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An Updated Study of Mortality Among North American Synthetic Rubber Industry Workers

Elizabeth Delzell, Nalini Sathiakumar, John Graff, Maurizio Macaluso, George Maldonado, and Robert Matthew

Includes a Commentary by the Institute's Health Review Committee

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HEI STATEMENT
Synopsis of Research Report 132

Mortality Among Workers Exposed to Butadiene

BACKGROUND

1,3-Butadiene (BD) is a volatile organic compound used in the production of synthetic rubber. Although industrial emissions contribute to its outdoor presence, mobile sources account for the majority of emissions in the United States and for much of human exposure. Outdoor levels are substantially lower than those found in ocupational settings.

Concern about BD toxicity was first raised in the 1980s when animal studies showed an association between BD exposure and tumor development at many sites. Epidemiologic studies suggested an increased risk of cancers of the lymphatic and blood-forming systems (lymphohematopoietic cancers; LHCs) in BD-exposed workers and a higher risk of chronic leukemia in workers with long-term exposure in the styrene-butadiene rubber (SBR) industry. However, because of possible effects of concurrent exposure to other chemicals, it was difficult to identify which chemical or combination of chemicals was responsible for the observed effects.

International agencies that have evaluated cancer risk from BD exposure have classified BD variously as "probably carcinogenic to humans"; "toxic" and "highly likely to be carcinogenic in humans"; and a "known human carcinogen".

Since the mid-1990s, HEI has funded epidemiologic and toxicologic research on the carcinogenicity of BD. In 1999, HEI funded Dr Elizabeth Delzell (University of Alabama) and her colleagues to update an earlier study in which they had investigated mortality among the largest occupational group exposed to BD: 18,000 men employed in SBR production between 1944 and 1991. In the current study, these workers were followed for an additional 6 years and the effects of exposure to other compounds were evaluated.

The study aimed to (1) determine if employment in the SBR industry, assessed by factors such as duration of employment or type of job, is associated with mortality from specific causes; and (2) evaluate if exposure to BD, or styrene, or dimethyldithiocarbamate (DMDTC; the agents of interest) is related to death from leukemia, other LHCs, or other selected cancers.

APPROACH

The current project extended the earlier retrospective study. It analyzed mortality among 18,000 men who had worked at least 1 year in any of eight SBR plants between 1944 and 1998, which added 18% more person-years of follow-up to the earlier study. It assessed cancer mortality, specifically from leukemia, non-Hodgkin lymphoma, and other LHCs.

Vital status was updated for all subjects who had been classified earlier as living or as lost to follow-up and was established for 97% of the cohort. Cause-of-death information was obtained for 98% of decedents.

Exposures were estimated using both qualitative and quantitative methods. Qualitative estimates used data obtained from work records and interviews, including such factors as duration of employment and job type. Quantitative estimates were derived using two methods: (1) analysis of sources of exposure associated with tasks in each job classification and during specific time periods; and (2) mathematical modeling to estimate workplace concentrations.

The models for BD exposure estimated several parameters. The estimates for each parameter contained considerable uncertainty about the true numeric values. A mean exposure estimate was calculated for each work area/job group. Cumulative exposure was computed for each worker by multiplying the estimated exposure in each of his work area/job groups by the number of days he worked in each, and by summing the resulting quantities over all of his jobs for his duration of employment. Neither the parameters used in this model nor the estimates that resulted from it were validated with actual measurements of workplace concentrations.

The investigators compared *observed* mortality rates for the workers with the mortality rates that

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This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr Elizabeth Delzell at the School of Public Health, University of Alabama at Birmingham. The following Research Report contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Health Review Committee.

would be *expected* for the general male population (external analyses). Ratios of observed-to-expected rates, known as standardized mortality ratios, were calculated by cause of death for all subjects combined and for subgroups defined by various employment factors. These analyses were carried out for specific forms of leukemia and other cancers. The investigators also compared mortality rates for subgroups of exposed workers with those for unexposed workers (internal analyses); in addition to the specified forms of leukemia and cancer, these analyses also included other causes of death.

Cumulative exposure estimates for BD, styrene, and DMDTC derived from mathematical models were used in regression analyses. Mortality relative rates for each of the agents of interest were estimated in models that included possible confounders; in some analyses, these included exposures to the other agents. (A mortality rate for one group is always reported *relative to the rate* in a comparison group.)

RESULTS AND INTERPRETATION

External analyses for the entire study period (1944–1998) found fewer deaths than expected from all causes combined and for all specific forms of cancer, except colorectal, prostate, and certain forms of LHCs, which all showed higher than the expected number of deaths. This may reflect the "healthy worker effect", often seen in occupational cohorts that by definition include individuals who are healthier than the general population. For the LHCs, leukemia showed the highest ratio of observed-to-expected number of deaths; these were concentrated in hourly workers, in selected work-area subgroups, in workers with 20 to 29 years since hire, and in those with 10 or more years of employment.

Internal analyses revealed associations between mortality rates from leukemia and cumulative exposures to BD, styrene, and DMDTC. When analyses of the effects of one agent did not take into account exposure to the other agents, results suggested that each compound independently affected rates of death from leukemia. Furthermore, the relative rates generally increased as cumulative exposure increased: mortality rates from leukemia in the highest exposure categories increased by 170% to 270% compared with rates for the no-exposure category. When analyses did take into account exposure to the other agents, only BD and DMDTC retained their association with increased leukemia mortality.

CONCLUSIONS

This investigation strengthens the epidemiologic evidence for the carcinogenicity of BD. In particular, it indicates that cumulative occupational exposure to BD may increase the relative mortality rate from LHCs (in particular leukemia) and that this elevation is heightened as cumulative exposure increases. These results persisted even when workplace exposures to other putative carcinogens, such as styrene and DMDTC, were taken into account. The investigation addressed more definitively than earlier studies the possibility that the observed relative rates associated with BD exposure may actually reflect exposure to styrene or DMDTC.

This study provides some evidence of an association between leukemia mortality and occupational exposure to DMDTC. This evidence, however, was not as strong as that linking BD with leukemia because it did not show a linear increase in relative rates as cumulative exposure to DMDTC increased. Nevertheless, to the extent that DMDTC is still used in the SBR industry or elsewhere, further research into its effects may be warranted. The critical finding for both the validity and generalizability of these results is that the relative mortality rates for BD exposure remained elevated when exposure to DMDTC was accounted for.

The quantitative interpretation of these results faces serious limitations, especially in their application to risk assessments in other occupational or general populations. The relative ranking of the exposures of workers appears to be reasonably accurate; nevertheless, because the estimated exposure levels were not validated by actual workplace measurements, they are a source of considerable uncertainty. The limited evidence available to date suggests that the BD exposure estimates used in the current study may be too high. If so, the risks calculated using these estimates could actually be associated with lower measured concentrations of exposure. Fortunately, a more comprehensive exposure assessment using industrial hygiene measurements has been conducted and its results have recently been accepted for publication. If that study confirms that estimates from the current investigation are accurate, this study will provide a firm basis for quantitative risk assessments. Without such validation, assessments using the estimated exposure levels would be highly uncertain.

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HEALTH EFFECTS INSTITUTE

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Research Report 132

An Updated Study of Mortality Among North American Synthetic Rubber Industry Workers

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HEI STATEMENT

This Statement is a nontechnical summary of the Investigators' Report and the Health Review Committee's Commentary.

INVESTIGATORS' REPORT

When an HEI-funded study is completed, the investigators submit a final report. The Investigators' Report is first examined by three ouside technical reviewers and a biostatistician. The report and the reviewers' comments are then evaluated by members of the HEI Health Review Committee, who had no role in selecting or managing the project. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, if necessary, revise the report.

Continued

COMMENTARY HEALTH REVIEW COMMITTEE

The Commentary about the Investigators' Report is prepared by the HEI Health Review Committee and staff. Its purpose is to place the study into a broader scientific context, to point out its strengths and limitations, and to discuss remaining uncertainties and implications of the findings for public health.

RELATED HEI PUBLICATIONS

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INVESTIGATORS' REPORT

An Updated Study of Mortality Among North American Synthetic Rubber Industry Workers

Elizabeth Delzell, Nalini Sathiakumar, John Graff, Maurizio Macaluso, George Maldonado, and Robert Matthews

ABSTRACT

This study evaluated mortality rates from leukemia and other diseases during the time period 1944 through 1998 among 17,924 men employed in the synthetic rubber industry. In this group, there were 6237 deaths, which is 14% fewer than the 7242 deaths expected based on general population rates. Numbers of observed versus expected deaths (shown hereafter as observed/expected) were 1608/1741 for all cancers combined, including 71/61 for leukemia, 53/53 for non-Hodgkin lymphoma (NHL*), and 26/27 for multiple myeloma. The higher than expected number of deaths from leukemia (16% increase) was concentrated in workers paid hourly who had started work 20 to 29 years earlier, had worked 10 or more years in the industry, and had worked in subgroups employed in polymerization, coagulation, maintenance labor, and laboratory operations. The overall higher leukemia mortality rate, as well as the higher rate in the subgroup of hourly workers who had 20 or more years since hire and 10 or more years worked, was not limited to a particular form of leukemia. Cumulative exposure to 1,3-butadiene (BD) was associated positively with all leukemias, with chronic myelogenous leukemia and, to a lesser extent, with chronic lymphocytic leukemia (CLL).

Exposure to styrene or to dimethyldithiocarbamate (DMDTC) also was associated positively with leukemia. Exposures to these two agents were correlated with exposure to BD; data were limited on the independent effects of each of the three chemicals on leukemia. After controlling for the effects of BD, we found no consistent exposure–response relation between either styrene or DMDTC and all leukemias, chronic myelogenous leukemia, or CLL. However, a positive association between any exposure to DMDTC and leukemia persisted. The data from this study indicate that employment in the synthetic rubber industry is related causally to leukemia. Uncertainty remains about the specific agent or agents responsible for the association. The carcinogenic mechanisms through which BD, styrene, or DMDTC could cause leukemia in humans have not been established, and epidemiologic support for a leukemogenic role is limited for these agents.

Styrene and DMDTC were associated positively with NHL. External support for this relation has not been reported from other epidemiologic studies. The study did not find any clear relation between exposure to BD, styrene, or DMDTC and multiple myeloma. Some subgroups of subjects had more than the expected number deaths from colorectal cancer, prostate cancer, and other diseases. These increases did not appear to be related to occupational exposure in the industry.

INTRODUCTION

BD and styrene are used widely in various industries (Hibbs 1990). Exposure to these chemicals occurs in these occupational settings and in the general environment via emissions from industrial and other sources. The possible effects of BD and styrene on lymphohematopoietic cancer (LHC) and other diseases in humans have been investigated previously, but unanswered questions remain.

In 1992 the International Agency for Research on Cancer (IARC) classified BD as a probable human carcinogen (group 2A) based on sufficient evidence of carcinogenicity in animals and limited evidence in humans (IARC 1992). In 1998 the IARC reviewed new information and retained the classification of BD as a probable human carcinogen

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

This Investigators' Report is one part of Health Effects Institute Research Report 132, which also includes a Commentary by the Health Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr Elizabeth Delzell, Department of Epidemiology, School of Public Health, 1665 University Blvd, University of Alabama at Birmingham, Birmingham AL 35294-0022.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award R82811201 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

(IARC 1999). Again, the evidence of carcinogenicity was deemed limited, that is, inconclusive, in humans. The National Toxicology Program's Report on Carcinogens, Ninth Edition, listed BD as a known carcinogen in humans (US Department of Health and Human Services 2000).

The IARC has classified styrene as possibly carcinogenic to humans (group 2B) based on limited evidence of carcinogenicity in laboratory animals and on inadequate evidence in humans (IARC 1994). A metabolite of styrene, styrene epoxide, is carcinogenic in animals (IARC 1994), but the human cancer-causing potential of this metabolite remains uncertain. The National Toxicology Program's Report on Carcinogens, Tenth Edition, listed styrene oxide as reasonably anticipated to be a human carcinogen (US Department of Health and Human Services 2002).

