canada for the Ontario plant. Leukemia, an outcome of primary interest, was analyzed both overall and as subtypes (lymphoid, myeloid). Leukemia subtype information was missing for 33 of the 120 cases (subtypes available after 1968/69). The median of 40 years of follow-up since first hire allowed for sufficient latency to analyze cancer mortality. Ascertainment was high: vital status was not ascertained for only 1% of the sample (N=286). The sample of over 22,000 workers was large, and there were increases in case numbers with the extended follow-up (ex. 106 leukemia deaths in men vs. 71 previously). Nonetheless, numbers of cases were not large for some outcomes (ex. 33 lymphoid leukemia deaths).

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Health Outcome(s) Assessed:	Immune/Hematological- Leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, Cancer; Cancer/Carcinogenesis- All cancers mortality, benign neoplasms mortality, leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, other cancers mortality, Cancer; Mortality- All cancers mortality, benign neoplasms mortality. Leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, other cancer mortality, Cancer; Mortality- Blood disorders mortality; mental disorders mortality; allergic, endocrine, and metabolic disease combined mortality; nervous system disease mortality; circulatory disease mortality; non-malignant respiratory disease mortality; digestive disease mortality; genitourinary disease mortality; external causes mortality; other known and unknown causes mortality; all cause mortality, Non-cancer; Immune/Hematological- Blood disorders mortality; allergic, endocrine, and metabolic disease combined mortality, Non-cancer; Neurological/Behavioral- Brain cancer mortality, Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality, Non-cancer; Cardiovascular- Circulatory disease mortality, Non-cancer; Reproductive/Developmental- Prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, Cancer; Reproductive/Developmental- Genitourinary disease mortality, Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, Cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality, Non-cancer; Nutritional/Metabolic- Allergic, endocrine, and metabolic disease combined mortality, Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality, Cancer; Lung/Respiratory- Lung cancer mortality, Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality, Non-cancer; External causes, other causes, unknown causes, all cause mortality- External causes mortality, other causes mortality, unknown causes mortality, all cause mortality, Non-cancer; Hepatic/Liver- Liver cancer mortality, Cancer; Renal/Kidney- Genitourinary disease mortality, Non-cancer; Thyroid- Allergic, endocrine, and metabolic disease combined mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6592911 Linked HERO ID(s): 1330953, 646914, 6592911

Domain	Metric	Rating	Comments
	Metric 3B: Selective Reporting	Low	The authors reported SMRs were presented overall and stratified by select employment characteristics. The study presented descriptive data on estimated BD exposure that included medians with IQRs for decedents with different types of cancer. Rate ratios with 95 % CIs were shown for any vs. no exposure to BD. However, only p-values were shown for the exposure-response relationship between quantitative BD exposure and mortality outcomes.
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Medium	Standardized Mortality Ratios (SMRs) were estimated using standard methods accounting for age, sex and calendar period using appropriate referent populations. SMRs did not incorporate indirect adjustments for potential confounders such as smoking. Within-cohort regression rate ratios calculated using Cox regression adjusted for age at outcome, year and age at hire, race, sex, plant and ever-hourly status. Models did not adjust for co-exposure to styrene or other chemicals.
Domain 5: Analysis			

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Study Citation:	Sathiakumar, N., Tipre, M., Leader, M., Brill, I., Delzell, E. (2019). Mortality among men and women in the North American synthetic rubber industry, 1943 to 2009. Journal of Occupational and Environmental Medicine 61(11):887-897.
Health Outcome(s) Assessed:	Immune/Hematological- Leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, Cancer; Cancer/Carcinogenesis- All cancers mortality, benign neoplasms mortality, leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, other cancers mortality, Cancer; Mortality- All cancers mortality, benign neoplasms mortality. Leukemia (lymphoid, myeloid subtypes) mortality, multiple myeloma mortality, Hodgkin's lymphoma mortality, non-Hodgkin's lymphoma mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, lung cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, other cancer mortality, Cancer; Mortality- Blood disorders mortality; mental disorders mortality; allergic, endocrine, and metabolic disease combined mortality; nervous system disease mortality; circulatory disease mortality; non-malignant respiratory disease mortality; digestive disease mortality; genitourinary disease mortality; external causes mortality; other known and unknown causes mortality; all cause mortality, Non-cancer; Immune/Hematological- Blood disorders mortality; allergic, endocrine, and metabolic disease combined mortality, Non-cancer; Neurological/Behavioral- Brain cancer mortality, Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality, Non-cancer; Cardiovascular- Circulatory disease mortality, Non-cancer; Reproductive/Developmental- Prostate cancer mortality, breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, Cancer; Reproductive/Developmental- Genitourinary disease mortality, Non-cancer; Gastrointestinal- Buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, Cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality, Non-cancer; Nutritional/Metabolic- Allergic, endocrine, and metabolic disease combined mortality, Non-cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality, Cancer; Lung/Respiratory- Lung cancer mortality, Cancer; Lung/Respiratory- Non-malignant respiratory disease mortality, Non-cancer; External causes, other causes, unknown causes, all cause mortality- External causes mortality, other causes mortality, unknown causes mortality, all cause mortality, Non-cancer; Hepatic/Liver- Liver cancer mortality, Cancer; Renal/Kidney- Genitourinary disease mortality, Non-cancer; Thyroid- Allergic, endocrine, and metabolic disease combined mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6592911 Linked HERO ID(s): 1330953, 646914, 6592911

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Medium	The authors used standard approaches to calculate SMRs, accounting for age, calendar year, race and place of residence. SMRs were presented showing the number of observed cases and included 95% confidence intervals. The reference populations came from the areas where plants were located (Texas, Kentucky, Louisiana, Ontario). Within-cohort analyses used Cox proportional hazard models to estimate associations between cause-specific mortality outcomes and any/no BD exposure. In addition, p-values were also reported for exposure-response associations using continuous BD ppm-years; however, effect estimates for this dose-response relationship were not presented. Moreover, the authors did not specify how BD variables were included in the exposure-response models (e.g., transformations or categories) and did not discuss evaluating basic model assumptions such as linearity of dose-response. The validity of the p-values shown for the exposure-response analysis cannot be evaluated without that information.
	Metric 5B:	Sensitivity	Medium	The sample size was large (>22,000 workers) and included more than 10,000 deaths. Case numbers and ability to detect associations varied for specific cancers, with few cases - as expected - for rare outcomes such as specific leukemia subtypes.

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Chemical:	1,3-Butadiene- Parent compound
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Domain	Metric	Rating	Comments
Additional Comments:	This paper analyzed the mortality experience of more than 22,000 workers (17,924 men, 4,861 women at 8 synthetic rubber plants, extending follow-up through 2009. Overall, 66% were occupationally exposed to butadiene, predominantly among men (77% exposed vs 26% of women). Few women (30%) were ever employed as hourly workers, contrasting with men (84%). Estimated cumulative exposure was several-fold higher in men than in women (median 54 vs. 8 ppm-years). SMRs suggested an increase in leukemia mortality among ever-hourly workers employed for 10+ years and particularly among workers employed for 10+ years who also had 20+ years since hire. Median BD exposure was markedly higher among decedents with lymphoid leukemia (225 ppm-years) vs the cohort as a whole (48 ppm-years) or for other cancers (ex. bladder 91 ppm-years). Ever exposure to BD was also associated with lung cancer in women, but estimated median BD exposure among women with lung cancer was low (12 ppm-years, vs 81 ppm years in men, among whom there was no association: RRs [95% CI] 1.97 [1.33, 2.90] vs 0.93 [0.78, 1.11] in women vs men). Limitations include inability to adjust for smoking, the potential for healthy worker bias in men due to restricting eligibility to workers employed for at least one year, and limited case numbers for rare cancers such as leukemia subtypes. In addition, the authors provided no details of how within-cohort exposure-response models relating BD to mortality were specified and presented p-values but not rate ratios for those associations. The validity of those results is uncertain.In addition to the limitations noted above, an important concern is the uncertain validity of the quantitative BD exposure estimates (Macaluso et al. 2004, HEROID 646914). These estimates were validated against available historical data from the Canadian plant in 1977 (Sathiakumar et al 2007, HEROID 4142022). The validation study abstract suggested the revised estimates were adequately correlated with typical and well-defined tasks (Spearman's r=0.81), but correlations were lower for typical but poorly defined jobs (r=0.56) and for atypical though well-defined jobs (r=0.29). That study recommended incorporating uncertainty estimates in future research using these estimates. As shown in Macaluso et al, the JEM-derived exposure estimates used in this analysis were higher than the initial estimates included in a report for TSCA (HEROID 5554378): median cumulative BD exposure estimates increased from 15 to 71 ppm-years. QC notes: The exposure validation manuscript (HEROID 4142022) was not included in the cohort at the time of this assessment; that manuscript was not evaluated, but information in the abstract was briefly noted in the comments. According to a separate validation (HEROID 4142022), the mean BD concentration estimates were slightly lower than the mean of historic measurements in the Canadian plant (4.7 ppm vs 5.2 ppm). Uncertainty limits for BD exposure presented in 646914 were not applied in analyses included here. The quantitative dose-response analyses included in this manuscript were		

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6592911 Linked HERO ID(s): 1330953, 646914, 6592911

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation:	Sielken, (2007). Quantitative risk assessment of exposures to butadiene in European Union occupational settings based on the University of Alabama at Birmingham epidemiology study: acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Leukemia mortality, Cancer; Mortality- Leukemia mortality, Cancer; Immune/Hematological- Leukemia mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6544022

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Sielken et al 2001 HEROID 1942871 conducted secondary analyses based on findings of previous studies that analyzed a cohort of North American styrene-butadiene rubber workers. The aim was to evaluate the extent to which changing several model inputs and assumptions might affect risk assessment estimates relating 1,3-butadiene (BD) exposure and leukemia mortality. The authors provided few details on the study population, citing Delzell et al 1996 (HEROID 051390) and related reports in which the cohort was characterized in greater detail. The cohort included more than 15,000 male workers employed for at least one year between 1943 and 1991 at one of 8 facilities in the US and Canada. Vital status was evaluated through January 1, 1992; 5% of the sample was lost to follow-up. A large proportion of workers were excluded because they had been employed for less than one year, which could induce healthy worker bias (e.g., only 12,605 of 25,500 US workers met eligibility criteria), as well as due to insufficient detail in work records to determine BD exposure. Despite concerns, there was no direct evidence of selection bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Sielken et al 1942871 cited other reports and publications that described methods used to estimate BD exposure in this cohort but did not provide any details. One of the model input changes they evaluate is the use of revised estimates of BD exposure for this cohort developed by the University of Alabama research team (Macaluso et al. Final report submitted to the International Institute of Synthetic Rubber Producers, 2000 was cited, subsequently published as Macaluso et al. 2004, HEROID 646914). Both initial and updated BD exposure estimates were based on a job exposure matrix (JEM) developed based on expert opinion. The revision had little impact on exposure ranking, but estimates increased (e.g. median exposure 71 vs 15 ppm-years). Initial estimates were not compared with objective measures. Updated values were higher than limited NIOSH measurements collected at one plant, but there was suspicion of leakage during sample collection, and 90% uncertainty intervals overlapped with measures [e.g., NIOSH mean (range) vs JEM mean (90% CI) values of 3 (0-24) vs 5 (0-58) for laboratory technicians and 2 (0-24) v 13 (2-113) for tank farm operators]. Imprecision, uncertainty, and the limited ability to validate BD exposure estimates are concerns, but there was no evidence of bias.
Domain 3: Outcome Assessment				

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Study Citation:	Sielken, (2007). Quantitative risk assessment of exposures to butadiene in European Union occupational settings based on the University of Alabama at Birmingham epidemiology study: acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Leukemia mortality, Cancer; Mortality- Leukemia mortality, Cancer; Immune/Hematological- Leukemia mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6544022

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The authors analyzed leukemia mortality (n=59). Previous reports stated that cause of death was determined using data linkages to mortality databases, death certificate review, and ICD codes (Delzell et al 1996 (HEROID 051390). Mean follow-up was 25 years (Delzell et al 1996 051390). While there was limited follow-up for workers hired close to the 1991 eligibility cutoff date, there may have been adequate latency for leukemia development and mortality in workers employed before the median hire date of 1960.
	Metric 3B:	Selective Reporting	Medium	The authors described the results of their analyses briefly in the text. The summary descriptions made it difficult fully evaluate their methods and assumptions. The changes in model inputs and assumptions evaluated were selected to be limited to factors that would increase the level of BD exposure associated with adverse effects.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	Models were adjusted for age, calendar year, years since hire, and styrene co-exposure. Residual confounding, for example by smoking, is a potential limitation, but there is no direct evidence of bias.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	This paper estimated the impact of changing inputs to the risk assessment model for BD exposure and leukemia mortality. The methods, assumptions, and data used are described very briefly, undermining the ability of reviewers to evaluate the validity of results. Three changes were proposed by the American Chemistry Council (Chemical Manufacturer's Association); a fourth, revised estimates of exposure, was developed independently of knowledge of the hazard assessment, by the research team. The results of changes to these inputs, based on the authors' summary report of their calculations, is as follows: (i) assigning the population mean cumulative exposure of 370 ppm-years vs. the midpoint of 250 ppm-years to the relevant exposure category (result summary: rate ratio decreased by 22.5%); (ii) characterizing excess cancer risk for a 70-year vs. for an 85-year lifetime (result summary: cumulative risk is lower at younger ages); (iii) estimating the inhalation rate as 18 vs. 20 cubic meters per day (result summary: 10% decrease in cancer potency) and (iv) replacing the initial exposure estimates with revised values (result summary: cancer potency estimate changes from 0.0087 per ppm to 0.0036 per ppm, i.e. more than two-fold). The revised exposure estimates have been incorporated in analyses using data from this cohort since 2004. Based on the authors' report, the using the revised exposure estimates to estimate the effective concentration (EC) of BD corresponding to an extra 1% lifetime risk of leukemia led to an increase from 1.2 ppm to 2.8 ppm. Surprisingly, the impact of the other three changes was much more substantial,

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Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Leukemia mortality, Cancer; Mortality- Leukemia mortality, Cancer; Immune/Hematological- Leukemia mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6544022

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Low	Sample size was large and the number of overall leukemia cases (n=81) was adequate. Statistical power was likely limited for analyses of leukemia subtypes, for myeloid neoplasm mortality, for models limited to subsamples below particular exposure thresholds, and for models that included highly correlated variables.Death numbers of most subtypes of leukemia range from 1 to 3, and death numbers of lymphoid and myeloid are not shown. Concerns were raised about the sensitivity to detect associations for the outcome.

Additional Comments: None

Overall Quality Determination Low

Study Citation:	Sielken, R. L., Valdez-Flores, C. (2013). Quantitative risk assessment of exposures to butadiene in EU occupational settings based on the University of Alabama at Birmingham epidemiological study. Regulatory Toxicology and Pharmacology 65(2):214-225.
Health Outcome(s) Assessed:	Mortality- Leukemia mortality, chronic myelogenous leukemia [CML] mortality, chronic lymphocytic leukemia [CLL] mortality, acute myelogenous or monocytic leukemia [ALM] mortality, all lymphoid neoplasms mortality, and all myeloid neoplasms mortality, Cancer; Immune/Hematological- Leukemia mortality, chronic myelogenous leukemia [CML] mortality, chronic lymphocytic leukemia [CLL] mortality, acute myelogenous or monocytic leukemia [ALM] mortality, all lymphoid neoplasms mortality, and all myeloid neoplasms mortality, Cancer; Cancer/Carcinogenesis- Leukemia mortality, chronic myelogenous leukemia [CML] mortality, chronic lymphocytic leukemia [CLL] mortality, acute myelogenous or monocytic leukemia [ALM] mortality, all lymphoid neoplasms mortality, and all myeloid neoplasms mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1798799

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Sielken et al 2013 HEROID 6592911 and the related report 654402 analyze data a cohort of styrene-butadiene rubber workers. The cohort has been well characterized elsewhere. The authors provide few details characterizing the study population, referring to the version of the data used as the "2004 data", which they noted used updated exposure estimates from six plants in the United States and Canada and included 81 decedents with leukemia. Eligibility criteria and total sample size were not provided in this manuscript; elsewhere the data were described as including more than 16,000 men employed in SBR production activities, who had been employed for at least one year between 1943 and 1991 (e.g. Cheng et al 2007, HEROID 646899). The exclusion of short-term workers is a potential limitation, as this could potentially induce risk of healthy worker bias. As reported by Cheng et al, 2007 (who also analyzed 81 leukemia deaths) vital status was ascertained through 1998, allowing for 7 to 55 years of follow-up. Though details on the extent of attrition, completeness of mortality ascertainment, and any additional exclusions were not provided, there was no evidence of bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Methods used to estimate occupational exposure to butadiene in this cohort were not described in the manuscript or report but have been characterized elsewhere. Exposure to 1,3-butadiene (BD) was estimated based on individual work histories that were linked to a time period, task and work-area specific job exposure matrix (JEM) developed based on expert opinion. There was limited validation of the JEM data as few objective measures were available; data were not available for all time periods, tasks and work areas. Exposure misclassification is a concern due to these limitations. However, there is no evidence of differential error in the exposure estimates.
Domain 3: Outcome Assessment				

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Health Outcome(s) Assessed:	Mortality- Leukemia mortality, chronic myelogenous leukemia [CML] mortality, chronic lymphocytic leukemia [CLL] mortality, acute myelogenous or monocytic leukemia [ALM] mortality, all lymphoid neoplasms mortality, and all myeloid neoplasms mortality, Cancer; Immune/Hematological- Leukemia mortality, chronic myelogenous leukemia [CML] mortality, chronic lymphocytic leukemia [CLL] mortality, acute myelogenous or monocytic leukemia [ALM] mortality, all lymphoid neoplasms mortality, and all myeloid neoplasms mortality, Cancer; Cancer/Carcinogenesis- Leukemia mortality, chronic myelogenous leukemia [CML] mortality, chronic lymphocytic leukemia [CLL] mortality, acute myelogenous or monocytic leukemia [ALM] mortality, all lymphoid neoplasms mortality, and all myeloid neoplasms mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
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Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The authors analyzed mortality from all leukemia, three mutually exclusive subtypes of leukemia (chronic myelogenous leukemia [CML], chronic lymphocytic leukemia [CLL] and acute myelogenous or monocytic leukemia [ALM]), all lymphoid neoplasms, and all myeloid neoplasms. ICD codes and Ns were provided. Previous reports stated that cause of death was determined using data linkages to mortality databases and death certificates (e.g., HEROID 646899). Mean follow-up time among workers included in this specific analysis was not provided; the authors conducted a separate analysis of those with more than 40 years of follow-up since initial hire but did not provide the N of proportion included. The lack of information is a limitation. However, there was no evidence of bias.
	Metric 3B:	Selective Reporting	Medium	Results were presented or described for the primary analyses stated as aims. In some results tables, details were omitted such as the sample and case Ns, the slope for the primary BD exposure variable vs only the added exposure variable.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	Models adjusted for age. The authors also examined whether the fit of models associating cumulative ppm-years of estimated BD exposure with mortality outcomes was improved by three sets of covariates, only two of which seemed appropriate. The first set was of covariates were years since hire, calendar year, race, and plant/facility. The second set represented co-exposures: styrene cumulative ppm-years (overall and at levels above or below 50), and dimethyldithiocarbamate [DMDTC] cumulative exposure. Third, the authors adjusted cumulative BD ppm-years for other indicators of BD exposure: the cumulative count of BD high intensity tasks [HITS, tasks at intensities above 100 ppm], cumulative BD ppm-years at exposure intensities above 100 ppm, and cumulative BD ppm-years at intensities below 100 ppm. BD HITS was a count variable and thus not simply duplicative of cumulative BP ppm-years. The authors did not provide an adequate justification for why simultaneously including duplicative exposure variables in the same model would not result in overadjustment bias, i.e. potentially attenuate causal associations. Potential residual confounding by smoking is an additional limitation.
Domain 5: Analysis				

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Chemical:	1,3-Butadiene- Parent compound
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Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Low	Descriptive data were not provided. Models to estimate the association between BD and mortality outcomes were fit using Cox proportional hazards regression, with age as the time variable. The primary aim of this methodological manuscript was to evaluate how to maximize the validity and utility of models examining the relationship between BD exposure and cancer mortality. The authors pursued this aim principally by: (i) evaluating whether an additional covariate increased model log likelihood values over limiting predictors to age and the primary exposure variable, cumulative BD ppm-years, and (ii) examining the statistical significance of associations fit after limiting the sample to workers below decreasing thresholds of cumulative exposure. The authors also examined the influence of incorporating a single lag, a 40-year minimum since initial exposure. As previously noted, models frequently incorporated duplicative BD exposure measures. Nonetheless, correlations among these variables were not quantified, and the authors did not discuss evaluating important model assumptions such as collinearity/variance inflation, effect modification, or non-linearity in dose-response. Model fit assessments were based on a single criterion – log likelihood values. The authors did not provide sample sizes to confirm that they were comparing nested models (required for this approach to be appropriate) and did not justify the selection of using only one criterion vs. also considering other fit indicators (e.g. Akaike's Information criterion) or model fit approaches (e.g. incorporating multiple covariates). Moreover, the authors did not indicate how the number of cases available changed in different models, which would also affect statistical power. For models examining associations in the subsample below various exposure thresholds, the authors did not provide the number of cases that remained available, essential to evaluate statistical power and validity. These oversights and lack of transparency undermine the ability of the reader to assess the validity and utility of the comparisons being made. However, there was no direct evidence of bias. While the validity of comparisons across models to determine which iterations had the best fit are uncertain, there was no evidence that findings of individual models were not valid. The health outcome for this evaluation is mortality including the standardized mortality rate (SMR). The method did not describe the standard population used to calculate the SMR, the confounder factors, or the adjustment process.
	Metric 5B:	Sensitivity	Low	Sample size was large and the number of overall leukemia cases (n=81) was adequate. Statistical power was likely limited for analyses of leukemia subtypes, for myeloid neoplasm mortality, for models limited to subsamples below particular exposure thresholds, and for models that included highly correlated variables.Death numbers of most subtypes of leukemia range from 1 to 3, and death numbers of lymphoid and myeloid are not shown. Concerns were raised about the sensitivity to detect associations for the outcome.

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HERO ID:	1798799

Domain	Metric	Rating	Comments
Additional Comments:	This study analyzed the relationship between occupational butadiene exposure and cancer mortality outcomes using data from a cohort of workers at 6 North American styrene-butadiene rubber plants. The study included 81 leukemia (Ns 16 to 26 for subtypes), 120 lymphoid neoplasm, and 56 myeloid neoplasm deaths. The authors provided few details on the cohort and the sample used in their analyses, but the cohort has been well characterized elsewhere. The primary aims of the manuscript were to evaluate whether the association between cumulative BD exposure and mortality was improved by including additional covariates or persisted below decreasing thresholds of BD exposure. Limitations included: (i) not evaluating collinearity or discussing potential overadjustment bias despite simultaneously including duplicative measures of exposure in the same models and (ii) providing insufficient information to ensure the validity and utility of comparisons across models, such as whether models consistently included the same number of participants and an adequate number of cases. The validity of conclusions related to the best fitting model is thus uncertain. Nonetheless, consistently with other analyses of this cohort, results suggested that higher cumulative BD exposure was associated with leukemia mortality, and that exposures at intensities above 100 ppm were more strongly associated with leukemia than lower intensity exposures.		

Overall Quality Determination Low

Study Citation:	Sielken, R. L., Valdez-Flores, C. (2011). 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. Regulatory Toxicology and Pharmacology 60(3):332-341.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Total leukemia mortality, acute myelogenous leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, Cancer; Mortality- Total leukemia mortality, acute myelogenous leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, Cancer; Immune/Hematological- Total leukemia mortality, acute myelogenous leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1940484

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Participants included in analyses were comprised of participants from the 2004 data set of the University of Alabama at Birmingham (UAB) epidemiological study of North American male workers in the styrene-butadiene-rubber industry. There were two previous iterations of the UAB datasets, including a 1995 and 2000 data set. The 1995 dataset included 17,964 men who worked at eight plants, with 92% of participants having exposure history available for exposure-response modeling. The 2000 dataset expanded and implemented new exposure estimates developed over five years. The 2004 dataset used for this analysis included seven more years of follow-up, through 1998, and incorporated the exposure estimates from 2000. This cohort included 16,585 workers from six plants for whom exposure-response data were available. Other publications cited by the authors (Cheng et al. 2007, HEROID 646899) stated that vital status through 1998 was 97% complete and noted that the cohort was limited to men who had been employed for at least one year prior to January 1, 1992. This eligibility requirement may have induced some risk of healthy worker bias if turnover of short-term workers was high and related to early symptoms related to health effects susceptibility. However, there was no evidence of important bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Occupational exposure to 1,3-butadiene was estimated using a job exposure matrix (JEM) that was updated in the year 2000 (Macaluso et al, 2004 HEROID 646914). This paper analyzed cumulative exposure estimates for 1,3-butadiene which were estimated overall, as well as partitioned into exposures accumulated at intensities above vs. below 100 ppm. Exposure estimates were developed by a team of industry experts including hygienists, epidemiologists, and engineers. Among other changes, the updated exposure estimates (the 2004 dataset) included new job tasks and made exposure scenarios more specific by separating previously broad groups of tasks. The authors noted that while the relative ranking of exposures across workers remained relatively unchanged, ”the upper 50% of the distribution of task- and calendar-year-specific exposure estimates shifted upwards.” In the 2004 dataset, authors attempted to validate these exposure estimates against job- and calendar-year specific exposure measurements from 1977-1991 available for at the largest of the plants. The authors of the current publication reported that well-defined tasks had a correlation between estimates and measurements of 0.81 (not reported by Macaluso et al). Correlations for measures vs. estimates for less well-defined other tasks were not described. Some exposure misclassification is likely, as there were few historical measurements, and there was limited ability to validate estimates. However, there was no evidence of bias.