The research described in this report expanded and reevaluated epidemiologic data on the largest group of BD-exposed human subjects that has been studied to date (Delzell et al 1996; Macaluso et al 1996; Sathiakumar et al 1998b). The main purposes were to determine if exposure to BD increases the risk of cancer in humans; to provide new information on the specific forms of cancer, if any; to assess the role of combined exposure to BD and two other chemicals (styrene and DMDTC); and to assess the impact of possible inaccuracies in exposure estimation on associations between BD and leukemia.

1,3-BUTADIENE

BD has been used since 1943 to make synthetic rubbers and other polymers and copolymers. Before the mid-1980s, some jobs in the synthetic rubber industry in the United States entailed exposure to BD concentrations greater than 25 ppm (8-hour time-weighted average [TWA]), with peak exposure concentrations of several hundred ppm (Fajen 1993; Macaluso et al 1996). Low-level environmental exposure occurs via emissions from facilities making or using BD, from motor vehicle exhaust, and from sidestream cigarette smoke.

Experimental studies have established that certain monoepoxide and diepoxide metabolites of BD (BDO and BDO_2) are genotoxic and that BD is an animal carcinogen (Himmelstein et al 1997). In mice, BD or its metabolites cause malignant lymphoma, hemangiosarcoma of the heart, and tumors of the lung, mammary gland, forestomach, and possibly other organs (Huff et al 1985; Irons et al 1986a,b, 1987, 1989; Melnick et al 1988, 1989, 1990). In rats, BD causes mammary gland tumors and other tumors related to endocrine function (Owen et al 1987).

BD is a more potent carcinogen in mice than in rats (Himmelstein 1997). The primary factors responsible for the higher sensitivity of mice appear to be species differences in the rate of BD metabolism, in the accumulation of specific metabolites in blood and other tissues, and in the genotoxic potential of the metabolites. Both in vivo and in vitro studies have shown that mice oxidize BD to genotoxic BDO and BDO_2 at a much faster rate than rats do (Jackson et al 2000). The highly toxic intermediate metabolite BDO_2 has been identified as a primary contributor to BD-induced carcinogenicity in mice (Richardson et al 1999; Henderson et al 2000). Rats have a lower ratio of activation-to-detoxification of BDO and BDO_2 (Richardson et al 1999; Henderson et al 2000; Recio et al 2000). It has also been shown that primates produce relatively less BDO and detoxify it more rapidly in comparison with mice (Henderson et al 1993). The metabolism of BD in humans is not fully understood, but in vitro studies have suggested that human metabolism more closely resembles that of the rat than of the mouse (Henderson et al 2000; Jackson et al 2000; Recio et al 2000).

Epidemiologic studies of BD in occupational settings have yielded inconsistent results (Meinhardt et al 1982; Downs et al 1987; Matanoski and Schwartz 1987; Matanoski et al 1990, 1993, 1997; Santos-Burgoa et al 1992; Divine et al 1993; Cowles et al 1994; Ward et al 1995, 1996; Divine and Hartman 1996). In several investigations of BD monomer production workers who had been possibly exposed to BD but not to styrene, DMDTC, or other chemicals used in polymer production, no association between BD and leukemia was found (Downs et al 1987; Divine et al 1993; Cowles et al 1994; Ward et al 1995, 1996; Divine and Hartman 1996). However, two of the studies reported increased rates of deaths from lymphosarcoma, a form of NHL (Downs et al 1987; Divine et al 1993; Ward et al 1995, 1996; Divine and Hartman 1996). The analysis of the results for lymphosarcoma was unclear, however, because the data were sparse and because there was no distinct pattern of increasing lymphosarcoma rates with increasing duration of possible exposure. In addition, quantitative estimates of exposure to BD were not developed and thus exposure–response was not examined.

In an update of the largest study conducted with BD monomer production workers, Divine and Hartman (2001) reported a significantly elevated standardized mortality ratio (SMR) for all LHCs (SMR = 141, 95% confidence interval [CI] = 105, 186). There were a few more observed than expected leukemia deaths (18/14, SMR = 129, CI = 77, 204). No trend in the SMR for leukemia was evident with increasing years worked: the SMR was 136 (CI = 62, 259) for the group employed for fewer than 5 years, 73 (CI = 8, 264) for the group employed for 5 to 19 years, and 151 (CI = 61, 312) for the group employed 20 or more years. All of

the leukemia deaths occurred among subjects hired in the 1940s (18/12, SMR = 152, CI = 90, 240). For NHL, the SMR was 148 (CI = 89, 231) and was greater for workers employed for fewer than 5 years (SMR = 197, CI = 101, 344) than for the group employed for 5 to 19 years (SMR = 127, CI = 25, 372), or for the group employed for 20 or more years (SMR = 90, CI = 25, 231).

The results of studies in the sector of the synthetic rubber industry that uses monomers to make styrene-butadiene rubber (SBR) and other rubbers differ to some extent from the findings of studies of BD monomer production workers. Since 1987, SBR investigations have reported more than the expected number of deaths from leukemia among subjects in particular work areas within the industry (Matanoski and Schwartz 1987; Matanoski et al 1990, 1993, 1997; Santos-Burgoa et al 1992; Delzell et al 1996; Macaluso et al 1996; Sathiakumar et al 1998b). In contrast, the number of deaths from NHL was not higher than expected in the overall group of workers or in the same work-area subgroups that had a higher leukemia mortality rate (Sathiakumar et al 1998b).

Unlike the investigations of BD monomer production workers, the studies of synthetic rubber industry workers evaluated the relation between LHC and quantitative estimates of exposure to BD. Macaluso and colleagues (1996) reported a positive relation between estimated cumulative exposure to BD and leukemia. Matanoski and coworkers (1997), examining essentially the same subjects as those evaluated by Macaluso and colleagues (1996) but using a different exposure estimation approach, reported that BD was positively associated in a exposure-dependent manner with leukemia and with Hodgkin lymphoma but not with NHL. (A later section of this report [Previous Studies of Subjects Included in the Present Research] describes the studies of Delzell and associates [1996, 2001], Macaluso and colleagues [1996], and Sathiakumar and associates [1998b] in detail.)

Irons and Pyatt (1998) have suggested that the association between BD and leukemia seen in studies of synthetic rubber industry workers may have been influenced by exposure to DMDTC (see the Introduction section about DMDTC below). Delzell and associates (2001) recently investigated the effect of DMDTC on leukemia mortality among synthetic rubber industry workers and found a positive association. Controlling for this agent as a possible confounder reduced, but did not eliminate, the BD–leukemia association. There was no discernible interaction between BD and DMDTC.

Several transitional epidemiologic studies have evaluated biomarkers of exposure to BD and biomarkers of genotoxic effects of such exposure. Albertini and colleagues (2001, 2003) investigated biomarkers of exposure, of genotoxic effects, and of susceptibility at two BD facilities in the Czech Republic. The study included 24 workers in monomer production, 34 in polymerization, and 25 in plant administration (unexposed). The biomarkers of exposure were hemoglobin adducts and urinary metabolites of BD; the biomarkers of genotoxic effects were gene mutations and chromosomal aberrations; and the biomarkers of susceptibility were polymorphisms in genes involved in BD metabolism. All of these markers were evaluated in terms of their relation to external measurements of exposure. Albertini and colleagues found that urinary concentrations of BD metabolites and hemoglobin adduct levels were sensitive markers of low-level occupational exposure to BD. However, neither mutations nor chromosomal changes were related to externally measured concentrations of BD, to urinary concentrations of BD metabolites, or to levels of hemoglobin adducts.

In a study of BD polymer workers in China, Hayes and coworkers (2000, 2001) noted that BD-exposed workers had higher levels of hemoglobin adducts than unexposed workers. Hayes and coworkers did not find specific genotoxic effects at the chromosomal or gene levels related to BD exposure.

Begemann and colleagues (2001) studied hemoglobin adduct levels as biomarkers of BD exposure among 30 workers exposed to BD and 10 unexposed workers at an Italian BD production plant and among 14 diesel-exposed workers from a potassium mine. There was no detectable difference in hemoglobin adduct levels between exposed and unexposed subjects. A relatively high adduct level of unknown origin occurred among unexposed subjects. This result may have obscured any small difference due to BD between exposed and unexposed subjects. Exposure to BD was substantially lower among the Italian workers than among exposed subjects included in the Czech Republic (Albertini et al 2001, 2003) and Chinese (Hayes et al 2000, 2001) studies.

STYRENE

Styrene, like BD, is produced by the petrochemical industry. It is used more widely than BD in making other petrochemicals, synthetic elastomers, plastics, and polyester paints. Generally, workers are exposed to relatively low styrene levels (TWA < 10 ppm) in styrene monomer and polymer production, in SBR, latex, and paint production, and in styrene polymer fabrication operations. Much higher exposures have been documented in reinforced plastics production (Pfaffli and Saamanen 1993; IARC 1994).

Studies of humans exposed to styrene have found no clear evidence of carcinogenicity (Coggon 1994). In their

investigation of synthetic rubber workers, Matanoski and colleagues (1997) reported that styrene was positively associated with NHL and with multiple myeloma but not with leukemia or Hodgkin lymphoma. Additional information on the health effects of styrene comes from studies of workers in the reinforced plastics manufacturing industry (Kogevinas et al 1993, 1994; Kolstad et al 1994, 1995; Wong et al 1994), from studies of workers in styrene monomer and polymerization facilities (Nicholson et al 1978; Hodgson and Jones 1985), and from a study of workers employed in developing and manufacturing styrene-based products (Bond et al 1992). These investigations observed increases in leukemia, NHL, and other LHCs, as well as in lung cancer in some subgroups of workers. However, the pertinent results were difficult to interpret because of small numbers of observed and expected deaths, a lack of consistent duration–response patterns, and methodologic limitations pertaining to exposure assessment and control of confounding by other chemicals present in the occupational settings studied.

Several analyses of data from a large investigation of reinforced plastics workers in Europe have focused on diseases other than LHC. These studies reported that styrene may be associated with mortality from nonmalignant genitourinary system disease (Welp et al 1996a) and chronic diseases of the central nervous system (Welp et al 1996b), and with the incidence of pancreatic cancer (Kolstad et al 1995). In addition, Matanoski and Tao (2002) reported a positive association between styrene exposure and ischemic heart disease among synthetic rubber industry workers.

BENZENE

Benzene was used in the synthetic rubber industry in laboratory testing (small-volume use) and as a solvent carrier in solution polymerization, primarily to make polybutadiene rubber (relatively large-volume use). Exposure to benzene is an established cause of acute myelogenous leukemia and may increase the risk of other forms of leukemia (IARC 1987; Savitz and Andrews 1997). Epidemiologic evidence for an effect of benzene on forms of LHC other than leukemia is unconvincing (Savitz and Andrews 1997).

Although benzene was used in some synthetic rubber production facilities, it does not appear to have had any major impact on the occurrence of leukemia in the industry (Macaluso et al 1996). This finding implies that benzene exposure levels were too low or that too few workers were exposed to produce a statistically detectable increase in leukemia.

DMDTC

DMDTC is a water-soluble chemical used in the synthetic rubber industry as a short stop compound (which terminates the polymerization process) beginning in the late 1940s or early 1950s. Irons and Pyatt (1998) proposed that DMDTC exposure explains the higher than expected rate of leukemia seen among SBR workers and the apparently contradictory results of studies of synthetic rubber workers and of BD monomer workers. The hypothesis stems partly from the known pharmacologic effects of dithiocarbamates, a category of chemicals related to DMDTC. Several dithiocarbamates (eg, diethyldithiocarbamate and disulfiram) are associated with bone marrow depressant effects, which lead to reduced counts of peripheral leukocytes and platelets.

Recent studies have highlighted the possible mechanistic importance of the inhibitory activity that dithiocarbamates exert on the activity of a transcriptional regulatory protein important in T lymphocyte activation. Pyatt and coworkers (1998) reported that DMDTC inhibits T lymphocyte activation and the clonogenic response of $CD4^+$ bone marrow cells. Irons and associates (2001) recently demonstrated that human bone marrow cells are relatively resistant to the direct effects of BD metabolites, and that only BDO_2 suppresses hematopoietic clonogenic response at physiologically relevant concentrations. In contrast, treatment of human $CD4^+$ lymphocytes with low concentrations of DMDTC resulted in significant suppression of clonogenic response and T lymphocyte function.