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Study Citation:	Sielken, R. L., Valdez-Flores, C. (2011). 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. Regulatory Toxicology and Pharmacology 60(3):332-341.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Total leukemia mortality, acute myelogenous leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, Cancer; Mortality- Total leukemia mortality, acute myelogenous leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, Cancer; Immune/Hematological- Total leukemia mortality, acute myelogenous leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1940484

Domain	Metric		Rating	Comments
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Vital status and cause of death were obtained via linkage to national databases. Leukemia diagnoses, the focus of this analysis, were pathologically confirmed based on a review of medical records (Delzell et al. 2006, HEROID 737525). For deaths in or after 1979, codes from the NDI-Plus were used, and ICD codes were used to classify deaths prior to 1979 with medical records review by a nosologist. Causes of death were reported with their associated International Classification of Diseases, 9th revision codes. This analysis included total leukemia, as well as three leukemia subtypes for which there was a sufficient number of decedents for analysis. These included acute myelogenous or monocytic leukemia (ICD9 205.0, 206.0), chronic lymphocytic leukemia (204.1), and chronic myelogenous leukemia (205.1). Overall, there were no major concerns about outcome misclassification, and a review of medical records to confirm cases identified with the outcome of interest lends confidence in the appropriate classification of relevant outcomes.
	Metric 3B:	Selective Reporting	Low	Reporting of results appears to have been somewhat selective. First, given that the methods and conclusions are based on model fit and dose-response relationships, it was a limitation that the authors mentioned results on this issue briefly in the discussion without further information: “The observed relationship between cumulative number of HITs and leukemia is not simple, smooth, or monotone.” Second, the authors compared model fit after adding three butadiene exposure measures shown to be highly correlated in the methods paper where they were estimated (Macaluso et al, 2004 HEROID 646914), but presented correlations for only one of these variables. The type of correlation (Pearson vs. Spearman) was not indicated, and it is unclear why the correlation reported by the authors was considerably lower than that provided in the methods paper on these estimates (0.29 vs 0.86). These oversights raise concerns regarding selective reporting.
Domain 4: Potential Confounding / Variability Control				

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1940484

Domain	Metric	Rating	Comments
	Metric 4A: Potential Confounding	Low	Covariates were included by a forward selection stepwise regression algorithm. Models were constrained to always include cumulative BD exposure; the algorithm identified additional variables that significantly improved model fit based on a likelihood ratio test. There were three types of candidate covariates. The first was non-exposure variables (years since hire, calendar year, race, plant). The second characterized co-exposures to styrene (STY) (overall ppm-years, ppm-years accumulated at higher and lower intensities, number of high-intensity tasks) and DMDTC (dimethyldithiocarbamate, in mg/cm-years). The third group was other BD exposure markers: frequency of high-intensity tasks (HITs), cumulative exposure accumulated at lower concentrations </= 100 ppm (ppm-years), and cumulative exposure accumulated at higher concentrations >100 ppm (ppm-years). The authors reported the correlation between BD HITS and cumulative total BD as R=0.29 (type of correlation not specified). In contrast, Macaluso et al, 2004 (HEROID 646914) reported Spearman correlations of 0.81 to 0.94 among total cumulative BD, BD peaks (i.e. HITS), and cumulative BD at concentrations <100 ppm. Overadjustment is a potential concern. An additional limitation is that the basis for including multiple correlated measures of BD was improved model fit, rather than reducing confounding bias of cumulative BD. However, there was no direct evidence that these adjustments resulted in biased estimates for cumulative BD.

Domain 5: Analysis

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Study Citation:	Sielken, R. L., Valdez-Flores, C. (2011). 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. Regulatory Toxicology and Pharmacology 60(3):332-341.
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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1940484

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Low	Cox regression models were utilized to estimate the association between cumulative butadiene in ppm-years and total leukemia, as well as leukemia subtypes. The focus of the analyses presented was to use p-values from log-likelihood tests to evaluate the potential contribution to overall model fit of adding a series of additional exposure variables to this baseline model including total cumulative butadiene. In addition to co-exposure variables for styrene and DMDTC, the added variables included butadiene accumulated at concentrations <= 100 ppm, butadiene accumulated at concentrations >100 ppm, and counts of the number of butadiene high intensity tasks. In addition to evaluating the influence of additional covariates, the authors compared associations with leukemia obtained using the full range of total cumulative BD exposure vs limiting the upper range to increasingly lower thresholds. Despite smaller case counts and person-years, and resulting reductions in statistical power, associations with total leukemia remained statistically significant through an upper range limit of up to 400 ppm-years. An important limitation is that despite an approach that made conclusions based solely on model fit, the authors did not present an adequate assessment of model assumptions. All models assumed a simple linear dose-response relationship, despite evidence noted in passing in the discussion that associations with one variable were not monotonic. Additional potentially important limitations to the analysis included the following: restricting the model tested to a single model form (Cox regression) without comparing alternatives; not evaluating collinearity these highly correlated variables; and not assessing the impact on fit of specifications that may improve ability to separate effects of highly correlated variables (e.g. adding product terms, using transformations of variables, or centering variables). Moreover, three of the measures examined for potential improvements in model fit represented cumulative exposure to the same chemical – butadiene - from the same sources at the same time. Yet the authors did not provide guidance on interpreting results that partitioned the effect of the same exposure across several variables. As noted by the authors, 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”. Without further analysis, it is not straightforward to determine whether the improvements in model fits suggested by the limited methods applied are meaningful.
	Metric 5B:	Sensitivity	Medium	The range of exposure levels presented in the study is appropriate, and the population was exposed to levels expected to have an effect. Outcome ascertainment was appropriate, and included only cases with adequate numbers for analysis. Tthere were no other concerns of pertaining to study sensitivity.

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Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1940484

Domain	Metric	Rating	Comments
Additional Comments:	This study re-analyzed the association between leukemia risk and cumulative occupational exposure to 1,3-butadiene in a large cohort of male North American styrene-butadiene rubber workers. A major goal of the analysis was to determine whether adding variables, including alternative measures of butadiene exposure, provided a better model for characterizing risk. The authors also examined whether associations between leukemia and cumulative BD exposure remained significant after adjusting for counts of BD high intensity tasks, at increasingly lower thresholds of cumulative exposure. Despite reduced case counts and person-years, associations with total leukemia remained statistically significant through a range restricted to <= 400 ppm-years of cumulative BD exposure. Limitations of the approach used include uncertainty about how to interpret and use findings from models that partitioned the effect of butadiene exposure across several variables, and the limited assessment of model assumptions, including collinearity and linearity. Interpreting the results of models that increasingly restricted the range of exposure analyzed with a focus on significance was also limited by the diminishing statistical power. Despite limitations in approach, the authors reported significant positive associations between BD exposure and both total leukemia and chronic lymphocytic leukemia.		

Overall Quality Determination Low

Study Citation:	Sielken, R. L., Valdez-Flores, C. (2001). Dose-response implications of the University of Alabama study of lymphohematopoietic cancer among workers exposed to 1,3-butadiene and styrene in the synthetic rubber industry. Chemico-Biological Interactions 135-136:637-651.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Leukemia mortality, Cancer; Mortality- Leukemia mortality, Cancer; Immune/Hematological- Leukemia mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1942871

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Sielken et al 2001 HEROID 1942871 conducted secondary analyses of the leukemia hazard associated with exposure to 1,3 butadiene (BD) based on findings in cohort of North American styrene-butadiene rubber workers. The aim was to evaluate the extent to which changing inputs and assumptions might affect risk assessment estimates. The authors provided few details on the study population, citing Delzell et al 1996 (HEROID 051390) and related reports in which the worker cohort was characterized. As described in those sources, the cohort included more than 15,000 male workers employed for at least one year between 1943 and 1991 at one of 8 facilities in the US and Canada. Vital status was evaluated through January 1, 1992; 5% of the sample was lost to follow-up. A large proportion of workers were excluded because they had been employed for less than one year, which could induce healthy worker bias (e.g., only 12,605 of 25,500 US workers met eligibility criteria), as well as due to insufficient detail in work records to determine BD exposure. The study does not specify the final number of participants included in this analysis, although this may be inferred in part from citations to previous publications. Despite concerns, there was no direct evidence of selection bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Sielken et al 1942871 cited sources that described methods used to estimate BD exposure in this cohort but did not provide any details. Briefly, exposure estimates were based on work histories and a job exposure matrix (JEM) that was developed based on expert opinion. The initial JEM was updated by the University of Alabama research team as described by Macaluso et al (Macaluso et al. Final report submitted to the International Institute of Synthetic Rubber Producers, 2000 cited, subsequently published as Macaluso et al. 2004, HEROID 646914). The updated estimates are one of the model input changes evaluated by Sielken et al 1942871. The revision had little impact on exposure ranking; however, updated estimates increased considerably vs. initial values (e.g. median ppm-years increased to 71 vs 15 ppm-years). Initial BD estimates were not evaluated against objective measures; the updated estimates were higher than a limited set of NIOSH measurements collected at one plant. However, there was suspicion of leakage during sample collection, and the 90% uncertainty intervals for the updated estimates overlapped with measured concentrations [e.g., NIOSH mean (range) vs JEM mean (90% CI) values were: 3 (0-24) vs 5 (0-58) for laboratory technicians and 2 (0-24) v 13 (2-113) for tank farm operators]. Imprecision, uncertainty, and the limited ability to validate the JEM estimates of BD exposure are concerns, but there was no evidence of bias.
Domain 3: Outcome Assessment				

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Study Citation:	Sielken, R. L., Valdez-Flores, C. (2001). Dose-response implications of the University of Alabama study of lymphohematopoietic cancer among workers exposed to 1,3-butadiene and styrene in the synthetic rubber industry. Chemico-Biological Interactions 135-136:637-651.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Leukemia mortality, Cancer; Mortality- Leukemia mortality, Cancer; Immune/Hematological- Leukemia mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1942871

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	This paper analyzed leukemia mortality (n=59). Previous publications on the cohort stated that cause of death was determined using data linkages to mortality databases, death certificate review, and ICD codes, and that the mean follow-up was 25 years (Delzell et al 1996, HEROID 051390). Latency time for leukemia development and mortality was likely adequate for a proportion of the sample, such as workers employed before the median hire date of 1960.
	Metric 3B:	Selective Reporting	Low	The manuscript evaluated the impact of selective changes to model inputs and assumptions. With the exception of updated exposure estimates, the changes examined were selected to increase the threshold of exposure characterized as associated with leukemia mortality. Inputs that would potentially lower the risk threshold were not discussed or examined (e.g. prevalent outcomes that were not yet decedents, undiagnosed outcomes). Effect estimates are presented without 95% confidence intervals or standard error.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	Models estimating the BD-leukemia mortality associations adjusted for age, calendar year, years since hire, and styrene co-exposure. Residual confounding by unmeasured variables such as smoking and other occupational exposures is a potential limitation.
Domain 5: Analysis				

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Study Citation:	Sielken, R. L., Valdez-Flores, C. (2001). Dose-response implications of the University of Alabama study of lymphohematopoietic cancer among workers exposed to 1,3-butadiene and styrene in the synthetic rubber industry. Chemico-Biological Interactions 135-136:637-651.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Leukemia mortality, Cancer; Mortality- Leukemia mortality, Cancer; Immune/Hematological- Leukemia mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	1942871

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Low	This paper estimated the impact of changing assumptions and inputs used in a risk assessment of leukemia mortality related to occupational BD exposure based on this cohort of workers. The methods employed by the authors are summarized very briefly, undermining the ability of reviewers to evaluate the validity of results. Three input changes were proposed by the American Chemistry Council (Chemical Manufacturer's Association); the fourth, revised estimates of BD exposure, was developed independently by the research team. The authors provided very limited detail to explain their calculations, but summarized the impact of input changes as follows: (i) estimating lifetime excess cancer risk for 70 years vs. for 85 years (summary: cumulative risk is lower at younger ages); (ii) estimating the inhalation rate as 18 vs. 20 cubic meters/day (summary: 10% decrease in cancer potency); and (iii) assigning the population mean vs. the midpoint for cumulative exposure categories (summary: using 370 vs. 250 ppm-years decreased the corresponding rate ratio by approximately 22.5%). For this last change, the authors did not specify why or whether this exposure category was relevant or representative, nor demonstrate changes across the entire exposure distribution. The impact of the 4th change, using revised exposure estimates, was that cancer potency estimates (beta coefficients) declined from 0.0087 per ppm to 0.0036 per ppm, i.e. more than two-fold. They reported that after the incorporating the updated exposure values, the estimated effective concentration (EC) of BD corresponding to an extra 1% lifetime risk of leukemia increased from 1.2 ppm to 2.8 ppm. In contrast to the relatively minor impact of the more than three-fold change in estimated exposure, the authors stated that implementing the other three input changes further increased the effective concentration estimate 5.4-fold, from 2.8 to 15.1 ppm. There was insufficient detail provided in the manuscript to determine the validity of applying these seemingly minor changes in assumptions in the manner proposed by the authors, given the magnitude of impact. In addition, the authors present most of their summary calculations without providing estimates of variability such as confidence intervals or standard errors.
	Metric 5B:	Sensitivity	Medium	The analyses of the cohort for which results were shown included more than 234,000 person-years of follow-up and 59 cases of leukemia. There was no evidence of inadequate sensitivity.

Additional Comments: The authors present a secondary analysis of data from a cohort of North American male styrene-butadiene rubber workers used in a risk assessment relating butadiene exposure to leukemia mortality. Calculations in which model inputs such as inhalation rates and the number of years considered to comprise "lifetime" risk were changed were summarized by the authors. However, there was insufficient detail provided to assess the utility or validity of the proposed input changes as implemented.