Bird and colleagues (2001) investigated exposure to DMDTC via dermal absorption in mice. Their research demonstrated that DMDTC was toxic to cells within the bone marrow, and when mice were also exposed to BD, DMDTC exposure increased the number of bone marrow micronuclei, a marker of clastogenicity.

PREVIOUS STUDIES OF SUBJECTS INCLUDED IN THE PRESENT RESEARCH

We had previously studied the same group of 17,964 North American synthetic rubber industry workers, about 75% of whom were exposed to BD and 83% to styrene (Macaluso et al 1996). Our earlier investigation of these workers evaluated mortality patterns during a 47-year period, from 1944 through 1991 (Delzell et al 1996; Macaluso et al 1996; Sathiakumar et al 1998b).

The overall study group had lower than expected mortality from all causes combined, from all cancers combined, and from most other major causes of death. Deaths from all LHCs and leukemia were significantly higher than expected

among hourly workers with 20 or more years since hire (years since hire is a surrogate for disease induction time) and 10 or more years of work in the industry. This group also had a slightly, but not significantly, higher rate of NHL deaths and had fewer than expected deaths from Hodgkin lymphoma and from multiple myeloma. Examination of LHC mortality patterns by time period of hire (1940s, 1950s, 1960 and later) among hourly SBR workers with 20 or more years since hire and 10 or more years worked indicated that the leukemia mortality rates were highest and were statistically significant for men hired in the 1950s (SMR = 375, CI = 171, 713). In this subgroup, a higher mortality rate also was present among men hired in the 1940s (5/1.9 deaths) or in 1960 or later (2/0.7 deaths), but these two results were not statistically significant.

Other key results for leukemia included (1) higher mortality rates among workers in plant areas with possibly high BD exposure (polymerization, maintenance labor, and laboratory areas); (2) a relative rate (RR) for BD-exposed (compared with unexposed) workers that increased irregularly with increasing cumulative BD exposure (given in ppm-years); this RR was 3.6 (CI = 1.0, 13.2) for the highest cumulative exposure category of 200+ ppm-years; and (3) no clear pattern of association with styrene or benzene. NHL and multiple myeloma were not consistently associated with BD or styrene exposure. Hodgkin lymphoma was not examined in detail because of the small number of subjects with this cause of death.

For subjects in SBR and related operations, results for cancers other than LHCs included lower-than-expected mortality from buccal cavity and pharynx cancer and from digestive system cancers and a small increase in deaths from larynx and lung cancers (Delzell et al 1996; Sathiakumar et al 1998b). Certain subgroups of workers had statistically significant increases in deaths from lung cancer, larynx cancer, or colon cancer. Analyses by work area indicated that these increases were unlikely to be due to monomer exposure.

Additional research on these workers included: (1) review of the medical records of 138 subjects whose death certificates noted LHC as the cause of death; (2) an extensive peer review and refinement of historical exposure estimates for BD and styrene and the addition of historical exposure estimates for DMDTC (Macaluso et al 2004); and (3) a further analysis of leukemia rates in relation to the revised estimates for BD and styrene and to the additional estimates for DMDTC (Delzell et al 2001). The review of medical records (1) found close to 100% agreement between the death certificate and medical record diagnoses when all LHCs were considered; (2) clarified the specific form of leukemia for 18 of 24 decedents whose death certificates had incomplete diagnostic information; and (3) identified nine decedents who had had both leukemia and NHL or Hodgkin lymphoma.

Additional work on historical exposure estimation included a comprehensive review of previously derived exposure estimates; calculation of DMDTC exposure estimates; and the development of a computer system for (1) documenting assumptions made about determinants of exposure to BD, styrene, and DMDTC, and (2) generating a series of exposure estimates for each stratum of the plant-specific, work area/job group–specific, calendar year–specific job–exposure matrix (JEM) for each chemical of interest by allowing assumptions about exposure determinants to vary.

After reviewing the previously derived exposure estimates of BD and styrene and developing estimates of DMDTC exposure, we reexamined the associations between BD and leukemia and between styrene and leukemia and assessed the relation between DMDTC and leukemia (Delzell et al 2001). Leukemia was positively associated with BD ppm-years, and the relation was stronger for exposure to BD concentrations higher than 100 ppm than for exposure to lower concentrations. Exposures to BD and styrene were highly correlated. Both BD and styrene ppm-years displayed a consistent exposure–response pattern in single-agent models, but for each chemical this pattern was weakened in analyses that controlled for the other agent. DMDTC was associated positively with leukemia, but without a exposure–response pattern. The pattern of results for BD and styrene in relation to leukemia was similar to that reported previously for the same subjects (Macaluso et al 1996), although revised TWA exposure estimates, compared with original estimates, were about four to six times higher for BD and two times higher for styrene (Macaluso et al 2004).

SPECIFIC AIMS

The present study updated and reassessed the mortality of the group of North American synthetic rubber industry workers described in the previous section (Delzell et al 1996, 2001; Macaluso et al 1996; Sathiakumar et al 1998b). These workers were possibly exposed to the monomers BD and styrene, to the short stop compound DMDTC, and to other chemicals used in making SBR and other synthetic elastomers. The specific research objectives were:

- to determine if occupational factors such as time period of hire, years worked, years since hire, and work area are

associated with cause-specific mortality among synthetic rubber industry workers; and

- to evaluate the relations between quantitative estimates of BD, styrene, or DMDTC exposure and leukemia, other LHCs, and selected cancers other than LHCs.

We evaluated LHC mortality in relation to the various occupational factors mentioned above, as well as in relation to quantitative exposure estimates, for several reasons. First, the quantitative exposure estimates that had been developed in our previous studies were subject to information bias. Evaluating mortality rates in relation to other occupational factors, such as years worked in the synthetic rubber industry and years in particular work areas, would provide information important for assessing the validity of the current study's results. Second, chemicals other than those for which we had developed quantitative exposure estimates may have had an impact on disease occurrence among synthetic rubber workers. For example, BD, styrene, and DMDTC have been the main foci of investigations of this worker group. But these workers were exposed to other chemicals, and examining mortality patterns by work area could be useful in determining if previously unsuspected hazards existed. Third, we planned to evaluate mortality patterns by the time period of hire because our previous research indicated a clear increase in leukemia rates among men who started work in the synthetic rubber industry in the 1950s, but results were equivocal for men whose employment began in 1960 or later.

METHODS AND STUDY DESIGN

OVERVIEW OF THE STUDY DESIGN

This investigation was a retrospective follow-up study of mortality among men who worked for at least 1 year at any of eight synthetic rubber plants, seven in the United States and one in Canada. The time period covered by the study was January 1, 1944, through December 31, 1998.

We used the quantitative estimates of exposure to butadiene, styrene, and DMDTC developed earlier (Macaluso et al 2004). The estimates were derived from in-depth analyses that relied on specific information from each plant and time period. This information included sources of exposure associated with tasks that comprise each job in the industry. We also developed models to estimate the concentrations of exposure from each source.

Records from various national and private agencies and tracing individual subjects provided information on subjects' vital status as of the end of 1998. Cause of death information came from death certificates; from the US National Death Index *Plus* (NDI) decedent data (Sathiakumar et al 1998a); from Statistics Canada decedent data; and, for LHC decedents, from physicians' or hospitals' medical records.

Stratified analyses compared mortality rates of all subjects combined and of subjects in particular work areas or other subgroups with general population mortality rates. Multivariable analyses, conducted on data from six of the eight plants studied, compared the mortality rates of subjects in a particular chemical exposure level with the rates of unexposed subjects. Uncertainty analyses assessed the impact of inaccuracies in exposure estimation on exposure–response data for the relation between BD and leukemia.

Work done during previous investigations included

- identifying subjects at each of the study plants;
- developing data on their work histories, vital status, and causes of death for 1944 through 1991;
- retrieving and reviewing the medical records of subjects who died of LHCs between 1944 and 1991;
- developing estimates of each subject's cumulative exposure to BD, styrene, and DMDTC; and
- analyzing the relation between employment factors (including cumulative exposure indices) and cause-specific mortality between 1944 and 1991.

For this study, no new subjects were added, but information on the original population was added. Work carried out for this study included

- updating information on vital status and causes of death for 1992 through 1998;
- retrieving and reviewing the medical records of men who died of LHCs between 1992 and 1998;
- comparing subjects' cause-specific mortality rates with those of state and provincial general populations for 1992 through 1998, as well as for the entire study period of 1944 through 1998;
- comparing subjects' mortality rates from leukemia of specific cell types—and the rates of the cancer category consisting of CLL or NHL—with those of state and provincial general populations between 1968 and 1998; and
- comparing rates, LHCs, other cancers, lymphoid neoplasms, and myeloid neoplasms among subgroups specified on the basis of their cumulative exposure to BD, styrene, and DMDTC for 1944 through 1998.

THE PLANTS STUDIED

Large-scale synthetic rubber production began in North America in the early 1940s (Hibbs 1990). Worldwide, SBR is the most extensively used rubber; it is produced by an emulsion process or by a solution process, emulsion being more common. Other synthetic rubbers containing BD include polybutadiene, neoprene (polymers of 2-chloro-1,3-butadiene, also called chloroprene), and nitrile (copolymers of BD and acrylonitrile). Other types of synthetic rubber containing styrene are styrene-BD-styrene and styrene-isoprene-styrene block copolymers. Common forms of synthetic rubber that do not contain BD or styrene include polyisoprene, butyl (copolymer of isobutylene and isoprene), halobutyl, and ethylene propylene rubbers.

Seven of the plants included in the study were in the United States and one was in Ontario Canada. Throughout much of their histories, emulsion SBR was a major product. Some of the plants made other synthetic rubbers as well as SBR, including polybutadiene, nitrile, and butyl rubber. All of the plants had tank farm, warehouse, laboratory, utilities, and maintenance operations, in addition to rubber production areas.

SBR production involved several major steps: polymerization, recovery, coagulation, and finishing. Emulsion polymerization of SBR involved mixing (in water) the monomers BD and styrene with soaps, activators (sulfoxylates), and initiators (peroxydisulfates, peroxides). The polymerization process, which takes place in 3000- to 6000-gallon reactor vessels, proceeds until about 70% to 75% of the monomers are converted into polymers, at which point short stop chemicals (eg, DMDTC, diethyl hydroxylamine) are used to terminate the process. The product of polymerization is a liquid (latex) that contains both polymers and unreacted monomers. The recovery process uses flash distillation to remove unreacted BD monomer from the latex, and steam stripping to remove unreacted styrene monomers. The recovered monomers are recycled back into the production process. After removing unreacted monomers, the latex is blended with antioxidants, oils (optional), and carbon black (optional) and then coagulated by adding dilute sulfuric acid or aluminum sulfate. This produces a rubber crumb. In finishing, the coagulated crumb is washed with water, mechanically dewatered, dried, formed into 70- to 90-pound bales, and loaded into crates for warehousing and shipping.

Six of the seven US plants were similar with respect to their original design. All opened in the early 1940s and began by using a batch emulsion and hot-polymerization process to make SBR. Major improvements and expansions in the six plants occurred in the mid-1950s and included changes from a hot- to a cold-production process and from batches to a continuous process. The other US plant, which opened in 1957, was constructed to use a continuous polymerization process. The Canadian plant originally made SBR using an emulsion process similar to that of the six US plants. However, the Canadian plant also made butyl rubber and had various petrochemical operations.

Beginning in the 1960s, the product lines of some of the plants expanded. Two US plants and the Canadian plant began to make solution-process polybutadiene rubber using various solvent systems (including toluene at one US plant, hexane at another US plant, and benzene, cyclohexane, and 1-butene at the Canadian plant). Other synthetic rubbers made by some of the plants included emulsion-process polybutadiene rubber (one plant), emulsion-process nitrile rubber (three plants), emulsion-process styrene-BD latex (three plants), and solution-process SBR (one plant). None of the plants commercially produced neoprene, polyisoprene, or ethylene propylene rubbers.