Overall Quality Determination Low

Study Citation:	Symanski, E., Lewis, Tee, P. G., Chen, T. Y., Chan, W., Lai, D., Ma, X. (2016). Air toxics and early childhood acute lymphocytic leukemia in Texas, a population based case control study. Environmental Health: A Global Access Science Source 15(1):70.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Acute Lymphocytic Leukemia, Cancer; Immune/Hematological- Acute Lymphocytic Leukemia, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	3358047

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	Incident cases of acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML) diagnosed among children under the age of 5 years between January 1, 1995 and October 31, 2011 were obtained from the Texas Cancer Registry. The study included cases with Texas birth records. Controls were sampled from Texas vital statistics birth records from 1991 to 2009 using a 10:1 ratio and were matched to cases on birth year and month. From a total of 1,741 leukemia cases and 17,410 population-based controls, the study excluded 2,025 records with missing geocoding address data, 428 non-singleton births and 119 infants with birth defects identified in the Texas birth defects registry. The authors stated that 16,579 children remained after applying these exclusion criteria. AML cases (n=170) were excluded due to limited statistical power. The final sample was restricted to 1,248 ALL cases and 12,172 matched controls. Inclusion and exclusion criteria for participants were specified, unlikely to induce bias, and rates of those excluded were reported. The health of controls was not discussed other than the absence of birth defects; the authors did not explicitly mention excluding controls with other childhood diseases potentially related to butadiene exposure. However, there was no evidence that comparison group selection induced any bias.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Exposure to 1,3-butadiene during pregnancy was assigned by linkage of geocoded maternal addresses at delivery using census-tract level modeled estimates from the U.S. EPA National-Scale Air Toxics Assessment (NATA). Model validity for 1,3-butadiene was not discussed. Estimates use data from the National Toxic Inventory of hazardous air pollutants from major point sources, area levels, monitoring data, and emissions as inputs, accounting for factors such as the rate and location of release, wind speed and direction. Estimates of 1,3-butadiene were available for four years during the relevant window: 1996, 1999, 2002 and 2005. Geocoded addresses were linked for batches of birth years as follows: 1991-1997 births to 1996 data, 1998-2000 births to 1999 data, 2001-2003 to 2002 data, and 2004-2011 to 2005 data. 1,3-butadiene exposure was analyzed as year-specific quartiles. Sources of error include using spatial variation (e.g., use of census tract level modeling as an estimate of personal exposure) as well as temporal variation (data were available for limited years, seasonal variation was not discussed). However, while exposure estimates are likely imprecise, there was no evidence of differential misclassification of estimated exposure.
Domain 3: Outcome Assessment				

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Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Acute Lymphocytic Leukemia, Cancer; Immune/Hematological- Acute Lymphocytic Leukemia, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	3358047

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Cases of ALL diagnosed before the age of 5 years were identified using the SEER recode of the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) updated by the WHO (2/9/2001) to define relevant histology types. ALL cases included codes 9826 and 9835–9837. The authors did not mention excluding controls diagnosed with other childhood cancers (e.g. lymphomas). However, there was no direct evidence, or of inadequate sensitivity or specificity of case ascertainment.
	Metric 3B:	Selective Reporting	Medium	The authors described their primary and sensitivity analyses in the methods section. Results were reported for all primary analyses and described for sensitivity analyses.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Maternal and infant characteristics abstracted from birth certificates were evaluated as potential confounders. Criteria for including covariates were a change in estimate of 10% in a minimally adjusted model, or $p<0.05$ in a backward selection model. Minimally adjusted models that included matching variables (birth year and month) and census tract; final models further adjusted for maternal age, maternal race/ethnicity, infant birth weight, and infant gender. Co-pollutant confounding was evaluated by additionally adjusting for other air toxics (benzene and polycyclic organic matter). Other covariates considered included maternal smoking in pregnancy, maternal education, marital status, census tract poverty level, preterm birth, and timing of prenatal care initiation. were compared to models with additional adjustments. There was no evidence of important residual confounding bias.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Associations were estimated using mixed effects logistic regression models with census tract as a random effect. Dose response was evaluated by analyzing exposure quartiles. However, the distribution of cases across exposure quartiles was not shown. Quantitative results were presented including effect estimates and confidence limits. Population characteristics were described; exposure distributions were presented graphically. A few observations with missing values (n=6) were excluded from analysis. Some co-pollutants were highly correlated (e.g. benzene and 1,3-butadiene Spearman's rho=0.81). However, diagnostics such as variance inflation factors did not indicate problematic collinearity. Potential exponential spatial correlation was also examined using an alternative error structure. To address the limited availability of exposure data, a sensitivity analysis restricted the study population to births within a year of the NATA estimates. Potential effect modification (e.g. by infant gender, poverty level) was not discussed. The distribution of 1,3-butadiene varied by year; a figure indicated that medians were on the order of about 0.06, 0.13, 0.07 and 0.05 ug/m3 in 1996, 1999, 2002 and 2005. The authors did not discuss whether or how temporal changes in quartile cutoffs were taken into account (e.g. testing exposure x year interaction terms). Despite concerns, there was no direct evidence of important error or bias in data analysis methods.

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Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Acute Lymphocytic Leukemia, Cancer; Immune/Hematological- Acute Lymphocytic Leukemia, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	3358047

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	Sample size was large, and there was variability in 1,3-butadiene exposure. Distributions among controls suggested exposure was spatially auto-correlated, but supplementary models suggested that this issue did not meaningfully influence results. There was no evidence of inadequate sensitivity.

Additional Comments: This case-control study (1,248 cases; 12,172 controls) analyzed the relationship between estimated ambient outdoor exposure to 1,3-butadiene and acute lymphocytic leukemia (ALL) diagnosed in children aged <5 years. Cases in the Texas cancer registry diagnosed in 1995 to 2011 were matched to controls identified from Texas birth certificates by birth year and month. Children included were born between 1991 and 2011. Exposure during pregnancy was estimated based on maternal address at delivery and census tract EPA National-Scale Air Toxics Assessment (NATA) estimates available for 1996, 1999, 2002 and 2005. Estimates available for 1,3 butadiene were available for very few years, and misclassification of personal exposure is a potentially important concern. In adjusted single pollutant models, the author's reported an odds ratio of 1.28 (95% CI 1.08-1.52) for the association between the highest vs. lowest quartile of 1,3-butadiene and childhood ALL. In co-pollutant models, after adjusting for benzene, though not after adjusting for polycyclic organic matter (POM), associations with 1,3-butadiene remained significant. Data analysis used exposure variables defined using quartiles for each year of NATA data; there were substantial changes in levels of exposure over time. Another potential concern is that quantitative differences in levels of exposure within these quartiles were not taken into account: effect estimates appear to pool associations with exposure ranked as low, medium, medium-high, and high, regardless of temporal shifts. Despite several concerns, there was no evidence of bias that would differentially misclassify exposure, potentially resulting in inflated effect estimates.

Overall Quality Determination Medium

Study Citation:	UAB, (1995). Initial submission: Letter from intl inst syn rubber prod to USEPA RE prelim results in cohort mortality study of employees of 8 styrene butadiene rubber plants, dated 05/19/95.
Health Outcome(s) Assessed:	Gastrointestinal- Buccal cavity and pharynx cancer mortality, Digestive organs cancer mortality, esophagus cancer mortality, stomach cancer mortality, large intestine cancer mortality, rectum cancer mortality, pancreas cancer mortality, Cancer; Hepatic/Liver- Liver cancer mortality, Cancer; Cancer/Carcinogenesis- All cancer mortality, buccal cavity and pharynx cancer mortality, digestive organs cancer mortality, esophagus cancer mortality, stomach cancer mortality, large intestine cancer mortality, rectum cancer mortality, liver cancer mortality, pancreas cancer mortality, larynx cancer mortality, lung cancer mortality, skin cancer mortality, prostate cancer mortality, bladder cancer mortality, kidney cancer mortality, central nervous system cancer mortality, lymphopoietic system cancer mortality, lymphosarcoma mortality, Hodgkin's disease mortality, other lymphatic tissue cancer mortality, other cancer mortality, Cancer; Mortality- Allergic; endocrine; metabolic; nutritional diseases mortality, mental;psychoneurotic; and personality disorders mortality, blood diseases mortality, nervous system diseases mortality, circulatory diseases mortality, respiratory diseases mortality, digestive disease mortality, genitourinary diseases mortality, external causes mortality, other specified causes mortality, unknown cause mortality, Non-cancer; Lung/Respiratory- Lung cancer mortality, larynx cancer mortality, Cancer; Neurological/Behavioral- Central nervous system cancer mortality, Cancer; Reproductive/Developmental- Prostate cancer mortality, Cancer; Skin/Connective Tissue- Skin cancer mortality, Cancer; Renal/Kidney- Kidney cancer mortality, bladder cancer mortality, Cancer; Immune/Hematological- Lymphopoietic system cancer mortality, lymphosarcoma mortality, Hodgkin's disease mortality, leukemia mortality, other lymphatic tissue cancer mortality, Cancer; Benign neoplasms- Benign neoplasm mortality, Cancer; Immune/Hematological- Allergic, endocrine, metabolic, nutritional disease mortality, Non-cancer; Neurological/Behavioral- Mental, psychoneurotic, and personality disorders mortality, nervous system diseases mortality, Non-cancer; Immune/Hematological- Blood diseases mortality, Non-cancer; Cardiovascular- Circulatory disease mortality, Non-cancer; Lung/Respiratory- Respiratory diseases mortality, Non-cancer; Gastrointestinal- Digestive diseases mortality, Non-cancer; Renal/Kidney- Genitourinary diseases mortality, Non-cancer; Immune/Hematological- Leukemia mortality, chronic lymphocytic leukemia mortality, chronic myelogenous leukemia mortality, acute myelogenous leukemia mortality, acute unspecified leukemia, Cancer; Cancer/Carcinogenesis- Leukemia mortality, chronic lymphocytic leukemia mortality, chronic myelogenous leukemia mortality, acute myelogenous leukemia mortality, acute unspecified leukemia, Cancer; Mortality- Leukemia mortality, chronic lymphocytic leukemia mortality, chronic myelogenous leukemia mortality, acute myelogenous leukemia mortality, acute unspecified leukemia, Cancer; Mortality- All cancer mortality, buccal cavity and pharynx cancer mortality, digestive organs cancer mortality, esophagus cancer mortality, stomach cancer mortality, large intestine cancer mortality, rectum cancer mortality, liver cancer mortality, pancreas cancer mortality, larynx cancer mortality, lung cancer mortality, skin cancer mortality, prostate cancer mortality, bladder cancer mortality, kidney cancer mortality, central nervous system cancer mortality, lymphopoietic system cancer mortality, lymphosarcoma mortality, Hodgkin's disease mortality, other lymphatic tissue cancer mortality, other cancer mortality, Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5665016

Domain	Metric	Rating	Comments
Domain 1: Study Participation			

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Domain	Metric	Rating	Comments
	Metric 1A: Participant Selection	Medium	This retrospective follow-up study examined synthetic rubber workers employed at eight plants in North America, and participation was restricted to male employees. Inclusion criteria required that workers be employed for at least one year before the closing date of the study, which was January 1, 1992. Some additional eligibility requirements were implemented for several of the plants. For plant 1, participants were required to have been employed in 1950 or later. For plant 2, participants were required to be actively employed or retired and alive in 1960 or later, as the earliest date for beginning follow-up for these individuals was January 1, 1960. For plant 6, members included in the cohort were required to have been employed in 1965 or later for appropriate identification. Finally, individuals from plant 8 involved in the mortality study were required to be employed in 1950 or later, and participants in the cancer incidence study were required to be employed in 1965 or later. It is important to note that some participants from these plants have been previously examined in studies performed by NIOSH and Johns Hopkin's University, and the authors of this analysis were unable to determine the number of subjects included in the other investigations. Personnel records were examined to confirm inclusion from the various plants, and the number of personnel was identified for each plant throughout the methods section. The authors report that many of the ineligible participants were excluded due to working for less than one year. Overall, the methods described for participant selection were appropriate. The primary concern is risk of healthy worker selection bias due to restricting eligibility to men employed for at least one year. Overall, it cannot be ascertained to what extent excluded workers may have differed from those included in terms of 1,3 butadiene exposure and cancer mortal-

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Domain	Metric	Rating	Comments
Domain 2: Exposure Characterization			

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Domain	Metric	Rating	Comments
	Metric 2A: Exposure Measurement	Medium	Exposure assessment was performed through the creation of a JEM. Work history data was obtained from personnel records, and complete work histories were reportedly available for approximately 97% of the cohort. Some participants had limited information on jobs, with authors only able to identify first or last jobs held in several of the plants. These work histories were then used to develop five process groups and 7 process subgroups (except for plants 3 and 6, which did not have specific work areas recorded). The authors then developed retrospective estimates of exposure to butadiene for subjects from plants 1, 2, 4, 5, 7 and 8, which had sufficient work history information. Each of the plants was revisited and a walk-through survey was conducted and they obtained information on area layout, equipment and material flow, process operations, job titles of workers employed in routine operations, job titles of workers employed in maintenance/cleanup, potential exposure sources, and exposure control systems. Quantitative exposure estimates were generated using process analysis, job analysis, exposure estimation and linkage of individual work histories with the exposure estimates. Process analysis included several components including a description of individual manufacturing processes at each plant, identification of separated work areas within each process, analysis of specific operations performed in each area, and identification of historical changes in plant technology. Job analysis included identification of specific tasks with exposure potential, characterization of task-specific determinants of exposure, specification of historical changes in the job, and The authors noted that validation was difficult due to industrial hygiene monitoring data being limited due to recent implementation. They also noted that a limitation of this study was that they could not perform in-depth

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Domain	Metric	Rating	Comments
Domain 3: Outcome Assessment			

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Domain	Metric	Rating	Comments
	Metric 3A: Outcome Ascertainment	Medium	For plants located in the United States (plants 1-7), vital status as of January 1, 1992 was determined from records from the plants, the Social Security Administration's death master file, the National Death Index (NDI), and the divisions of motor vehicles (DMVs) of Texas, Louisiana, and Kentucky. Individuals who terminated employment prior to 1979 and who had no vital status information were considered lost to follow-up. For individuals from Canada (plant 8), the authors examined plant personnel and benefits records for 1950 through 1992, as well as through linkage with the Canadian Mortality Data Base (CMDB), which is maintained by Statistics Canada. Canadian decedents were identified through review of death certificates from Statistics Canada, and were coded according to the ICD revision in place at time of death. For citizens of the United States who were deceased, the authors obtained death certificates from plants and state bureaus of vital statistics. A nosologist reviewed the certificates and coded cause of death according to the International Classification of Diseases, 9th edition and coding rules in effect at time of death. 9th revision codes were converted to 8th revision codes for analysis.For individuals from plant 8 who were examined for cancer incidence, information was obtained from the Ontario Cancer Registry for the period of 1965 through 1992. It is important to note that any cancer noted as a contributory cause of death was coded. The methods utilized for outcome ascertainment were appropriate and did not raise any major concerns about potential outcome misclassification. While there was no discussion about validation of these methods, utilization of vital statistics information from relevant agencies lends confidence to their classification.