SBR production workers were exposed to many chemicals, including BD and styrene monomers, emulsifiers, activators, modifiers, catalysts, short stops, dilute acids, antioxidants, oils, carbon black, and solvents. At plants where nitrile rubber was made, some workers may have been exposed to acrylonitrile. In the past, benzene was used in small quantities at most plants, primarily in certain laboratory procedures and maintenance operations, as well as in some solution-polymerization operations, mentioned above. Worker exposure to all of the chemicals listed above varied considerably by process area and by job within the plants.

SUBJECTS

Subject eligibility criteria were identical to those of our earlier investigations (Delzell et al 1996, 2001; Macaluso et al 1996; Sathiakumar et al 1998b). In brief, all subjects were men who had (1) worked at the plants for at least 1 year before the end of 1991 (ie, the latest date of hire was in 1990); and (2) were actively working in or after a specific calendar year between 1943 and 1965, which varied by plant depending on the availability of employment records (ie, a worker could have been hired before that date but must have still been working on or after that date).

The present study included 17,924 of the 17,964 subjects who were in our previous study (Delzell et al 1996). New scrutiny of work histories indicated that each of 31 men in the original study group had worked in two different plants and had two separate sets of records, which we combined for current analyses (by combining records, we reduced the total number of subjects by 31). Reassessment of work history data also indicated that eight men (five from US plants, three from the Canadian plant) worked for slightly

less than one year; and review of individual records revealed that one worker was a woman. We removed these ineligible subjects from the study.

We did not add any new subjects hired after 1990 at the study plants. Those workers would have had a short follow-up period and would have had predominantly low exposure to the agents of interest. For these reasons, the small amount of epidemiologic information gained from such subjects did not justify the considerable costs of identifying them, collecting data on them, and adding them to the study.

As in the previous study, certain analyses included the entire group of 17,924 workers. Other analyses included only the 15,612 men who were known to have worked in SBR and related operations (Delzell et al 1996). This restriction removed 2312 Canadian workers whose employment records indicated that they had worked exclusively in butyl rubber or styrene production or did not specify where they had worked. Butyl rubber production does not entail exposure to BD, styrene, or DMDTC; styrene production does not entail exposure to BD or DMDTC.

Analysis of mortality rates by level of exposure to BD, styrene, and DMDTC was limited to the 16,579 subjects for whom we developed quantitative exposure estimates. This group excluded 1345 men who had worked at either of two plants that had records judged to be inadequate for exposure estimation.

Subject information available from our previous studies included name, social security number (for US subjects), birth date, race (white and nonwhite), vital status as of the end of 1991, death date for those who died in or before 1991, plant hire and termination dates, and detailed job information. Our previous research procedures had used a number of checks to ensure that identification of eligible subjects was complete (Delzell et al 1996; Sathiakumar et al 1998b). These included cross-checking a subject roster compiled from plant personnel records with other employee records, such as seniority lists, organization charts, benefits records, plant hire and termination logs (lists of employees entering and leaving the workforce, typically compiled on a weekly or monthly basis), and lists of employees submitted quarterly or twice a year by the employer to the US Internal Revenue Service (IRS) for the purpose of reporting earnings.

WORK HISTORIES

In our previous studies of these subjects (Delzell et al 1996; Macaluso et al 1996; Sathiakumar et al 1998b), we had obtained personnel records from each of the eight participating plants and developed detailed electronic work history files. Each subject's work history file included—for each job—the start and end dates, a text description of the work area and job title, a three-digit code for the work area/job title combination, and the payroll classification (hourly or salaried) of the position.

From subjects' work history files we had derived a list of 8281 unique work area/job title combinations. Using plant-specific information on production, maintenance, and other operations, and on jobs and tasks within each type of operation, we assigned each of the 8281 combinations to one of 308 work area/job groups. Each of these groups consisted of processes and jobs considered to be similar. For each of the seven US plants, we classified all 308 work area/job groups as SBR-related. For the Canadian plant, we identified 272 work area/job groups and classified 145 as SBR-related and 127 as non-SBR–related.

For each of the eight study plants, we had combined SBR-related work area/job groups into five major work areas: production, maintenance, labor, laboratories, and other operations. For six of the eight plants, work histories were sufficiently detailed to permit specification of three work area subgroups of production (polymerization, coagulation, finishing), two subgroups of maintenance (shop maintenance, field maintenance), and two subgroups of labor (production labor, maintenance labor).

EXPOSURE ESTIMATION

We have described historical exposure estimation procedures in detail elsewhere (Macaluso et al 1996, 2004). In brief, we had originally developed TWA estimates of BD, styrene, and benzene concentrations for work area/job groups and individual subjects at only the six plants that had work histories sufficiently detailed for specifying both major work area/job groups and subgroups. In the Canadian plant, which was one of these six plants, we developed exposure estimates both for the SBR-related and for the non-SBR–related operations.

The present study did not evaluate benzene exposure in the synthetic rubber industry. Our earlier research had indicated that exposure to benzene probably was low and was not associated with LHC (Macaluso et al 1996). Subsequent investigations did not scrutinize benzene exposure estimation procedures in detail.

Estimation procedures for BD and styrene included: (1) at each plant, identifying a series of work area/job groups, each of which was homogeneous with respect to its component tasks and possible exposure; (2) for each plant-specific work area/job group, identifying the component tasks that entailed exposure and documenting historical changes in those tasks; (3) calculating plant, work

area/job group, and time-specific average exposure concentrations (ppm) and compiling these into JEMs; and (4) linking the monomer exposure concentration estimates in the JEMs with each subject's work history to obtain cumulative exposure estimates for each worker. Our methods are described below. Additional details may be found in papers by Macaluso and coworkers (1996, 2004).

In developing exposure estimates, we did not use industrial hygiene data gathered at these plants for several reasons: (1) extensive changes have been made in production processes and engineering controls in the synthetic rubber industry since it began in the 1940s; (2) historical exposure measurements are sparse before 1975; and (3) exposure measurements taken since 1975 did not cover all work area/job groups at all plants and may have underestimated BD concentrations.

Specifications of Work Area/Job Groups

To develop exposure information for each of the work area/job groups and for historical changes in exposure possibilities within each group, we conducted in-depth walkthrough surveys at each of the six plants, met with knowledgeable plant staff, obtained engineering and construction records, and interviewed workers who had a history of long-term employment in specific work area/job groups. The interviews provided information on process layout, equipment and material flow, process operations, job titles of workers employed in routine operations or maintenance and cleanup, possible exposure sources, and exposure control systems.

We carried out a work area/job group analysis to identify (1) component tasks that may have been associated with exposure, (2) task-specific determinants of exposure (equipment used, duration and frequency of the task, work practices, presence of exposure reduction mechanisms), and (3) historical changes in the work area/job group that may have influenced exposure determinants. We compiled this information into historical job profiles that summarized information from all sources of exposure for the work area/job group.

Development of Task-Specific Exposure Estimates

Our next step in estimating exposure was to specify, for each task, a possible exposure scenario and summary task description that explained how a worker would be exposed while performing the task. We considered three different exposure scenarios: specific task-related exposure originating from a point source of monomer emissions; background exposure resulting from work in buildings; and background exposure resulting from work in open areas. We then specified a mathematical model to calculate the exposure concentrations in ppm.

To calculate exposure originating from a task-specific point source, such as exposure during minor pump maintenance or sampling latex from a reactor, we used a near-field air dispersion model derived from the Pasquill-Gifford equation (Lipton and Lynch 1987). In this model, the three determinants of air concentrations of monomers were the monomer generation (emission) rate, the distance of the worker's breathing zone from the source of exposure, and the wind velocity across the area. For each task we compiled data on these variables. We based emission rate estimates on information obtained during interviews (eg, for a reactor sample taken during batch polymerization or the approximate volume of the sample) and on chemical parameters (eg, vapor pressure of the chemical and the evaporation surface). For distance between the source and the breathing zone, we relied on interviews and direct observations.

For background exposure due to work in buildings, we computed the exposure concentration using a dilution ventilation formula (American Conference of Governmental Industrial Hygienists 1992). In this model, the two determinants of ambient monomer concentration were the generation rate (eg, a monomer emission rate, which expresses the amount of monomer evaporating in a unit of time) and the ventilation rate (which expresses the amount of dilution due to air flowing through the work area in the same unit of time). To compute the average emission rate during one work shift, we summed exposure from each possible source of monomer release in an area. Exposure sources included equipment leaks, loading and unloading tasks, sampling tasks, and routine maintenance and cleaning tasks. We estimated ventilation rates from direct observations of the work area, descriptions obtained through interviews, and available engineering or safety data. For background exposure due to work in open areas, such as a tank farm, we developed a subjective estimate of the exposure concentration by assuming that exposure was present throughout the work shift at levels higher than in offices or outside the plant. Subjective background estimates generally were very low (often < 1 ppm) and had little influence on the average exposure level of workers who also carried out tasks that could entail exposure above the background.

Development of Exposure Estimates for Each Work Area/Job Group

The production process entailed functions that were well defined and other functions that were not well defined. For each plant, therefore, we specified a separate set of primary and secondary work area/job groups.

Each primary work area/job group consisted of a well-specified set of tasks. For example, for SBR polymerization reactor operators in one of the plants, total BD exposure was a combination of background exposure and exposure experienced in two specific tasks: operating valve racks for reactor charging and dropping, and performing minor maintenance in the area.

We compiled task-specific exposure estimates into a task–exposure matrix and identified the tasks that comprised each primary work area/job group. Then, to obtain 8-hour TWA estimates for each primary work area/job group, we developed algorithms to combine task-specific estimates with background estimates. First, we multiplied the exposure estimate (ppm) for each task by the task-specific minutes of exposure that occurred during a work shift to obtain the task-specific number of ppm-minutes; second, we multiplied the remaining portion of the time in the shift by the estimated background concentration to obtain the number of ppm-minutes of background exposure; and third, we added the two estimates of ppm-minutes and divided the sum by 480 minutes to obtain the 8-hour TWA in ppm. Thus, for each task in a primary work area/job group, the algorithms considered the frequency and duration of the task during an 8-hour work shift.

For each primary work area/job group, we also computed the annual number of exposures to peak concentrations for BD (> 100 ppm) and for styrene (> 50 ppm). We identified the per-shift frequency of tasks that entailed peak exposures and multiplied that by 225 shifts per year (to arrive at the number of peak exposures/year). To capture high exposures of short duration, this definition did not take into account the duration of a peak exposure.

The tasks that comprised each secondary work area/job group were less well specified. Therefore, we derived exposure estimates for each secondary group by obtaining the weighted average of exposure estimates among all primary work area/job groups that comprised the secondary group. For operators in secondary groups, weights corresponded to the relative frequency of workers in each of the primary groups. For example, consider the secondary work area/job group consisting of SBR polymerization operators whose work histories did not indicate a specific area within polymerization, such as tank farm, pigment preparation, reactor, or recovery. For this secondary group, exposure estimates were an average of the estimates computed for tank farm, pigment preparation, reactor, and recovery operators, weighted by the relative frequency of workers employed in each of these four well-specified areas among all operators in the polymerization area. For foremen and other salaried workers (who typically have jobs with lower exposure) in a secondary group, we applied an additional weight corresponding to an arbitrary percentage (eg, 25%) of the estimated exposure of operators in the work area/job group.

We linked exposure estimates for each work area/job group with the work histories of individual workers and computed a final lifetime cumulative exposure value for each worker. First we multiplied the specific amount of time in each calendar year that a worker spent in each work area/job group by the concentration (ppm) or the annual number of peak exposures (or both) estimated for that work area/job group in each calendar year; second, we summed the products over all the years covered by a worker's employment history to obtain cumulative exposure values of ppm-years or total number of peaks (referred to hereafter as total peaks).

At the time, this exposure estimation approach was innovative and controversial, and efforts to validate the exposure estimates were limited in scope (Macaluso et al 1996). For these reasons, we undertook to review and refine the original exposure estimates. In our review process, a panel of industry and other experts in industrial hygiene and chemical engineering reached a consensus about which factors were crucial in estimating historical monomer exposures. Developing a consensus involved a comprehensive review of the assumptions we had made in estimating exposure at the plants; compiling a list of questions to ask knowledgeable personnel at each plant about the crucial factors, assumptions, and model parameters; obtaining and reviewing responses to these questions; and specifying ranges of credible values for factors that affect exposure estimates.

We also revisited all six plants to interview key engineering and process personnel and to obtain additional documentation on work practices, operations, and engineering controls. We obtained a substantial amount of additional documentation of changes over time in plant operations and measured wind speed (one of the exposure determinants) and used the new information to refine assumptions about exposure estimation model parameters (Macaluso et al 2004).

In addition, two experts on the panel, an industrial hygienist and a chemical engineer, developed DMDTC exposure estimates (Appendix E, available on request). Developing these estimates used an approach similar to that used for BD and styrene to identify plant-specific exposure sources and determinants of exposure and to estimate task-specific exposures in various time periods. We first derived average DMDTC 8-hour TWA exposure concentrations (mg/cm) specific to each work area/job group and each time period; then we linked these estimates with subjects' work histories to obtain cumulative exposure estimates (given in mg/cm–years), again using procedures similar to those used for BD and styrene.

Units of cumulative exposure to DMDTC were expressed as mg/cm–years rather than ppm-years. DMDTC is a large molecule with low vapor pressure and it was used in a sodium salt and water solution. Thus, the most important route of exposure to DMDTC was dermal contact. Both the concentration of DMDTC in the solutions used in the manufacturing process and the area of the worker's skin that came into contact with the solution had to be considered in estimating exposure. Exposure calculations multiplied the concentration of DMDTC (in mg/L) in the solution by the area of skin (in cm^3) and by the exposure duration. Application of a unit conversion constant of 1000 cm^3/L yeilded DMDTC exposure concentrations in units of mg/cm.

The review of exposure assessment procedures suggested that our original estimates were low (Macaluso et al 2004). The revised BD exposure levels for each work area/job group and each worker were as much as one order of magnitude higher than the original estimates, particularly during the first 30 years of a plant's operations. Revised styrene exposure levels also were higher than original estimates, but differences were not as large as for BD. Despite extensive changes, the revised set of exposure estimates was equivalent to the original set of estimates in ranking individual employees according to cumulative exposures. The Spearman correlation coefficient for the comparison of the original with the revised cumulative exposure estimates among all subjects was 0.90 ($P < 0.0001$) for BD and 0.85 ($P < 0.0001$) for styrene.

Concurrently with the review and revision of the original exposure estimates, we developed an integrated system of computer programs to assist with documenting and calculating exposure estimates. This system consisted of an interactive Statistical Analysis System-AF interface that integrated text descriptions of each task with information about the exposure scenario, the exposure estimation assumptions, and calculations to document the exposure estimates for each task and time period. The interface enabled us to review and modify estimation assumptions, to recalculate estimates specific to tasks and work area/job groups, and to obtain for each agent the approximate probability distribution of concentrations or peak exposure estimates for each combination of plant, work area/job group, and calendar year.

The software system also facilitated developing two additional exposure metrics by partitioning BD exposure estimates for each work area/job group into TWA concentrations at or below versus above the threshold of 100 ppm that we used to assess peak exposures. For example: A work area/job group might entail exposure to 10 ppm BD for 2 hours per shift and to 500 ppm for 5 minutes per shift. The exposure below the threshold of 100 ppm would include 1700 ppm-minutes at $\leq$ 100 ppm. The exposure above the threshold would include 2000 ppm-minutes at > 100 ppm. The total 8-hour TWA would be 7.7 ppm, composed of 3.5 ppm at or below the threshold and 4.2 ppm above the threshold. (In the remainder of the text and in the tables, these metrics are referred to as partitioned BD ppm-years.)

Macaluso and colleagues (2004) have described the development of approximate probability distribution estimates for each combination of plant, work area/job group, and year of the JEM for each agent. Appendix A further summarizes exposure estimation procedures by illustrating how the approximate probability distribution of the estimates of BD exposure were derived for one combination of plant, task, and year, and how these estimates were used to obtain the corresponding distribution for a combination of plant, work area/job group, and year.

In brief, for each task that entailed exposure other than background, we derived the distributions of exposure estimates for tasks by specifying lower and upper boundaries for the emission rate, the ventilation rate and air speed, and, when appropriate, the distance of the worker from a point source of emissions. We then computed an approximate probability distribution of the BD exposure concentration for a task by assuming that each parameter in the exposure model followed a triangular distribution with mode at the midpoint between the boundaries, identifying the 1st, …, 99th percentile of its distribution, and computing the exposure concentrations for all possible combinations of exposure quantiles. We further computed the approximate distribution of the sum, over one work shift, of BD exposure (in ppm-minutes) associated with a particular task by assuming that the task's duration and frequency followed a triangular distribution. We evaluated the resulting empirical distributions to find the approximate 1st, …, 99th percentile of the exposure concentration estimate specific to each task and time period. To obtain the approximate empirical probability distribution of BD exposure for each work area/job group for a particular year, we summed the pertinent task-specific concentrations for the group and assumed that exposure levels were independently distributed across all tasks. We computed subjects' approximate distribution of cumulative ppm-years assuming that exposure levels were independently distributed across years and work area/job groups.

All main analyses of total and partitioned BD ppm-years, total BD peaks (> 100 ppm), styrene ppm-years, total styrene peaks (> 50 ppm), and cumulative DMDTC exposure (mg/cm–years) used exposure data obtained by linking subjects' work histories to a JEM that contained TWA exposure concentrations corresponding to the mean

of the approximate probability distribution of specific estimates for each plant, work area/job group, year, and agent.

In contrast, uncertainty analyses of BD ppm-years (discussed further in the section Statistical Methods and Data Analysis / Uncertainty Analyses) used JEMs consisting of exposure concentrations that corresponded to randomly selected percentiles of the approximate probability distribution of BD exposure concentrations for each specific plant, work area/job group, and year.

DETERMINING VITAL STATUS

Our previous investigation (using data as of the end of 1991) had identified 4665 subjects as having died, 12,565 as presumed living, and 734 with unknown vital status (Delzell et al 1996). To establish vital status for the 12,605 subjects from US plants, we had used records of the plants, the US Social Security Administration's (SSA's) death master file, the NDI, the Health Care Financing Administration, and the divisions of motor vehicles of several states. For the 5359 Canadian subjects, we had identified decedents by a record link with the national Canadian Mortality Data Base (CMDB) of Statistics Canada, and we classified as presumed living all Canadian subjects without a death record.

For US subjects in this study, we used a modification of a standard protocol (Schall et al 1997) to update vital status information through 1998 for the 9189 subjects who had been classified at the end of the previous study as alive (n = 8455) or as lost to follow-up (n = 734). Vital status ascertainment began with linking information on subjects with SSA records on decedents and with IRS records on persons with recent tax activity. These links identified decedents and provided information on locations and dates of their deaths. Also, the SSA and IRS record links identified subjects who could be classified as alive by virtue of their having recently filed a federal tax return. No useful SSA or IRS data was found for the remaining subjects. We also carried out a record link with Pension Benefits Information (a private company that has data from the SSA, the Railroad Retirement Board, the US Department of Defense, and the mortality files of 12 states). For all subjects who had been lost to follow-up, we searched the NDI to confirm that none of them had died during or after 1979, the year that NDI started.

We visually reviewed all results from these links to identify true matches and evaluated each possible match for consistency between our data and the external data with regard to name, birth date, race, and gender. For any subjects who had died since the end of our previous study, we verified whether the death date from the external agency was the same as or after the subject's employment separation date.

Database links identified 7342 US subjects as still alive, 4547 as deceased, and 679 as lost to follow-up as of the end of 1998. We also attempted to locate and contact a sample of the 679 subjects lost to follow-up to determine directly if they were alive. The sample selected for individual vital status tracing included all men who would have been 65 years of age or older if they were still alive as of the end of 1998 (n = 368) plus a 10% sample of the men who would have been younger than 65 years of age (n = 45). To locate these subjects' addresses and telephone numbers, we used Internet sources, LEXIS/NEXIS records, and searches with AQM Information Solutions (Brockton MA). (LEXIS/ NEXIS is a commercial computerized database that can assist with locating the addresses of people residing in the United States. AQM Information Solutions specializes in retrieving consumer information from a continuously updated national database of nearly 200 million consumers in 50 states, Guam, Virgin Islands, and Puerto Rico.) We contacted each subject or his family by telephone to confirm his vital status using a brief questionnaire. The questionnaire asked the respondent (subject or family member) to confirm his birth date, the plant where he worked, and his approximate employment dates. When direct contacts and interviews identified a subject as deceased, we asked for information on the location (state) and date of death. After individual tracing was complete, we had identified an additional 104 US subjects as alive and 5 subjects as deceased. Final vital status data on US subjects indicated that 7446 were living, 4552 were deceased, and 570 were lost to follow-up.

We identified deaths among Canadian plant workers by linking their records with CMDB records. Statistics Canada performed the actual linking. We classified as "presumed living" all Canadian plant workers not identified as deceased by the CMDB link. We submitted data on a sample of Canadian workers (n = 1439) to Cambridge Statistical Research Associates (Irvine CA) to identify any deaths that may have occurred in the United States. The sample included 1439 subjects who were identified as alive at the end of the previous study. Of these, 884 had retired; 555 had not retired and had 20 or more years since hire. We did not identify any decedents in this sample.

Using these procedures, we established the vital status of 97% of the study group. Only 570 (3%) subjects were lost to follow-up.

DETERMINING CAUSE OF DEATH

In our previous study, cause of death information had come from death certificates obtained for 3274 (96%) of 3397 US decedents. Most analyses of mortality rates used International Classification of Diseases (ICD), Eighth Revision, codes that were assigned by a study nosologist for the underlying cause of death recorded on the death certificate.

Of the 3274 US decedents with a death certificate obtained during the previous study, 1499 had died before 1979, and 1775 had died during the period 1979 through 1991. For the group who had died before 1979, the nosologist for the current study recoded the underlying cause of death from the death certificates by using the ICD Revision that was in effect at the time of each death rather than relying on the Eighth Revision (the correct ICD Revision is required by the software used for many analyses in the present study). For any major discrepancies (n = 51) in categories of cause of death indicated by the original codes compared with the newly assigned ICD codes, a nosologist from the US National Center for Health Statistics (NCHS) reviewed and resolved the discrepancies. Of these 51 death certificates, for 28 the NCHS code agreed with the newly assigned code, and for 23 the NCHS code did not agree. We retained the ICD codes assigned by the NCHS nosologist for these 51 decedents.

For the 1775 subjects who died between 1979 and 1991, we replaced the original ICD codes with ICD codes obtained from the NDI. The NDI, which contains information on more than 95% of deaths since 1979 in the United States, now provides through its NDI *Plus* data the ICD codes assigned by the NCHS to the underlying cause of death and to each additional cause of death, to a maximum of 20, listed on a person's death certificate (US Department of Health and Human Services 1999). Use of NDI *Plus* ICD codes in analyses that compare a study group's cause-specific mortality rates with national, state, or regional general population rates is advantageous because it minimizes the possibility of observation bias (Sathiakumar 1998a).

Before replacing the original ICD codes with NDI *Plus* ICD codes, we compared the NDI *Plus* codes with death certificate diagnoses. All death certificates for subjects who died of LHCs had a correct NDI *Plus* ICD code for LHC as either an underlying or contributing cause of death. Of the 78 subjects with LHC coded as the underlying cause of death in the previous study, 75 (96%) had a concordant NDI *Plus* designation of LHC as the underlying cause of death. For the remaining three decedents (all leukemias), the LHC code was included as a contributing cause. For all other codes for major categories of cause of death, the percentage of agreement between the previous and current studies ranged from 75% to 100%; 21 of 27 major categories had 95% or greater agreement (Appendix B).

We did not retrieve a death certificate for all decedents newly identified in the current study. Instead, we used NDI *Plus* ICD codes to determine causes of death. We retrieved a death certificate only if the NDI record link was doubtful or if the NDI *Plus* ICD codes indicated LHC (ICD codes 200–208) or a blood disorder (ICD codes 280–289) as a cause of death. For all decedents with ICD codes 200–208, the death certificate text description of causes of death confirmed the particular form of LHC indicated by the NDI *Plus* code.