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Domain	Metric	Rating	Comments
	Metric 3B: Selective Reporting	Medium	The results reported within this study align with the analyses described in the methods section, and there were no concerns of selective reporting.
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Low	The authors assessed a number of potential covariates in their analyses, including age, calendar period, years since hire, race, and styrene exposure (for analysis of butadiene). The authors also considered the individual plants as a potential confounder, but it did not significantly impact the RRs for butadiene or styrene. A key confounder that was not included as a confounding variable is smoking, potentially due to lack of smoking information for participants. Confounders were assessed with Poisson regression analyses, although the authors did not provide many details about the strategy used to identify potential covariates, contributing to a low rating for this metric.
Domain 5: Analysis			

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Domain	Metric	Rating	Comments
	Metric 5A: Analysis	Medium	Overall and cause-specific mortality for participants was assessed using standardized mortality ratios comparing rates with the general population mortality rates. Subjects from plants 1-7 were compared with USA male general population rates, or compared with Ontario male rates for those individuals from plant 8. Some analyses also compared US participants with general population rates from their respective states including Texas, Kentucky, and Louisiana. SMRs were calculated for the cohort as a whole, as well as for subcohorts based on plant, payroll classification, duration of employment, period of hire, years since hire, process group, process subgroup, butadiene qualitative exposure group, and styrene qualitative exposure group. The authors provided SMRs and their associated 95% confidence intervals, and noted that SMRs were statistically significant at the 5% significance level if the confidence interval does not include the null value of 100. Cancer incidence rates for individuals from plant 8 were calculated by dividing the number of new cases by the person-years accumulated by the cohort from 1965-1992. These values were then compared to cancer incidence rates for the general male population of Ontario. Standardized incidence ratios and their 95% confidence intervals were calculated similarly to SMRs.

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Study Citation:	UAB, (1995). Initial submission: Letter from intl inst syn rubber prod to USEPA RE prelim results in cohort mortality study of employees of 8 styrene butadiene rubber plants, dated 05/19/95.
Health Outcome(s) Assessed:	Gastrointestinal- Buccal cavity and pharynx cancer mortality, Digestive organs cancer mortality, esophagus cancer mortality, stomach cancer mortality, large intestine cancer mortality, rectum cancer mortality, pancreas cancer mortality, Cancer; Hepatic/Liver- Liver cancer mortality, Cancer; Cancer/Carcinogenesis- All cancer mortality, buccal cavity and pharynx cancer mortality, digestive organs cancer mortality, esophagus cancer mortality, stomach cancer mortality, large intestine cancer mortality, rectum cancer mortality, liver cancer mortality, pancreas cancer mortality, larynx cancer mortality, lung cancer mortality, skin cancer mortality, prostate cancer mortality, bladder cancer mortality, kidney cancer mortality, central nervous system cancer mortality, lymphopoietic system cancer mortality, lymphosarcoma mortality, Hodgkin's disease mortality, other lymphatic tissue cancer mortality, other cancer mortality, Cancer; Mortality- Allergic; endocrine; metabolic; nutritional diseases mortality, mental;psychoneurotic; and personality disorders mortality, blood diseases mortality, nervous system diseases mortality, circulatory diseases mortality, respiratory diseases mortality, digestive disease mortality, genitourinary diseases mortality, external causes mortality, other specified causes mortality, unknown cause mortality, Non-cancer; Lung/Respiratory- Lung cancer mortality, larynx cancer mortality, Cancer; Neurological/Behavioral- Central nervous system cancer mortality, Cancer; Reproductive/Developmental- Prostate cancer mortality, Cancer; Skin/Connective Tissue- Skin cancer mortality, Cancer; Renal/Kidney- Kidney cancer mortality, bladder cancer mortality, Cancer; Immune/Hematological- Lymphopoietic system cancer mortality, lymphosarcoma mortality, Hodgkin's disease mortality, leukemia mortality, other lymphatic tissue cancer mortality, Cancer; Benign neoplasms- Benign neoplasm mortality, Cancer; Immune/Hematological- Allergic, endocrine, metabolic, nutritional disease mortality, Non-cancer; Neurological/Behavioral- Mental, psychoneurotic, and personality disorders mortality, nervous system diseases mortality, Non-cancer; Immune/Hematological- Blood diseases mortality, Non-cancer; Cardiovascular- Circulatory disease mortality, Non-cancer; Lung/Respiratory- Respiratory diseases mortality, Non-cancer; Gastrointestinal- Digestive diseases mortality, Non-cancer; Renal/Kidney- Genitourinary diseases mortality, Non-cancer; Immune/Hematological- Leukemia mortality, chronic lymphocytic leukemia mortality, chronic myelogenous leukemia mortality, acute myelogenous leukemia mortality, acute unspecified leukemia, Cancer; Cancer/Carcinogenesis- Leukemia mortality, chronic lymphocytic leukemia mortality, chronic myelogenous leukemia mortality, acute myelogenous leukemia mortality, acute unspecified leukemia, Cancer; Mortality- Leukemia mortality, chronic lymphocytic leukemia mortality, chronic myelogenous leukemia mortality, acute myelogenous leukemia mortality, acute unspecified leukemia, Cancer; Mortality- All cancer mortality, buccal cavity and pharynx cancer mortality, digestive organs cancer mortality, esophagus cancer mortality, stomach cancer mortality, large intestine cancer mortality, rectum cancer mortality, liver cancer mortality, pancreas cancer mortality, larynx cancer mortality, lung cancer mortality, skin cancer mortality, prostate cancer mortality, bladder cancer mortality, kidney cancer mortality, central nervous system cancer mortality, lymphopoietic system cancer mortality, lymphosarcoma mortality, Hodgkin's disease mortality, other lymphatic tissue cancer mortality, other cancer mortality, Cancer; Nutritional/Metabolic- Allergic, endocrine, metabolic, and nutritional disease mortality, Non-cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	5665016

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	The range of exposure levels reported by the authors are adequate to evaluate the primary hypotheses in the study, and the population of interest was exposed to levels expected to have an impact on response. Methods for outcome ascertainment were also appropriate, and there were no major concerns pertaining to study sensitivity.

Additional Comments: This retrospective cohort follow-up study included a large number of workers in the styrene-butadiene-rubber industry from North America. The authors employed extensive methods to develop quantitative exposure estimates for butadiene, although they did not that there was likely exposure misclassification. There were also difficulties in validating the cumulative exposure estimates for this cohort. Some concerns were raised about potential confounding, as they did not report all of the potential covariates examined or the methods used for identifying potential covariates. Outcome ascertainment was appropriate, and there were no major concerns about outcome misclassification.

Overall Quality Determination Medium

Study Citation:	UAB, (2007). A follow-up study of women in the synthetic rubber industry.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lung cancer mortality, breast cancer mortality, all cancer mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality, Cancer; Mortality- Lung cancer mortality, breast cancer mortality, all cause mortality, all cancer mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality, Cancer; Lung/Respiratory- Lung cancer mortality, nonmalignant respiratory disease mortality, larynx cancer mortality, Cancer; Reproductive/Developmental- Breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, Cancer; Neurological/Behavioral- Brain cancer mortality, Cancer; Cardiovascular- Circulatory disease mortality, Non-cancer; Gastrointestinal- Esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, pancreatic cancer mortality, buccal cavity and pharynx cancer mortality, Cancer; Immune/Hematological- Lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, Cancer; Hepatic/Liver- Liver cancer mortality, Cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality, Cancer; non-specific organs/systems- All cause mortality, all cancer mortality, other cancer mortality, benign neoplasms mortality, allergic/endocrine/metabolic disease mortality, external causes mortality, other known mortality, unknown causes mortality, Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality, Non-cancer; Immune/Hematological- Blood disorders mortality, Non-cancer; Mortality- Benign neoplasms mortality, blood disorders mortality, mental disorders mortality, allergic, endocrine & metabolic disease mortality, nervous system disease, circulatory disease mortality, nonmalignant respiratory disease mortality, digestive disease mortality, genitourinary disease mortality, external causes mortality, other known causes mortality, unknown causes mortality, Non-cancer; Renal/Kidney- Genitourinary disease mortality, Non-cancer; Lung/Respiratory- Nonmalignant respiratory disease mortality, Non-cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6544020

Domain	Metric	Rating	Comments
Domain 1: Study Participation			

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Study Citation:	UAB, (2007). A follow-up study of women in the synthetic rubber industry.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lung cancer mortality, breast cancer mortality, all cancer mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality, Cancer; Mortality- Lung cancer mortality, breast cancer mortality, all cause mortality, all cancer mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality, Cancer; Lung/Respiratory- Lung cancer mortality, nonmalignant respiratory disease mortality, larynx cancer mortality, Cancer; Reproductive/Developmental- Breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, Cancer; Neurological/Behavioral- Brain cancer mortality, Cancer; Cardiovascular- Circulatory disease mortality, Non-cancer; Gastrointestinal- Esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, pancreatic cancer mortality, buccal cavity and pharynx cancer mortality, Cancer; Immune/Hematological- Lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, Cancer; Hepatic/Liver- Liver cancer mortality, Cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality, Cancer; non-specific organs/systems- All cause mortality, all cancer mortality, other cancer mortality, benign neoplasms mortality, allergic/endocrine/metabolic disease mortality, external causes mortality, other known mortality, unknown causes mortality, Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality, Non-cancer; Immune/Hematological- Blood disorders mortality, Non-cancer; Mortality- Benign neoplasms mortality, blood disorders mortality, mental disorders mortality, allergic, endocrine & metabolic disease mortality, nervous system disease, circulatory disease mortality, nonmalignant respiratory disease mortality, digestive disease mortality, genitourinary disease mortality, external causes mortality, other known causes mortality, unknown causes mortality, Non-cancer; Renal/Kidney- Genitourinary disease mortality, Non-cancer; Lung/Respiratory- Nonmalignant respiratory disease mortality, Non-cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6544020

Domain	Metric	Rating	Comments
	Metric 1A: Participant Selection	Medium	This retrospective occupational cohort study examined associations between 1,3-butadiene exposure and a range of cause-specific mortality in female synthetic rubber plant workers. Participants were n=4,863 women who had worked at any of 8 North American plants (7 in United States, 1 in Canada) that made styrene-butadiene rubber for at least one day between 1943 and 1991 and had acceptable personnel records. Exact years of eligibility varied by plant due to processing activities (1943-1991 at Plants 2, 3, 4, 6, and 8A; 1950-1991 at Plants 7 and 8b; 1960-1991 at Plant 5; 1965 - 1991 at Plant 1). Follow-up for vital status occurred through 2002. A total of n=6,796 women were initially identified as potentially eligible through personnel records. Exclusion criteria were: missing information on surname, social security number, date of birth, or employment dates (n=938); termination before beginning of follow-up (n=505); not employed at the study plant (n=315); and male (n=175). The final study cohort consisted of 4,863 women. Loss to follow up was minimal (follow-up completed for 97% of study population).Comparisons are made between workers in the cohort with varying exposure levels and to the general population. The latter comparison reveals potential for healthy worker bias. However, the included study population was not compared to the total eligible population, making the potential for selection bias difficult to assess. There is potential that healthier workers remained in jobs leading to exposure for longer periods of time; however, the study tracked all job and personnel changes throughout the follow-up period and included groups with lower levels of expected exposure.

Domain 2: Exposure Characterization

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Study Citation:	UAB, (2007). A follow-up study of women in the synthetic rubber industry.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lung cancer mortality, breast cancer mortality, all cancer mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality, Cancer; Mortality- Lung cancer mortality, breast cancer mortality, all cause mortality, all cancer mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality, Cancer; Lung/Respiratory- Lung cancer mortality, nonmalignant respiratory disease mortality, larynx cancer mortality, Cancer; Reproductive/Developmental- Breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, Cancer; Neurological/Behavioral- Brain cancer mortality, Cancer; Cardiovascular- Circulatory disease mortality, Non-cancer; Gastrointestinal- Esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, pancreatic cancer mortality, buccal cavity and pharynx cancer mortality, Cancer; Immune/Hematological- Lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, Cancer; Hepatic/Liver- Liver cancer mortality, Cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality, Cancer; non-specific organs/systems- All cause mortality, all cancer mortality, other cancer mortality, benign neoplasms mortality, allergic/endocrine/metabolic disease mortality, external causes mortality, other known mortality, unknown causes mortality, Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality, Non-cancer; Immune/Hematological- Blood disorders mortality, Non-cancer; Mortality- Benign neoplasms mortality, blood disorders mortality, mental disorders mortality, allergic, endocrine & metabolic disease mortality, nervous system disease, circulatory disease mortality, nonmalignant respiratory disease mortality, digestive disease mortality, genitourinary disease mortality, external causes mortality, other known causes mortality, unknown causes mortality, Non-cancer; Renal/Kidney- Genitourinary disease mortality, Non-cancer; Lung/Respiratory- Nonmalignant respiratory disease mortality, Non-cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6544020

Domain	Metric	Rating	Comments
	Metric 2A: Exposure Measurement	Medium	Exposure to 1,3-butadiene was estimated using a job-exposure matrix (JEM) developed for the included plants. The JEM was constructed from information on the tasks performed for each job and documented changes in those task procedures over time. Personnel records were used to obtain subject work histories, including job titles, job changes, start dates, work areas, and end dates. Jobs were classified into synthetic butadiene rubber-related operations, administration, or residual operations. Ultimately, 133 unique work area/job group codes were developed. The JEM intensity estimates were then linked to each study subject's work history. Cumulative exposure estimates were calculated. Estimates for one of the eight plants was compared to personal measurement of butadiene; correlations between estimates and measurements varied depending on whether the work area/job title was well-defined or poorly-defined, and whether or not the job type was typically found in styrene-butadiene rubber plants. Estimates for well-defined jobs were "consistently lower than measurements." JEM estimates did appear to incorporate the use of personal protective equipment (Macaluso et al., 2004 HERO ID 646914). Estimation of exposure was based on each subject's work history at the plants of interest, which in some cases may not have represented lifetime occupational exposure. Some degree of exposure misclassification is likely but expected to be nondifferential. Overall, this is a fairly comprehensive JEM paired with complete work histories to estimate exposure.