Cause of death codes for Canadian decedents came from the CMDB. These codes were based on the Revision of the ICD in effect at the time of death. We reviewed the death certificates of all Canadian decedents to confirm ICD codes for LHCs and to identify decedents with LHC as a contributing cause of death.

MEDICAL RECORDS

In a previous study, we had attempted to obtain medical records for 127 subjects who had died before 1992 and whose death certificates had mentioned LHC or a blood disorder (Delzell et al 2001). Such records were available for 48 of 58 subjects with leukemia, 27 of 31 with NHL, 8 of 9 with multiple myeloma, 7 of 8 with Hodgkin lymphoma, and 7 of 8 with other blood disorders. Medical record review found that 1 subject whose death certificate indicated NHL actually had pancreatic cancer. All other medical records confirmed an LHC. The records of 8 subjects mentioned both leukemia (CLL) and NHL. The records of 1 subject mentioned both leukemia (unspecified myelogenous) and Hodgkin lymphoma. For 1 subject with a death certificate diagnosis of myelodysplasia, medical records indicated acute unspecified leukemia.

For the current study, we attempted to obtain the medical records of the 53 workers who died between 1992 and 1998 and whose death certificates mentioned LHC as an underlying (n = 47) or contributing (n = 6) cause of death. Records were available for 20 of 22 subjects with leukemia, 22 of 25 with NHL (1 of these also had CLL), 4 of 6 with multiple myeloma, and for the 1 subject with Hodgkin lymphoma. Review of the available data by a pathologist confirmed the death certificate reports of all 20 leukemias and all 4 multiple myelomas with medical records. However, the medical record review found that 2 subjects whose death certificates indicated NHL had actually had lung cancer or head and neck cancer (primary anatomic site not specified). One record, like the death certificate, indicated that the subject had NHL and CLL. Medical records were not adequate to identify specific histopathologic forms of NHL.

We used medical record diagnoses to classify LHC decedents for internal analyses (see the Statistical Methods and Data Analysis section below). However, in order to avoid information bias, we retained the death certificate diagnoses and ICD codes to use in all external analyses, which compared subjects' mortality rates with those of the general population.

As explained in the next section, some analyses considered NHL and CLL combined (referred to as CLL–NHL), and other analyses evaluated all lymphoid neoplasms combined or all myeloid neoplasms combined. We combined CLL and NHL because, like CLL, about 85% of NHLs are B cell malignancies (Harris et al 1999). Also, CLL and a rare form of NHL (small lymphocytic lymphoma) are now considered to be the same disease and together account for about 5% of all NHLs (Harris et al 1999).

The World Health Organization (WHO) Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues has proposed dividing LHCs into two major categories, each one having a number of component subgroups: lymphoid neoplasms and myeloid neoplasms (Harris et al 1999). In our study, medical record and death certificate data were sufficient to allow us to classify LHCs into these two major categories, but not into the further subgroups proposed by the WHO. To consider the possibilities that (1) neoplasms in each major category could have similar etiologic factors and (2) the etiologic factors might differ between the two categories, certain analyses, described in the next section, examined the effects of BD, styrene, and DMDTC separately for lymphoid and myeloid neoplasms. Lymphoid neoplasms included lymphoid leukemia, NHL, Hodgkin lymphoma, and multiple myeloma. Myeloid neoplasms included myeloid and monocytic leukemia, erythroleukemia, myelofibrosis, myelodysplasia, polycythemia vera, and myeloproliferative disease.

APPROVAL OF THE PROTOCOL

The Institutional Review Board of the University of Alabama at Birmingham reviewed and approved the study protocol. We submitted regular reports to the board during the conduct of the study.

STATISTICAL METHODS AND DATA ANALYSIS

OVERVIEW

Analyses consisted of two general types of comparison. External analyses compared subjects' mortality rates to the mortality rates of the male general population of the states where the US plants were located (Texas, Kentucky, or Louisiana) or to the rates of the male general population of Ontario, where the Canadian plant was located. Internal analyses compared the mortality rates of an exposed subject subgroup (eg, a particular monomer-exposure group) with the mortality rates of a referent group (a group of unexposed subjects). We also carried out uncertainty analyses to assess the impact of exposure estimation errors on the relation between BD ppm-years and leukemia.

EXTERNAL ANALYSES

External analyses used the SMR (see below) as the measure of association for evaluating the mortality experience of all subjects combined or of subgroups defined on the basis of selected employment factors; these included plant, work area/job group or subgroup, time period of hire, years since hire, years worked, and combinations of some of these variables. The effect of years worked (<10, ≥ 10 years) on LHCs and other diseases was examined within categories of years since hire (ie, < 20 years, 20–29 years, ≥ 30 years since hire). In these analyses, years since hire served as a surrogate for disease induction time.

We computed the SMR for a particular cause of death as the ratio ($\times 100$) of the number of deaths observed among subjects to the number of deaths expected based on the general population of the US state or Ontario. To compute the expected numbers of deaths, we first accumulated person-years of observation for each subject according to race, 5-year age category, and 5-year calendar time period. Person-year accumulation began on the date when the subject had accumulated 1 year of employment, on the date of entry into a particular worker subgroup, or on the date when personnel records at the subject's plant were considered complete, whichever was latest. Person-year accumulation ended on the date of death, on the date of loss to follow-up, or on the study closing date (December 31, 1998), whichever was earliest. Next, we multiplied the specific race, age, and calendar-period person-years by the corresponding state or province mortality rates and summed the resulting quantities to obtain expected numbers of deaths. We estimated 95% CIs of the SMRs under the assumption that the observed numbers of deaths followed a Poisson distribution.

Most external analyses included all 17,924 subjects from the eight plants. External analyses of major work area/job groups were limited to the 15,612 subjects employed in SBR-related operations at the eight plants, and analyses of work area/job subgroups were limited to the 14,273 subjects employed in SBR-related operations at the six plants that had detailed work histories.

We also carried out external analyses for specific forms of leukemia and for CLL–NHL. We restricted the analyses of specific forms of leukemia and CLL–NHL to the time period 1968 through 1998 for US subjects and 1969 through 1998 for Canadian subjects. Before 1968 in the United States and before 1969 in Canada, the ICD coding

systems used for general population rates did not distinguish among specific forms of leukemia in a manner consistent with systems used in more recent decades. The analyses for these restricted time periods included 16,859 (94%) of the 17,924 total study subjects.

The Occupational Cohort Mortality Analysis Program (OCMAP; University of Pittsburgh, Pittsburgh PA) provided most of the software for data analysis as well as state-specific cancer and noncancer mortality rates for much of the general population (Marsh et al 1998).

For most causes of death and time periods, state-specific cancer and noncancer mortality rates were available through OCMAP. For the earliest time periods (as noted below), we used US population rates provided by the United States Death Rate (USDR) program developed by Monson (1974) instead of state-specific rates.

To analyze noncancer causes of death: For 1944 through 1959, we used USDR national rates; for 1962 through 1998, we used OCMAP rates; for the years of 1960 and 1961, we used the 1962 through 1964 OCMAP rates as replacement data.

To analyze cancer causes of death for 1944 through 1949, we used USDR national rates; however, for this time period, no rates for NHL and multiple myeloma were available from USDR. Therefore, we used OCMAP rates for 1950 through 1954 to calculate expected numbers of deaths for these two cancers from 1944 through 1949. For 1950 through 1998, we used OCMAP rates.

Statistics Canada provided rates for categories of gender, age, and calendar period for the population of Ontario for 1950 through 1998.

Appendix C summarizes the categories of cause of death analyzed and the sources used to obtain comparison rates for each category.

INTERNAL ANALYSES

Internal analyses used Poisson regression models to examine mortality rates from leukemia, NHL, multiple myeloma, all lymphoid neoplasms, all myeloid neoplasms, and other diseases in relation to BD, styrene, and DMDTC exposure. These were conducted within the six-plant study group (those plants with work histories sufficiently detailed to assess individual subjects' exposures) and without reference to an external comparison population (Breslow and Day 1987; Callas et al 1998).

Butyl rubber workers contributed observations in the exposure referent categories (ie, to the categories of no BD exposure, no styrene exposure, no DMDTC exposure), along with subjects who worked in SBR-related or unspecified operations but who were judged not to have had potential exposure to one or more of the agents of interest.

The Poisson regression models provided maximum-likelihood estimates of the RR for one agent, adjusting for other agents and for additional possible confounders, including age, years since hire, race, and calendar period during the study. All these models used indicator terms for exposure quartiles for each agent rather than continuous exposure variables. Thus, the RR for a particular quartile may be interpreted as the rate in that quartile divided by the rate in the referent (zero or low-exposure) category. Internal analyses of LHC and of lymphoid and myloid neoplasms included all decedents whose death certificates mentioned these cancers and whose diagnosis was not contradicted by medical records. Internal analyses of other forms of cancer included all decedents with those forms of cancer as the underlying or a contributing cause of death.

In one set of Poisson regression analyses, we used the Statistical Analysis System procedure GENMOD (SAS Institute [Cary NC] 1993) to obtain maximum-likelihood estimates of RRs for exposure to BD ppm-years; styrene ppm-years; DMDTC mg/cm–years; BD ppm-years due to exposure concentrations $\leq$ 100 ppm and > 100 ppm; total BD peaks; or total styrene peaks. We specified exposure categories according to the distribution of cumulative exposure among leukemia decedents, using quartiles of cumulative exposure among those leukemia decedents with nonzero exposure (Greenland 1995). Exploratory modeling considered age, years since hire, calendar period, and race as possible confounders. Final models included only age and years since hire, in addition to the agents of interest, because removing race and calendar period from the models had little impact on agent-specific RRs and enhanced the precision of the analyses. The models for the Poisson regression analyses included indicator terms for all agents and covariates being considered. We evaluated the effects of latency by applying a 10-year lag to cumulative exposure (Langholtz et al 1999).

UNCERTAINTY ANALYSES

Uncertainty analyses evaluated the impact of possible inaccuracies in BD exposure estimation on RRs for leukemia (Greenland 1998). In these analyses we examined leukemia mortality rates in relation to each of 1000 sets of BD ppm-years estimates. Each set of estimates for these analyses came from a JEM consisting of BD exposure concentrations obtained by randomly selecting percentiles of the approximate probability distribution of estimates for each combination of plant, work area/job group, and year.

To obtain the *i*th (*i*, from 1 to 1000) set of exposure estimates for a particular plant: for each work area/job group

at that plant (1) we randomly selected a percentile between 1 and 99 for each primary work area/job group; (2) from each year-specific approximate probability distribution of exposure estimates for that primary work area/job group, we obtained the BD ppm value that corresponded to the selected percentile; (3) we used the BD estimates selected for the primary work area/job group to compute BD estimates for secondary work area/job groups; and (4) we compiled for each year the complete work area/job group BD exposure JEM for the *i*th iteration. After combining the BD exposure concentrations selected for each plant during the *i*th iteration of the procedure to obtain JEM (*i*), we linked JEM (*i*) to work history data to obtain the *i*th set of BD ppm-years for each subject (see Appendix A). We then analyzed the relation between BD ppm-years and leukemia for the data from each of the 1000 JEMs.

Appendix F (available on request) summarizes the results of the random selection of percentiles, the creation of the 1000 BD JEMs (Figure F.1), and the preparation of 1000 data sets of subjects' estimates of BD ppm-years for the uncertainty analyses. Tables F.1 through F.6 display the distribution of the selected percentiles by plant and work area/job group for each of the six plants whose work histories were sufficiently detailed to assess individual subjects' exposures. As expected, percentiles chosen for each primary work area/job group in the six plants ranged from 1 to 99. Median values for the randomly selected percentiles ranged from 43.5 for one work area/job group in plant 7 to 54.0 for three work area/job groups in plant 7 and one work area/job group in plant 1. Table F.7 lists the minimum, maximum, median, and mean values for selected percentiles by plant for the first 50 of the 1000 data sets. Among the 1000 data sets, minimum and maximum selected percentiles ranged from 1 to 20 and from 83 to 99, respectively. Median percentiles ranged 27.5 to 73.0, and the arithmetic mean of selected percentiles ranged from 35.0 to 67.2.