Domain 3: Outcome Assessment

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Study Citation:	UAB, (2007). A follow-up study of women in the synthetic rubber industry.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lung cancer mortality, breast cancer mortality, all cancer mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality, Cancer; Mortality- Lung cancer mortality, breast cancer mortality, all cause mortality, all cancer mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality, Cancer; Lung/Respiratory- Lung cancer mortality, nonmalignant respiratory disease mortality, larynx cancer mortality, Cancer; Reproductive/Developmental- Breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, Cancer; Neurological/Behavioral- Brain cancer mortality, Cancer; Cardiovascular- Circulatory disease mortality, Non-cancer; Gastrointestinal- Esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, pancreatic cancer mortality, buccal cavity and pharynx cancer mortality, Cancer; Immune/Hematological- Lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, Cancer; Hepatic/Liver- Liver cancer mortality, Cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality, Cancer; non-specific organs/systems- All cause mortality, all cancer mortality, other cancer mortality, benign neoplasms mortality, allergic/endocrine/metabolic disease mortality, external causes mortality, other known mortality, unknown causes mortality, Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality, Non-cancer; Immune/Hematological- Blood disorders mortality, Non-cancer; Mortality- Benign neoplasms mortality, blood disorders mortality, mental disorders mortality, allergic, endocrine & metabolic disease mortality, nervous system disease, circulatory disease mortality, nonmalignant respiratory disease mortality, digestive disease mortality, genitourinary disease mortality, external causes mortality, other known causes mortality, unknown causes mortality, Non-cancer; Renal/Kidney- Genitourinary disease mortality, Non-cancer; Lung/Respiratory- Nonmalignant respiratory disease mortality, Non-cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6544020

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Cause of death data were extracted from subject death certificates according to the ICD codes of the edition relevant to the time of follow-up. Plant records were used to track name changes that would be reflected in vital status records. Vital status of US subjects was obtained from plant records, the Social Security Administration, the National Death Index, Cambridge Statistical Research Associates, Centers for Medicare and Medicaid Services, and individual tracing. Vital status of Canadian subjects was obtained from linkages conducted by Statistics Canada with the CMDB (acronym definition not provided).For deaths occurring in the United States prior to 1979, death certificates were obtained from state vital records bureaus, with independent review and coding of cause of death by two nosologists. For deaths occurring in the United States after 1979, cause of death codes were obtained from NDI Plus. For deaths of individuals who worked at the Canadian plant, ICD codes were derived from the CMDB. Individuals reviewing vital status records were blinded to subject work histories and estimated exposures. There is some concern for outcome misclassification due to differences in coding practices over time; however, the impact to findings would be minimal.
	Metric 3B:	Selective Reporting	Medium	Results for anticipated analyses are reported.

Domain 4: Potential Confounding / Variability Control

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Study Citation: UAB, (2007). A follow-up study of women in the synthetic rubber industry.

Health Outcome(s) Assessed: Cancer/Carcinogenesis- Lung cancer mortality, breast cancer mortality, all cancer mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality, Cancer; Mortality- Lung cancer mortality, breast cancer mortality, all cause mortality, all cancer mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality, Cancer; Lung/Respiratory- Lung cancer mortality, nonmalignant respiratory disease mortality, larynx cancer mortality, Cancer; Reproductive/Developmental- Breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, Cancer; Neurological/Behavioral- Brain cancer mortality, Cancer; Cardiovascular- Circulatory disease mortality, Non-cancer; Gastrointestinal- Esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, pancreatic cancer mortality, buccal cavity and pharynx cancer mortality, Cancer; Immune/Hematological- Lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, Cancer; Hepatic/Liver- Liver cancer mortality, Cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality, Cancer; non-specific organs/systems- All cause mortality, all cancer mortality, other cancer mortality, benign neoplasms mortality, allergic/endocrine/metabolic disease mortality, external causes mortality, other known mortality, unknown causes mortality, Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality, Non-cancer; Immune/Hematological- Blood disorders mortality, Non-cancer; Mortality- Benign neoplasms mortality, blood disorders mortality, mental disorders mortality, allergic, endocrine & metabolic disease mortality, nervous system disease, circulatory disease mortality, nonmalignant respiratory disease mortality, digestive disease mortality, genitourinary disease mortality, external causes mortality, other known causes mortality, unknown causes mortality, Non-cancer; Renal/Kidney- Genitourinary disease mortality, Non-cancer; Lung/Respiratory- Nonmalignant respiratory disease mortality, Non-cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality, Cancer

Chemical: 1,3-Butadiene- Parent compound

HERO ID: 6544020

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	No information was provided on how potential confounders were identified. Information on potential confounders was obtained from personnel records.All study participants were women. SMR analyses were matched to the state/province of plant location and accounted for cause of death, race, age, and calendar time. The following potential confounders were considered for inclusion in regression models: age, years since hire, ever-hourly status (proxy for SES), calendar period, and race. Ultimately, age, years since hire, and ever-hourly status were included in regression models due to other covariates "having little impact on. . . RRs." Multi-pollutant models including two other occupational exposures (styrene and dimethyldithiocarbamate) were constructed. Other potential occupational co-exposures were not evaluated.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Poisson regression was used to estimate relative rates of cause-specific mortality associated with 1,3-butadiene exposure among workers adjusted for confounders and two occupational co-exposures. Only lung cancer and breast cancer mortality were included as outcomes in Poisson models, as they were the only outcomes with greater than 10 exposed decedents. Various forms of the exposure variable were explored, including cumulative ppm-years, ppm-years $>$ 100, and high-1,3-butadiene exposure tasks. Exposure variables were categorized in all analyses. In addition to analyses examining within-cohort associations, standardized mortality ratios were calculated using the general population as a reference for a large number of mortality causes. All results were reported with 95% confidence intervals.

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Study Citation:	UAB, (2007). A follow-up study of women in the synthetic rubber industry.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lung cancer mortality, breast cancer mortality, all cancer mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality, Cancer; Mortality- Lung cancer mortality, breast cancer mortality, all cause mortality, all cancer mortality, buccal cavity and pharynx cancer mortality, esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, liver cancer mortality, pancreatic cancer mortality, larynx cancer mortality, uterine cancer mortality, ovarian cancer mortality, bladder cancer mortality, kidney cancer mortality, brain cancer mortality, lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, other cancer mortality, Cancer; Lung/Respiratory- Lung cancer mortality, nonmalignant respiratory disease mortality, larynx cancer mortality, Cancer; Reproductive/Developmental- Breast cancer mortality, uterine cancer mortality, ovarian cancer mortality, Cancer; Neurological/Behavioral- Brain cancer mortality, Cancer; Cardiovascular- Circulatory disease mortality, Non-cancer; Gastrointestinal- Esophageal cancer mortality, stomach cancer mortality, colorectal cancer mortality, pancreatic cancer mortality, buccal cavity and pharynx cancer mortality, Cancer; Immune/Hematological- Lymphohematopoietic cancer mortality, Non-Hodgkin lymphoma mortality, Hodgkin lymphoma mortality, leukemia mortality, multiple myeloma mortality, Cancer; Hepatic/Liver- Liver cancer mortality, Cancer; Renal/Kidney- Bladder cancer mortality, kidney cancer mortality, Cancer; non-specific organs/systems- All cause mortality, all cancer mortality, other cancer mortality, benign neoplasms mortality, allergic/endocrine/metabolic disease mortality, external causes mortality, other known mortality, unknown causes mortality, Cancer; Neurological/Behavioral- Mental disorders mortality, nervous system disease mortality, Non-cancer; Immune/Hematological- Blood disorders mortality, Non-cancer; Mortality- Benign neoplasms mortality, blood disorders mortality, mental disorders mortality, allergic, endocrine & metabolic disease mortality, nervous system disease, circulatory disease mortality, nonmalignant respiratory disease mortality, digestive disease mortality, genitourinary disease mortality, external causes mortality, other known causes mortality, unknown causes mortality, Non-cancer; Renal/Kidney- Genitourinary disease mortality, Non-cancer; Lung/Respiratory- Nonmalignant respiratory disease mortality, Non-cancer; Gastrointestinal- Digestive disease mortality, Non-cancer; Nutritional/Metabolic- Pancreatic cancer mortality, Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	6544020

Domain	Metric	Rating	Comments
	Metric 5B: Sensitivity	Medium	The sample size was large (n = 4,863). No other concerns regarding selective reporting were identified.

Additional Comments: This occupational cohort study of female styrene-butadiene rubber plant workers examined the association between exposure to 1,3-butadiene and mortality due to a wide range of specific causes. The study used adequate methods and a large sample size. There is some potential for exposure misclassification due to the use of a job exposure matrix that was validated against workplace measurements at only one of the study sites; however, impacts to the findings are expected to be minimal. Exposure to the first quartile of 1,3-butadiene levels was significantly associated with lung cancer mortality compared to no exposure (RR: 2.7, 95% CI: 1.4, 5.1).

Overall Quality Determination Medium

Study Citation:	Valdez-Flores, C., Erraguntla, N., Budinsky, R., Cagen, S., Kirman, C. R. (2022). An updated lymphohematopoietic and bladder cancers risk evaluation for occupational and environmental exposures to 1,3-butadiene. Chemico-Biological Interactions 366:110077.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Mortality from all leukemias, lymphoid leukemia, myeloid leukemia, multiple myeloma, non-Hodgkin's lymphoma, and bladder/urinary cancer., Cancer; Immune/Hematological- Mortality from all leukemias, lymphoid leukemia, myeloid leukemia, multiple myeloma, and non-Hodgkin's lymphoma., Cancer; Renal/Kidney- Mortality from bladder/urinary cancer., Cancer; Mortality- Mortality from all leukemias, lymphoid leukemia, myeloid leukemia, multiple myeloma, non-Hodgkin's lymphoma, and bladder/urinary cancer., Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	11531254

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	This re-analysis of associations between occupational exposure to 1,3-butadiene and mortality from select cancers uses data from a cohort of styrene-butadiene rubber (SBR) workers employed at six North American facilities between 1943 and 1992 (Sathiakumar et al 2021 HEROID 9038746; Sathiakumar et al 2021b HEROID 10192219). These updated data included 22,785 male and female workers with vital status follow-up through 2009. Strengths include the large cohort size and lengthy follow-up. Other analyses of these data (Sathiakumar HEROID 9038746) reported a median (IQR) duration of employment through 1991 of 11.8 (3.4–24) years in males and 1.7 (0.4–5.9) years in females, and a median (IQR) of 40.0 (30–49) years since hire. A potential limitation noted in other analyses is that the eligibility of male workers (79% of the cohort) was limited to persons employed for at least one year (Sathiakumar 9038746). This eligibility requirement may have induced risk of healthy worker bias if turnover of short-term workers was high. However, there was no evidence of significant selection bias.
Domain 2: Exposure Characterization			
	Metric 2A: Exposure Measurement	Medium	Details on exposure characterization were described elsewhere (Macaluso et al., 2004 HEROID 646914). Estimated exposure to butadiene (BD) was based on job-exposure matrices (JEMs) that captured work areas and job groups, and historical changes in operations. Few objective measures were available for comparison with estimate concentrations. A limited evaluation of validity indicated that the 90% uncertainty intervals for JEM concentration estimates overlapped with ranges of reported measurements collected in select years. The primary exposure variable of interest was total cumulative BD exposure in ppm-years; 34% of workers in this sample were classified as not exposed to BD. In addition to overall cumulative BD exposure, authors analyzed the following related BD exposure metrics: (i) cumulative frequency counts of exposures to "high intensity tasks (HITs)" concentrations, i.e. tasks with BD exposures >= 100 ppm; (ii) cumulative exposure to BD from work tasks at concentrations <=100 ppm; and (iii) cumulative exposure to BD at concentrations >100 ppm. The validity and precision of BD exposure estimates is uncertain, but there was no evidence of bias or of significant measurement error.
Domain 3: Outcome Assessment			

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Study Citation:	Valdez-Flores, C., Erraguntla, N., Budinsky, R., Cagen, S., Kirman, C. R. (2022). An updated lymphohematopoietic and bladder cancers risk evaluation for occupational and environmental exposures to 1,3-butadiene. Chemico-Biological Interactions 366:110077.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Mortality from all leukemias, lymphoid leukemia, myeloid leukemia, multiple myeloma, non-Hodgkin's lymphoma, and bladder/urinary cancer., Cancer; Immune/Hematological- Mortality from all leukemias, lymphoid leukemia, myeloid leukemia, multiple myeloma, and non-Hodgkin's lymphoma., Cancer; Renal/Kidney- Mortality from bladder/urinary cancer., Cancer; Mortality- Mortality from all leukemias, lymphoid leukemia, myeloid leukemia, multiple myeloma, non-Hodgkin's lymphoma, and bladder/urinary cancer., Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	11531254

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Outcomes analyzed included mortality from all leukemias (n=132), leukemia subtypes (lymphoid, myeloid), multiple myeloma (n=60), non-Hodgkin's lymphoma (n=110), and bladder/urinary cancer (n=95). Details on methods of vital status and cause of death ascertainment were provided elsewhere (Sathiakumar et al 2021b HEROID 9038746). Briefly, endpoints were identified using ICD codes via linkage to databases that included the Social Security Administration, the National Death Index, and the Canadian Mortality Data Base. Complete cause of death information was available for cancers. Vital status ascertainment was largely complete (99%). There was no evidence of error or bias in cancer outcome ascertainment. However, since mortality was analyzed, any participants with prevalent cases of these outcomes were not identified.
	Metric 3B:	Selective Reporting	Medium	Results were described or presented for all analyses discussed as central aims.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	Age was included in all models. The authors examined the influence of adjusting models for sex, race, calendar year, years since hire, and co-exposure to styrene, as well as for several BD exposure metrics. Adjustment for additional BD exposure metrics in a major concern for overadjustment bias, particularly as these variables were highly correlated (0.86 to 0.94). There were several other potential concerns. First, co-exposure confounding by dimethyldithiocarbamate was not evaluated, though there was no evidence of important confounding bias in earlier analyses of the cohort (Cheng et al, 2007 HEROID 646899). Second, potential confounding by smoking was not evaluated as no data on smoking was available. The authors noted both smoking status and BD exposure were associated with hourly worker vs salaried worker status; analyses did not adjust for hourly worker status. Third, unlike other analyses of this cohort, the authors did not adjust for plant/facility as a proxy for unmeasured workforce or work environment characteristics. There was no direct evidence of important residual confounding from these additional factors.
Domain 5: Analysis				

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Study Citation:	Valdez-Flores, C., Erraguntla, N., Budinsky, R., Cagen, S., Kirman, C. R. (2022). An updated lymphohematopoietic and bladder cancers risk evaluation for occupational and environmental exposures to 1,3-butadiene. Chemico-Biological Interactions 366:110077.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Mortality from all leukemias, lymphoid leukemia, myeloid leukemia, multiple myeloma, non-Hodgkin's lymphoma, and bladder/urinary cancer., Cancer; Immune/Hematological- Mortality from all leukemias, lymphoid leukemia, myeloid leukemia, multiple myeloma, and non-Hodgkin's lymphoma., Cancer; Renal/Kidney- Mortality from bladder/urinary cancer., Cancer; Mortality- Mortality from all leukemias, lymphoid leukemia, myeloid leukemia, multiple myeloma, non-Hodgkin's lymphoma, and bladder/urinary cancer., Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	11531254

Domain	Metric		Rating	Comments
	Metric 5A:	Analysis	Low	Analyses used multivariate Cox regression to estimate associations. The primary focus of analyses was to compare the relationship between cumulative BD exposure and each endpoint with vs. without added covariates or alternate specifications; effect estimates from alternative models were used to estimate BD exposures associated with added risk of each outcome. The authors identified variables or specifications that improved model fit based on likelihood ratio testing. There was limited discussion of model assumptions. Exposure variables were used continuously, i.e. assuming log-linear dose response. A potential limitation is that deviations from linearity were examined for leukemia, but not discussed for other endpoints. A major concern is the decision and approach taken to adjust cumulative BD effect estimates for three BD exposure metrics with which this variable was highly correlated. Spearman correlations with total BD ppm-years for the three exposure variables found to influence model fit were as follows: cumulative BD HITS = 0.86, cumulative BD >100 ppm = 0.94, cumulative BD<= 100 ppm = 0.94; Macaluso et al 2004, HEROID 646914). The authors did not present collinearity diagnostics for these models. Moreover, the authors did not include substantive reasoning or provide a directed acyclic graph to clarify the rationale for these adjustments. While it is feasible that adverse health effects of cumulative BD exposure accumulated at higher vs. lower intensities may differ, interactions among these variables were not examined; they were included as independent variables without product terms or cross-classification. The authors did not provide guidance on interpreting the smaller slope for total cumulative BD ppm-years obtained after partitioning its effect of BD on endpoints by adjusting for covariates such as BD HITs. Similarly, interactions between BD and co-exposure to styrene were not explored. As noted by Gregorich et al 2021 (PMID: 33920501), a clear interpretation and rationale is important to avoid misguidance keeping a clearly redundant variable in a prediction model. Moreover, calculations of added risk associated with BD exposure appeared to be derived using effect estimates for total cumulative BD ppm-years and did not appear to integrate the joint effect of the correlated exposure variables included in some model. Such estimates would not reflect the influence of net exposure. The uncertain validity of the statistical methods employed and substantive interpretation of the central analyses that are a central focus are major concerns.
	Metric 5B:	Sensitivity	Medium	Overall, the sample size was large and number of cases adequate for analysis. Case numbers were insufficient for sex-stratified analyses among women.

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Study Citation:	Valdez-Flores, C., Erraguntla, N., Budinsky, R., Cagen, S., Kirman, C. R. (2022). An updated lymphohematopoietic and bladder cancers risk evaluation for occupational and environmental exposures to 1,3-butadiene. Chemico-Biological Interactions 366:110077.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Mortality from all leukemias, lymphoid leukemia, myeloid leukemia, multiple myeloma, non-Hodgkin's lymphoma, and bladder/urinary cancer., Cancer; Immune/Hematological- Mortality from all leukemias, lymphoid leukemia, myeloid leukemia, multiple myeloma, and non-Hodgkin's lymphoma., Cancer; Renal/Kidney- Mortality from bladder/urinary cancer., Cancer; Mortality- Mortality from all leukemias, lymphoid leukemia, myeloid leukemia, multiple myeloma, non-Hodgkin's lymphoma, and bladder/urinary cancer., Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	11531254

Domain	Metric	Rating	Comments
Additional Comments:	This study presents a re-analysis of associations between occupational BD exposure and mortality from outcomes that include leukemia and bladder cancer in the North American SBR worker cohort. The focus of analyses was to evaluate the influence of additionally adjusting total cumulative BD exposure for variables that include other BD exposure metrics. The authors concluded that additionally adjusting for these related exposure variables improved the predictive value of models for several endpoints. However, a subject matter-based rationale for these adjustments, and interpretation of the resulting effect estimates, was unclear. Spearman correlations between total cumulative BD exposure reported elsewhere were as follows: cumulative BD HITS (frequency of exposure to high-intensity tasks) = 0.86; cumulative BD at exposure >100 ppm = 0.94; and cumulative BD at exposure <= 100 ppm = 0.94). The authors did not report collinearity diagnostics, and did not use interaction terms, transformations, or cross-classifications to facilitate interpreting the joint effects of these correlated variables. A related concern is that calculations of added risk associated with BD exposure appeared to be derived using effect estimates for total cumulative BD ppm-years. Added risk estimates did not appear to integrate the joint effects of multiple BD variables. The substantive reasoning behind the methods used, and thus the validity of conclusions with respect to the impact of BD exposure on health, is uncertain.		

Overall Quality Determination Low

Study Citation:	Whitworth, K. W., Symanski, E., Coker, A. L. (2008). Childhood Lymphohematopoietic Cancer Incidence and Hazardous Air Pollutants in Southeast Texas, 1995–2004. Environmental Health Perspectives 116(11):1576-1580.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lymphohematopoietic cancer incidence (leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, acute lymphocytic leukemia, acute myeloid leukemia), Cancer; Immune/Hematological- Lymphohematopoietic cancer incidence (leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, acute lymphocytic leukemia, acute myeloid leukemia), Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	622776

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Medium	This ecological study collected information on cases of lymphohematopoietic cancer among children <20 years of age from the Texas Cancer Registry. The Texas Cancer Registry is reported to be a gold-certified population-based registry. Cases were chosen if they were diagnosed between 1995 and 2004 and resided in any of the following counties around Houston Texas: Harris, Montgomery, Liberty, Chambers, Fort Bend, Brazoria, Waller, and Galveston. The study identified 997 cases pf lymphohematopoietic cancer. Participants were excluded if their reported address was a hospital or other medical facility, or if the provided address could not be geocoded to an address using AtlasGIS. For the purpose of creating a comparison population, the study obtained population estimates stratified by race/ethnicity, sex, and age group for all of the included census tracts from the 2000 U.S. Census bureau, and excluded 24 cases since the census tract data estimated a "zero population total" for their strata. The final sample included 670 cases of leukemia, 146 cases of Hodgkin's disease, and 137 cases of non-Hodgkin's lymphoma for analysis. While there are limited details provided on the census tracts used for comparison, there is no direct evidence that selection bias is likely.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Low	Estimates of 1,3-Butadiene were obtained from the EPA 1999 National-Scale Air Toxics Assessment (NATA) project, which measures hazardous air pollutants in ambient air to characterize population risk. NATA used the Assessment System for Population Exposure Nationwide (ASPEN) simulation model to estimate levels of 1,3-Butadiene for every census tract of the contiguous US, and is based on emissions data for the year in which estimates are made (for this study, 1999) and accounts for meterologic data (wind speed and direction), rate and height of release, reactive decay, deposition, and secondary formation. The study reports that ASPEN also incorporates some background monitoring data. The study used the "all sources combined" option to estimate ambient concentrations of 1,3-butadiene. While there is no information to account for potential variation in behavior that would impact exposure (moving, time spent outside) there is no reason to suspect this would be differential by case status. However, there are concerns for temporality as the study does not consider latency or yearly variation in 1,3-Butadiene concentrations. Additionally, many cases were diagnosed before 1999.
Domain 3: Outcome Assessment				

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Study Citation:	Whitworth, K. W., Symanski, E., Coker, A. L. (2008). Childhood Lymphohematopoietic Cancer Incidence and Hazardous Air Pollutants in Southeast Texas, 1995–2004. Environmental Health Perspectives 116(11):1576-1580.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lymphohematopoietic cancer incidence (leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, acute lymphocytic leukemia, acute myeloid leukemia), Cancer; Immune/Hematological- Lymphohematopoietic cancer incidence (leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, acute lymphocytic leukemia, acute myeloid leukemia), Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	622776

Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	Lymphohematopoietic cancers were identified from the Texas Cancer Registry and were reported using ICD-10 codes. Outcomes included leukemia (C91-C95), non-Hodgkins lymphoma (C82-C85), and Hodgkin's disease (C81). Further specifications were made for acute lymphocytic leukemia and acute myeloid leukemia, but specific ICD-10 codes are not provided. It is reasonable to assume that the codes for leukemia (C91-C95) were used as some of those codes are specific to those outcomes, but this is not explicitly stated. There is overall a low concern for outcome misclassification.
	Metric 3B:	Selective Reporting	Medium	No registered protocol or methods papers mentioned, however all results were reported - significant or not.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Confounders included age at diagnosis, sex, race/ethnicity, and community SES as confounders. Community SES was constructed as a composite of socioeconomic status based on census-tract-level data from the 2000 Census, via principal components analysis. Factors included in community SES were median household income, median house value, median rent, percent high school diploma, percent college diploma, percent professional degree, percent employed, and percent below the poverty line. The risk ratios presented in the paper are adjusted for these factors. While it is not specified how age at diagnosis, sex, and race/ethnicity were determined it can be assumed this was provided from the Texas Cancer Registry. Ambient levels of benzene were also evaluated, but were not included in 1,3-butadiene models due to their high collinearity. Benzene and 1,3-butadiene were considered as a "joint" exposure variable based on the rank exposure level of each chemical.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The association between census-tract levels of 1,3-butadiene and leukemia outcomes was assessed using Poisson regression analysis. Analyses were done separately for leukemia subtypes. Sensitivity analyses were performed by age group, and exposure was characterized separately as quartiles as well as an ordinary variable. Results are presented as relative risks with 95% confidence limits. Analyses use three separate levels of exposure (Low/Medium/High), but the corresponding concentrations for those exposure levels are not provided.
	Metric 5B:	Sensitivity	Medium	The number of cases for each outcome is greater than 90, which indicates that they had sufficient power to detect an effect. The exposure range is relatively narrow, but likely wide enough to allow for contrast despite overall exposure being relatively low (median 0.16 ug/m3, 25th-75th percentiles: 0.11 - 0.21 ug/m3). The study may not represent the sensitive time period for development of the outcome.

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Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lymphohematopoietic cancer incidence (leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, acute lymphocytic leukemia, acute myeloid leukemia), Cancer; Immune/Hematological- Lymphohematopoietic cancer incidence (leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, acute lymphocytic leukemia, acute myeloid leukemia), Cancer
Chemical:	1,3-Butadiene- Parent compound
HERO ID:	622776

Domain	Metric	Rating	Comments
Additional Comments:	An ecological study assessing hazardous air pollutant levels in Texas against lymphohematopoietic cancer incidence in children per census tract (953 cases). It appears to be a quality study, aside from a limitation in exposure assessment: the study correlates cancer incidence with only 1 year of HAP data that is during the time period of diagnoses (1999 vs 1994-2004) and may not have been etiologically relevant exposure for some, if not all, cancer incidences. Additionally, the study was limited by the modeled exposure and the fact that 1,3-butadiene and benzene exposures were closely correlated and could not be assessed individually. The study observed significantly increased rates of all leukemia in tracts with highest levels of 1,3-butadiene (RR=1.40).		