RESULTS

SUBJECTS' CHARACTERISTICS

The 17,924 subjects included 15,583 white men (87%) and 2341 nonwhite men (13%) (Table 1). Of these, 15,010 (84%) had been paid as hourly (ever-hourly), whereas 2914 (16%) had never been paid hourly (never-hourly). As of the end of 1991, the median plant year of hire was 1958 and subjects had worked for a median of 11 years. As of the end of 1998 (the current study), the median years since hire was 33; the median age was 62; 11,117 (62%) subjects were alive; 6237 (35%) were deceased; and 570 (3%) were lost to follow-up. Of the total study group, 15,612 (87%) had worked in SBR operations; of these 13,477 (86%) were ever-hourly and 2,135 (14%) were never-hourly employees.

EXTERNAL COMPARISONS OF MORTALITY RATES

The study group had a total of 540,586 person-years of follow-up, including 457,185 (85%) person-years in 1944 through 1991 and 83,401 (15%) person-years in 1992 through 1998, the time period added by the current study (Table 2). Of the total 6237 deaths between 1944 and 1998, 4659 (75%) occurred in the original study period of 1944 through 1991, and 1578 (25%) occurred in 1992 through 1998. Cause of death information was available for 98% of the 6237 decedents. When the overall study group was compared with state or provincial general populations, the SMR for all causes of death combined was 86 (6237/7242 deaths, CI = 84, 88). The SMR was slightly lower for 1944 through 1991 (SMR = 85, CI = 82, 87) than for 1992 through 1998 (SMR = 90, CI = 86, 95). A similar pattern was present for all cancer deaths combined, for which the SMR was 92 (CI = 88, 97) in the overall study period (1944 through 1998): the SMR was lower for 1944 through 1991 (SMR = 90, CI = 85, 96) than for 1992 through 1998 (SMR = 98, CI = 89, 107). Subjects had fewer than expected deaths from other major causes for the entire study period; SMRs ranged from 58 (CI = 41, 81) for mental disorders to 100 (CI = 57, 162) for benign neoplasms. Circulatory disease was the cause of death category with the highest values: 2932 observed compared with 3282 expected deaths (SMR = 89, CI = 86, 93).

For the entire study period (1944 through 1998), there were fewer than expected deaths from all specific forms of cancer, except for colorectal cancer (SMR = 109, CI = 94, 125), prostate cancer (SMR = 104, CI = 88, 121), and certain forms of LHC (Table 2). The LHC category included 53 deaths from NHL (SMR = 100, CI = 75, 130), 12 deaths from Hodgkin lymphoma (SMR = 111, CI = 58, 195), 71 deaths from leukemia (SMR = 116, CI = 91, 147), and 26 deaths from multiple myeloma (SMR = 95, CI = 62, 140).

In comparing SMRs for the original study period of 1944 through 1991 with those for the entire study period of 1994 through 1998, the SMR was lower for NHL (SMR = 93 vs SMR = 112); higher for Hodgkin lymphoma (SMR = 113 vs SMR = 98) and multiple myeloma (SMR = 110 vs SMR = 66); and about the same for leukemia (SMR = 116 vs SMR = 117). None of these results was statistically significant.

SMRs tended to be lower for nonwhite than for white subjects (data not shown). However, the increase in prostate cancer deaths in the overall study group was concentrated in nonwhite men (SMR = 116, CI = 80, 163). Both nonwhite and white men had more than expected deaths from colorectal cancer (nonwhite, SMR = 114, CI = 72, 171;

Table 1. Number of Subjects by Selected Characteristics for White and Nonwhite Men and All Subjects Combined[a]

	White *n* (%)	Nonwhite *n* (%)	Total *n* (%)
Total	15,583	2341	17,924
Plant / location / year follow-up started			
1 Kentucky 1965	1237 (8)	154 (7)	1391 (8)
2 Texas 1944	664 (4)	112 (5)	776 (4)
3 Louisiana 1944	1510 (10)	479 (20)	1989 (11)
4 Louisiana 1944	1542 (10)	542 (23)	2084 (12)
5 Texas 1960	427 (3)	136 (6)	563 (3)
6 Texas 1944	1955 (13)	373 (16)	2328 (13)
7 Ontario 1950	5356 (34)	—	5356 (30)
8 Texas 1944	2892 (19)	545 (23)	3437 (19)
Payroll status			
Ever-hourly	12,732 (82)	2278 (97)	15,010 (84)
Never-hourly	2851 (18)	63 (3)	2914 (16)
Year of hire			
Before 1950	4109 (26)	547 (23)	4656 (26)
1950–1959	4333 (28)	567 (24)	4900 (27)
1960–1969	3338 (21)	419 (18)	3757 (21)
1970 and later	3803 (24)	808 (35)	4611 (26)
Median	1958	1962	1958
Years worked as of the end of 1991			
< 10	7223 (46)	1086 (46)	8309 (46)
10–19	3325 (21)	540 (23)	3865 (22)
20+	5035 (32)	715 (31)	5750 (32)
Median	11	12	11
Years since hire			
< 20	2990 (19)	521 (22)	3511 (20)
20–29	3494 (22)	765 (33)	4259 (24)
30+	9099 (58)	1055 (45)	10,154 (57)
Median	33	29	33
Vital status			
Alive	9787 (63)	1330 (57)	11,117 (62)
Deceased	5384 (35)	853 (36)	6237 (35)
Unknown	412 (3)	158 (7)	570 (3)
Age at end of study			
< 60	6696 (43)	1251 (53)	7947 (44)
60–69	4272 (27)	536 (23)	4808 (27)
70–79	3217 (21)	414 (18)	3631 (21)
80 or older	1398 (9)	140 (6)	1538 (9)
Median	62	58	62

[a] All results are from analyses that used data as of the end of 1998 except years worked, which was determined as of 1991 because work histories were not obtained for the time period after 1991.

Table 2. Observed/Expected Number of Deaths, SMRs, and 95% CIs by Cause of Death and Time Period of Follow-Up for All Subjects

Cause of Death	1944–1991 (PY = 457,185)	1992–1998 (PY = 83,401)	1944–1998 (PY = 540,586)
All Causes			
Obs/Exp	4659/5490	1578/1751	6237/7242
SMR	85	90	86
95% CI	82 , 87	86 , 95	84 , 88
All Cancers			
Obs/Exp	1116/1238	492/503	1608/1741
SMR	90	98	92
95% CI	85 , 96	89 , 107	88 , 97
Specific Cancers			
Buccal cavity and pharynx			
Obs/Exp	18/36	4/11	22/47
SMR	50	36	47
95% CI	30 , 79	10 , 93	29 , 71
Esophagus			
Obs/Exp	25/33	19/14	44/47
SMR	77	133	94
95% CI	50 , 114	80 , 208	68 , 126
Stomach			
Obs/Exp	48/60	16/15	64/75
SMR	79	107	85
95% CI	59 , 105	61 , 174	65 , 108
Colorectum			
Obs/Exp	138/126	55/52	193/178
SMR	110	106	109
95% CI	92 , 130	80 , 137	94 , 125
Liver			
Obs/Exp	17/28	15/15	32/43
SMR	62	100	75
95% CI	36 , 99	56 , 165	51 , 106
Pancreas			
Obs/Exp	49/64	27/23	76/88
SMR	76	116	87
95% CI	56 , 101	76 , 168	68 , 108
Larynx			
Obs/Exp	17/18	0/6.4	17/24
SMR	96	0	71
95% CI	56 , 54	0 , 57	41 , 113
Lung			
Obs/Exp	406/438	157/180	563/618
SMR	93	87	91
95% CI	84 , 102	74 , 102	84 , 99

Table continues next page

Table 2 (*continued*). Observed/Expected Number of Deaths, SMRs, and 95% CIs by Cause of Death and Time Period of Follow-Up for All Subjects

Cause of Death	1944–1991 (PY = 457,185)	1992–1998 (PY = 83,401)	1944–1998 (PY = 540,586)
Specific Cancers (*continued*)			
Prostate			
Obs/Exp	91/93	63/56	154/149
SMR	98	113	104
95% CI	79 , 120	87 , 145	88 , 121
Bladder			
Obs/Exp	26/29	11/12	37/41
SMR	89	93	90
95% CI	58 , 131	47 , 167	64 , 125
Kidney			
Obs/Exp	26/28	13/12	39/41
SMR	92	107	96
95% CI	60 , 134	57 , 182	68 , 131
Brain			
Obs/Exp	28/30	9/10	37/40
SMR	93	90	93
95% CI	62 , 135	41 , 172	65 , 128
LHCs			
NHL			
Obs/Exp	33/35	20/18	53/53
SMR	93	112	100
95% CI	64 , 131	68 , 173	75 , 130
Hodgkin lymphoma			
Obs/Exp	11/9.8	1/1.0	12/11
SMR	113	98	111
95% CI	56 , 202	2 , 545	58 , 195
Leukemia			
Obs/Exp	51/44	20/17	71/61
SMR	116	117	116
95% CI	86 , 153	71 , 181	91 , 147
Multiple myeloma			
Obs/Exp	20/18	6/9.1	26/27
SMR	110	66	95
95% CI	67 , 170	24 , 143	62 , 140
Other cancers			
Obs/Exp	112/147	56/52	168/197
SMR	76	109	85
95% CI	63 , 92	82 , 141	73 , 99

Table continues next column

Table 2 (*continued*). Observed/Expected Number of Deaths, SMRs, and 95% CIs by Cause of Death and Time Period of Follow-Up for All Subjects

Cause of Death	1944–1991 (PY = 457,185)	1992–1998 (PY = 83,401)	1944–1998 (PY = 540,586)
Specific Noncancer Causes			
Benign neoplasms			
Obs/Exp	11/12	5/3.9	16/16
SMR	90	130	100
95% CI	45 , 162	42 , 302	57 , 162
Blood disorders			
Obs/Exp	18/19	5/10	23/29
SMR	95	48	78
95% CI	56 , 150	16 , 111	50 , 117
Mental disorders			
Obs/Exp	15/39	21/23	36/62
SMR	39	92	58
95% CI	22 , 64	57 , 141	41 , 81
Allergic, endocrine, and metabolic disease			
Obs/Exp	74/108	48/64	122/172
SMR	69	75	71
95% CI	54 , 86	55 , 99	59 , 85
Nervous system disease			
Obs/Exp	57/61	38/35	95/96
SMR	94	107	99
95% CI	71 , 122	76 , 147	80 , 121
Circulatory disease			
Obs/Exp	2303/2569	629/713	2932/3282
SMR	90	88	89
95% CI	86 , 93	82 , 95	86 , 93
Nonmalignant respiratory disease			
Obs/Exp	248/352	146/161	394/512
SMR	71	91	77
95% CI	62 , 80	77 , 107	70 , 85
Digestive disease			
Obs/Exp	146/233	41/62	187/296
SMR	63	66	63
95% CI	53 , 74	47 , 89	55 , 73
Genitourinary disease			
Obs/Exp	55/87	21/30	76/118
SMR	63	69	65
95% CI	48 , 82	43 , 106	51 , 81
External causes			
Obs/Exp	370/573	76/82	446/655
SMR	65	92	68
95% CI	58 , 72	73 , 116	62 , 75
Other known			
Obs/Exp	129/199	49/64	178/263
SMR	65	76	68
95% CI	54 , 77	57 , 101	58 , 78
Unknown	117	7	124

white, SMR = 108, CI = 92, 125) and leukemia (nonwhite, SMR = 163, CI = 78, 300; white, SMR = 111, CI = 85, 143).