Overall Quality Determination Medium

Study Citation:	Yuan, J. M., Gao, Y. T., Wang, R., Chen, M., Carmella, S. G., Hecht, S. S. (2012). Urinary levels of volatile organic carcinogen and toxicant biomarkers in relation to lung cancer development in smokers. Carcinogenesis 33(4):804-809.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lung cancer (incident), Cancer; Lung/Respiratory- Lung cancer (incident), Cancer
Chemical:	1,3-Butadiene- Metabolite: Monohydroxybutyl mercapturic acid (MHBMA), comprised of 1-hydroxy-2-(N-acetylcysteinyl)-3-butene and 1-(N-acetylcysteinyl)-2-hydroxy-3-butene
HERO ID:	1508766

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	This nested case-control study examined associations between lung cancer risk and urinary levels of a 1,3-butadiene metabolite (monohydroxybutyl mercapturic acid [MHBMA]) in male smokers from the Shanghai Cohort Study. 18,244 men between 45-64 years old living in four communities in Shanghai, China were recruited for the Shanghai Birth Cohort Study from January 1986 to September 1989 (participation reported to be 80% of the eligible population). By follow-up through December 31, 2006, 706 men were diagnosed with lung cancer (based on annual in-person interviews and the Shanghai Cancer Registry) and only 4.6% (n=839) were lost to follow up. 574 lung cancer cases who were current smokers at enrollment, when urine samples were collected, were included in the current study. Controls (n=574) were randomly selected from the cohort who were without lung cancer, were smokers at baseline and matched to cases by age at enrollment (within 2 years), date of biospecimen collection (within 1 month), and neighborhood at recruitment. Participants were excluded if their urine samples were depleted during analytical processes (225 cases and 170 controls) or if they had missing values for one or more of the mercapturic acid metabolites being measured. The final study population included 343 cases and 392 controls. Authors do not provide a comparison of those excluded due to depleted urine samples/those with missing data and the included population. However, cases and controls were selected from the same eligible population and were matched on age, sex, neighborhood, and smoking status. There was no mention of significant demographic differences between groups, minimizing substantial concern for bias (mean +/- sd age in cases vs controls 69.4 +/- 6.3 vs 69.1 +/- 6.0 years).
Domain 2: Exposure Characterization			

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Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lung cancer (incident), Cancer; Lung/Respiratory- Lung cancer (incident), Cancer
Chemical:	1,3-Butadiene- Metabolite: Monohydroxybutyl mercapturic acid (MHBMA), comprised of 1-hydroxy-2-(N-acetylcysteinyl)-3-butene and 1-(N-acetylcysteinyl)-2-hydroxy-3-butene
HERO ID:	1508766

Domain	Metric		Rating	Comments
	Metric 2A:	Exposure Measurement	Medium	Spot urine samples collected at baseline were used to assess levels of urinary MHBMA via LC-APCI-MS/MS (details in Carmella et al., 2009, HEROID 1455636). MHBMA comprises 1-hydroxy-2-(N-acetylcysteinyl)-3-butene and 1-(N-acetylcysteinyl)-2-hydroxy-3-butene. Samples from cases and controls were included in the same batches and laboratory staff were blinded to case/control status. The LOD for MBMA was 3.0 pmol/ml and the interday precision of assays was 8.9% relative standard deviation. Percent of samples <LOD is not reported, however, distribution information appears to show that all samples were >LOD (e.g., geometric mean [95% CI] 8.3 [7.2-9.7] pmol/mg Cr among controls). Urinary levels were adjusted for creatinine to account for dilution. Only those with available data for all tobacco smoke constituent metabolites were included in analyses, eliminating concern about treatment of missing values. A potential limitation is that exposure was assessed using a single spot urine sample. It is unclear to what extent habitual exposure during the etiologically relevant window may be misclassified by a single sample. However, such misclassification is not expected to be differential. The mean (sd) interval between biospecimen collection and diagnosis was 12.4 (4.6) years, ranging from 1 month to 20.5 years. While a proportion of cases were diagnosed shortly after urine sample collection, there was no evidence of systematic changes in smoking habits or other sources of 1,3-butadiene exposure that would influence biomarker concentrations among those individuals. This study did not include other urinary metabolites of 1,3-butadiene reported elsewhere to be more abundant than MHBMA (e.g., NHANES data reported by Nieto et al 2016, HEROID 10192276). However, there was no evidence that the choice of 1,3-butadiene biomarker would induce bias.
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Cases of incident lung cancer and lung cancer death were obtained through in-person interviews conducted annually (for surviving cohort members) and through regular monitoring of the population-based Shanghai Cancer Registry and the Shanghai Municipal Vital Statistics Office. A majority had histopathological confirmation; the remainder had clinical diagnoses including radiography or computed tomography. The authors did not discuss reliability of the cancer registry, confirmation of diagnoses based on self-reported data, or the proportion of participants successfully followed up annually, but there was no evidence of important error or bias. A possible limitation is the potential for early-stage lung cancer, not yet diagnosed, among some controls. However, there was no evidence that undetected disease was highly prevalent or that any such individuals would have introduced bias.
	Metric 3B:	Selective Reporting	Medium	Results are presented for anticipated analyses based on information from the methods.
Domain 4: Potential Confounding / Variability Control				

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Study Citation:	Yuan, J. M., Gao, Y. T., Wang, R., Chen, M., Carmella, S. G., Hecht, S. S. (2012). Urinary levels of volatile organic carcinogen and toxicant biomarkers in relation to lung cancer development in smokers. Carcinogenesis 33(4):804-809.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lung cancer (incident), Cancer; Lung/Respiratory- Lung cancer (incident), Cancer
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HERO ID:	1508766

Domain	Metric		Rating	Comments
	Metric 4A:	Potential Confounding	Medium	Participants were all male and all current smokers at recruitment and were matched on age (+/1 2 years), date of specimen collection (+/- 1 month), and neighborhood of residence (1 of 4 small geographically defined communities in Shanghai) at recruitment. Models adjusted for the matching variables, along with duration of biospecimen storage, number of cigarettes smoked per day, and number of years of smoking at baseline. Supplementary models examined effects additionally adjusted for validated biomarkers of two other smoking-related lung carcinogens (PAH biomarker urinary r-1,t-2,3,c-4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene (PheT) and NNK biomarker total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (NNAL)). The authors did not report examine the influence of adjusting for other smoking-related biomarkers measured in the study (e.g. benzene biomarker S-phenyl mercapturic acid (SPMA), Spearman's r=0.26), but there was no evidence of co-exposure confounding. Potential confounding by factors such as income, education, physical activity, occupation, ethnicity, and changes in smoking habits after baseline was not discussed. However, there was no evidence of residual confounding, or of important systematic differences in characteristics of participants recruited from the same small area. The authors discussed potential confounding or modifying role of unknown factors related to both MBHMA metabolism and cancer risk, but there was no direct evidence of such bias.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Effect estimates and 95% CI are reported for all analyses. Quartiles of urinary MHBMA were generated using distributions of controls and associations with lung cancer risk were analyzed via unconditional logistic regression models. Distribution data for urinary MHBMA are provided, and exposure data were logarithmically transformed to account for skew. Analyses included those with complete data only. Sensitivity analyses excluded patients diagnosed with lung cancer <12 months after sample collection and examined associations with lung cancer risk by histology.
	Metric 5B:	Sensitivity	Medium	The study had a sample size that appeared adequate to detect an effect (n=392 controls; 343 cases), exposure was measured prior to development of lung cancer, and there was variability in exposure. In some cases, the latency period between exposure measure and diagnosis of lung cancer was inadequate. However, there is no evidence that this was a source of important error or bias in the current study.

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Study Citation:	Yuan, J. M., Gao, Y. T., Wang, R., Chen, M., Carmella, S. G., Hecht, S. S. (2012). Urinary levels of volatile organic carcinogen and toxicant biomarkers in relation to lung cancer development in smokers. Carcinogenesis 33(4):804-809.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis- Lung cancer (incident), Cancer; Lung/Respiratory- Lung cancer (incident), Cancer
Chemical:	1,3-Butadiene- Metabolite: Monohydroxybutyl mercapturic acid (MHBMA), comprised of 1-hydroxy-2-(N-acetylcysteinyl)-3-butene and 1-(N-acetylcysteinyl)-2-hydroxy-3-butene
HERO ID:	1508766

Domain	Metric	Rating	Comments
Additional Comments:	This nested case-control study examined the association between lung cancer risk and urinary MHBMA levels, a biomarker of 1,3-butadiene exposure, among male smokers. Data came from the Shanghai Cohort study. The study was limited to cases and controls who were smokers at baseline. Urinary MHBMA was measured in a spot urine collected at baseline. Cases had incident lung cancer diagnosed a mean of 12.4 years (range one month to 20.5 years) after urine collection and included all eligible cases with sufficient urine for analysis (n=343 of 574). Controls (n=392) were randomly selected current smokers at baseline without a diagnosis of lung cancer, matched to cases on age, date of urine collection, and neighborhood of residence. Controls were interviewed annually as part of cohort surveillance. The study found an increased odds of lung cancer associated with higher urinary MHBMA among these male smokers after adjusting for variables that included smoking patterns. Associations were attenuated after adjusting for select biomarkers of smoking-related exposures other than 1,3-butadiene, and null after adjusting for urinary total cotinine, an indicator of overall smoking exposure. The study employed adequate methods for participant selection, exposure measurement, outcome ascertainment, and statistical analysis. There was no evidence of important bias or error, although such error cannot be ruled out.		

Overall Quality Determination Medium

Study Citation:	Pudrith, C., Dudley, W. N. (2019). Sensorineural hearing loss and volatile organic compound metabolites in urine. American Journal of Otolaryngology 40(3):409-412.
Health Outcome(s) Assessed:	Ocular/Sensory- Sensorineural hearing loss, Non-cancer
Chemical:	1,3-Butadiene- Metabolite: 3,4-dihydroxybutyl (DHBMA), 3-hydroxy-3-butenyl (MHBMA2).
HERO ID:	5660361

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	This cross-sectional study examined associations between 1,3-butadiene metabolites measured in urine and sensorineural hearing loss using data from the 2011-2012 cycle of the National Health and Nutritional Examination Surveys (NHANES), a nationally-representative study of the non-institutionalized civilian population of the United States. Participants were adults age 20-69 with a valid hearing test, a urine sample for analyses of volatile organic compounds, no middle ear issues, and who avoided exposure to loud noises for 12 hours before hearing testing. Tympanometry data was used to identify and exclude participants with flat tympanograms and those whose tympanograms indicated negative middle ear pressure (i.e., people with hearing loss due to other conditions). Approximately 10% of the total 2011-2012 NHANES population met inclusion criteria (n=849 participants included in the current study). A comparison of participants included in this study to the broader NHANES population was not provided. While selection bias cannot be ruled out, there is no direct evidence from the available information that selection was jointly related to exposure and outcome.
Domain 2: Exposure Characterization			
	Metric 2A: Exposure Measurement	Low	Two metabolites of 1,3-butadiene were measured in urine samples: 3,4-dihydroxybutyl (DHBMA) and 3-hydroxy-3-butenyl (MHBMA2). Details of urine sample collection were not provided. Exposures were quantified using ultra-performance liquid chromatography coupled with electrospray tandem mass spectrometry. LODs, detection rates, and methods for handling values below the LOD (if any) were not provided.
Domain 3: Outcome Assessment			
	Metric 3A: Outcome Ascertainment	Medium	The outcome of interest was sensorineural hearing loss, assessed using the mean bilateral high-frequency thresholds at 4000, 6000, and 8000 HZ (PTA4,6,8). Hearing tests were performed with an AD226 audiometer. No further information regarding outcome assessment was provided. The available information does not raise serious concern regarding outcome misclassification.
	Metric 3B: Selective Reporting	Medium	The main analysis described in the methods section was presented in the results section.
Domain 4: Potential Confounding / Variability Control			
	Metric 4A: Potential Confounding	Low	The outcome variable (hearing loss) was age-adjusted. Long-term noise exposure history was collected via questionnaire evaluated as a potential confounder via stratification (i.e., history of noise exposure vs. no history of noise exposure). Residual confounding by noise exposure within these broadly defined strata is likely. No other confounders were evaluated.

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Health Outcome(s) Assessed:	Ocular/Sensory- Sensorineural hearing loss, Non-cancer
Chemical:	1,3-Butadiene- Metabolite: 3,4-dihydroxybutyl (DHBMA), 3-hydroxy-3-butenyl (MHBMA2).
HERO ID:	5660361

Domain	Metric		Rating	Comments
Domain 5: Analysis				
	Metric 5A:	Analysis	Low	Analyses were conducted separately for individuals with versus without a history of noise exposure. Within each group, participants were grouped into quartiles of exposure. Levene's test was used to test for homogeneity of variance in the outcome across groups. Following categorization of the exposure variable, data were analyzed using analysis of covariance (ANCOVA), accounting for the family-wise error rate via calculation of the false discovery rate. Results presented were the F-test values and p-values. Exposure distributions were only provided for metabolites that were significantly associated with hearing loss (Table 3). Mean and standard error values of the hearing loss outcome variable were presented by exposure quartile only among exposures with significant associations in ANCOVA analysis.
	Metric 5B:	Sensitivity	Medium	The sample size was adequate (n=849 participants including n=557 without a history of noise exposure and n=292 with a history of noise exposure). LODs and detection rates were not provided and exposure distributions were only provided for exposures significantly associated with hearing loss; as such, it is unclear whether exposure contrasts were adequate.

Additional Comments: This cross-sectional study of 2011-2012 adult NHANES participants evaluated associations between 1,3-butadiene metabolites measured in urine and hearing loss. Major concerns include the lack of information on exposure assessment and the potential for residual confounding. Among individuals without a history of noise exposure, 3,4-dihyroxybutyl (DHBMA) concentrations in urine were significantly associated with hearing loss (p=0.003) after correction for the false discovery rate.

Overall Quality Determination Low