SMRs were higher for ever-hourly than for never-hourly workers for most causes of death. Exceptions where never-hourly workers had an SMR above 100 and ever-hourly workers had an SMR below 100 included Hodgkin lymphoma (ever-hourly SMR = 77, CI = 31, 158; never-hourly SMR = 305, CI = 99, 711) and multiple myeloma (ever-hourly SMR = 86, CI = 53, 133; never-hourly SMR = 146, CI = 54, 317) (Table 3). For ever-hourly workers, we observed 63 versus 51 expected deaths from leukemia (SMR = 123, CI = 94, 157), whereas for never-hourly workers we observed 8 versus 9.8 expected deaths (SMR = 82, CI = 35, 161). For NHL, deaths among ever-hourly workers were higher than expected (SMR = 111, CI = 82, 147), whereas among never-hourly workers they were lower than expected (SMR = 44, CI = 12, 112).

Further analyses examined mortality patterns by years since hire and years worked among ever-hourly workers (Table 3). SMRs for all causes of death combined increased along with increasing years since hire from a low of 64 (945/1472) for the combined subgroups with less than 20 years since hire to a high of 99 (3162/3186) for the combined subgroups with 30 or more years since hire. The trend was similar for all cancers combined. Several of the six subgroups defined by years since hire/years worked had more than expected colorectal cancer deaths, and the increase was statistically significant in the subgroup with 20 to 29 years since hire and with 10 or more years worked (SMR = 147, CI = 103, 205). Prostate cancer deaths were significantly increased in the ever-hourly subgroup with 30 or more years since hire and less than 10 years worked (SMR = 155, CI = 113, 206). Several of the subgroups of ever-hourly workers also had more than expected deaths from leukemia. The SMR for leukemia was highest in the subgroup with 20 to 29 years since hire and 10 or more years worked (SMR = 258, CI = 156, 403 [Table 3]; nonwhite, SMR = 387, CI = 106, 992; white, SMR = 237, CI = 133, 391 [data not shown]). Increases in deaths from NHL and multiple myeloma, like leukemia, were concentrated in but not limited to the subgroup with 20 to 29 years since hire and 10 or more years worked. However, these results were based on small numbers of subjects and were not statistically significant. Five of the seven observed deaths from Hodgkin lymphoma among ever-hourly workers occurred in the subgroup with less than 20 years since hire.

Analyses of specific forms of leukemia and of CLL–NHL were restricted to the time periods 1968 through 1998 for US subjects and 1969 through 1998 for Canadian subjects. These analyses included 65 (92%) of the 71 deaths from leukemia and 49 (92%) of the 53 NHL deaths that occurred during the overall study period of 1944 through 1998. SMRs for all subjects were 128 (CI = 77, 200) for lymphocytic leukemia, 127 (CI = 84, 183) for myelogenous leukemia, and 123 (CI = 73, 194) for other leukemias, including unspecified forms (Table 4). Of the 19 lymphocytic leukemias, one was acute (SMR = 42, CI = 1, 234), 16 were chronic (SMR = 151, CI = 87, 247), and two were unspecified. Of the 28 myelogenous leukemias, 14 were acute (SMR = 102, CI = 56, 171), 11 were chronic (SMR = 167, CI = 83, 299), and three were unspecified. The category of other and unspecified leukemias (SMR = 123, CI = 73, 194) included one monocytic leukemia, 11 acute leukemias of unspecified cell type, and six leukemias that were not specified by cell type or as acute or chronic.

Ever-hourly workers had an overall leukemia SMR of 135 (CI = 103, 175) for the period of 1968 through 1998 (data not shown) and had an elevated SMR for each specific form of leukemia analyzed, except for acute lymphocytic and acute myelogenous leukemias (Table 4). Analyses of specific forms of leukemia by ever-hourly subgroups of years since hire/years worked indicated that in the subgroup with 20 to 29 years since hire and 10 or more years worked, the overall increase in leukemia deaths in the 1968 through 1998 period (SMR = 284, CI = 168, 449) was not limited to a specific type, although the SMR was highest for chronic myelogenous leukemia (SMR = 655, CI = 240, 1426). The SMRs for CLL were elevated in the subgroups with 20 to 29 years since hire and with 30 or more years since hire, but these results were based on small numbers and were not statistically significant. CLL–NHL deaths were increased in the subgroup with 20 to 29 years since hire and 10 or more years worked (SMR = 190, CI = 101, 325) and in the subgroup with 30 or more years since hire and 10 or more years worked (SMR = 149, CI = 102, 210).

Subjects in each major work area/job group of SBR-related operations and in each work area/job subgroup had fewer observed deaths than expected from all causes combined; SMRs ranged from 77 (subjects employed in laboratories) to 91 (subjects in field maintenance); these groups also had fewer observed than expected deaths in most major disease categories (data not shown). All groups had fewer than expected cancer deaths, except for maintenance workers; this group had more than expected deaths from several forms of cancer, but all of the increases were small.

Subjects in SBR-related production operations had more than expected deaths from leukemia, particularly if they worked in polymerization (SMR = 204, CI = 121, 322) or coagulation (SMR = 231, CI = 111, 425) (Table 5). All but 2 of the 10 subjects who had leukemia and who worked in coagulation also had worked in polymerization, whereas 10 of 18 workers in polymerization who had leukemia had

Table 3. Observed/Expected Number of Deaths, SMRs, and 95% CIs for Selected Cancers and Selected Subgroups, 1944–1998[a]

	All Causes	All Cancers	Colorectal Cancer	Prostate Cancer	Hodgkin Lymphoma	Multiple Myeloma	All Leukemias	NHL
All subjects								
Obs/Exp	6237/7242	1608/1741	193/178	154/149	12/11	26/27	71/61	53/53
SMR	86	92	109	104	111	95	116	100
95% CI	84 , 88	88 , 97	94 , 125	88 , 121	58 , 195	62 , 140	91 , 147	75 , 130
Ever-hourly								
Obs/Exp	5480/6174	1414/1470	161/150	130/128	7/9.1	20/23	63/51	49/44
SMR	89	96	107	102	77	86	123	111
95% CI	86 , 91	91 , 101	91 , 125	85 , 121	31 , 158	53 , 133	94 , 157	82 , 147
Never-hourly								
Obs/Exp	757/1068	194/271	32/28	24/21	5/1.6	6/4.1	8/9.8	4/9.1
SMR	71	72	115	115	305	146	82	44
95% CI	66 , 76	62 , 82	79 , 162	74 , 172	99 , 711	54 , 317	35 , 161	12 , 112
All ever-hourly subjects by years since hire and years worked								
< 20 since hire and < 10 worked								
Obs/Exp	582/882	83/133	10/13	1/5.2	2/3.3	0/1.6	4/7.0	0/4.9
SMR	66	63	80	19	61	0	57	0
95% CI	61 , 72	50 , 78	38 , 147	1 , 108	7 , 221	0 , 236	16 , 146	0 , 76
< 20 since hire and 10+ worked								
Obs/Exp	363/590	89/112	9/11	3/4.0	3/1.7	3/1.5	6/4.4	1/3.6
SMR	62	80	83	75	178	207	136	28
95% CI	55 , 68	64 , 98	38 , 157	15 , 218	37 , 519	43 , 605	50 , 296	1 , 155
20–29 since hire and < 10 worked								
Obs/Exp	497/535	119/121	11/11	7/7.7	1/0.8	2/1.7	4/4.1	5/3.5
SMR	93	98	99	90	129	117	98	143
95% CI	85 , 101	81 , 118	49 , 177	36 , 186	3 , 720	14 , 423	27 , 251	46 , 333
20–29 since hire and 10+ worked								
Obs/Exp	876/981	241/237	35/24	12/14	1/1.4	6/3.4	19/7.4	11/6.5
SMR	89	102	147	88	70	175	258	170
95% CI	84 , 95	89 , 116	103 , 205	46 , 154	2 , 392	64 , 380	156 , 403	85 , 305
30+ since hire and < 10 worked								
Obs/Exp	1064/1006	298/269	30/27	46/30	0/0.6	3/4.6	10/8.9	7/8.0
SMR	106	111	113	155	0	65	113	87
95% CI	100 , 112	99 , 124	76 , 162	113 , 206	0 , 591	13 , 189	54 , 207	35 , 179
30+ since hire and 10+ worked								
Obs/Exp	2098/2180	584/598	66/65	61/67	0/1.4	6/10	20/20	25/18
SMR	96	98	101	90	0	58	102	141
95% CI	92 , 100	90 , 106	78 , 129	69 , 116	0 , 271	21 , 126	62 , 158	91 , 208

[a] Acute and chronic columns do not sum to the total because the total includes leukemias not specified as acute or chronic.

Table 4. Observed Versus Expected Numbers of Deaths, SMRs, and 95% CIs for Cell Type–Specific Leukemias and CLL–NHL Combined for Selected Subgroups, 1968–1998[a]

	Lymphocytic Leukemia			Myelogenous Leukemia			Other Leukemias	CLL–NHL
	Total	Acute	Chronic (CLL)	Total	Acute	Chronic		
All subjects								
Obs/Exp	19/15	1/2.4	16/11	28/22	14/14	11/6.6	18/14	65/56
SMR	128	42	151	127	102	167	123	116
95% CI	77 , 200	1 , 234	87 , 247	84 , 183	56 , 171	83 , 299	73 , 194	90 , 148
Ever-hourly								
Obs/Exp	17/12	1/2.0	15/8.8	24/18	11/11	11/5.5	17/12	60/46
SMR	138	51	171	131	97	200	139	130
95% CI	80 , 221	1 , 282	96 , 281	84 , 195	48 , 173	100 , 358	81 , 222	99 , 167
Never-hourly								
Obs/Exp	2/2.5	0/0.4	1/1.8	4/3.8	3/2.4	0/1.1	1/2.4	5/9.7
SMR	81	0	57	106	127	0	42	51
95% CI	10 , 293	0 , 913	1 , 319	29 , 271	26 , 370	0 , 338	1 , 231	17 , 120
All ever-hourly subjects by years since hire and years worked								
< 20 since hire and < 10 worked								
Obs/Exp	0/0.5	0/0.3	0/0.2	4/1.5	4/0.8	0/0.6	0/0.7	0/2.4
SMR	0	0	0	272	478	0	0	0
95% CI	0 , 738	0 , 1317	0 , 2049	74 , 696	130 , 1224	0 , 636	0 , 543	0 , 152
< 20 since hire and 10+ worked								
Obs/Exp	0/0.4	0/0.2	0/0.2	0/1.1	0/0.6	0/0.4	2/0.6	0/2.1
SMR	0	0	0	0	0	0	357	0
95% CI	0 , 878	0 , 2459	0 , 1677	0 , 338	0 , 595	0 , 900	43 , 1290	0 , 180
20–29 since hire and < 10 worked								
Obs/Exp	1/0.9	0/0.2	1/0.6	1/1.6	0/0.9	1/0.5	2/0.9	4/3.7
SMR	109	0	169	64	0	195	220	109
95% CI	3 , 607	0 , 1942	4 , 942	2 , 357	0 , 392	5 , 1087	27 , 794	30 , 279
20–29 since hire and 10+ worked								
Obs/Exp	4/1.7	0/0.3	3/1.2	9/2.8	3/1.7	6/0.9	5/1.8	13/6.8
SMR	233	0	254	320	174	655	276	190
95% CI	63 , 597	0 , 1153	52 , 742	146 , 607	36 , 509	240 , 1426	90 , 644	101 , 325
30+ since hire and < 10 worked								
Obs/Exp	4/2.7	0/0.3	4/2.0	5/3.6	2/2.3	3/1.0	1/2.6	11/9.8
SMR	150	0	200	138	85	300	39	112
95% CI	41 , 384	0 , 1085	54 , 512	44 , 322	10 , 307	62 , 877	1 , 216	56 , 200
30+ since hire and 10+ worked								
Obs/Exp	8/6.1	0/0.7	7/4.6	5/7.7	2/4.9	1/2.1	7/5.8	32/21.4
SMR	131	0	152	65	41	48	122	149
95% CI	57 , 258	0 , 527	61 , 313	21 , 152	5 , 148	1 , 267	49 , 250	102 , 210

[a] Acute and chronic columns do not sum to the total because the total includes leukemias not specified as acute or chronic.

Table 5. Observed/Expected Number of Deaths, SMRs, and 95% CIs for Workers in SBR-Related Work Area/Job Groups, 1944–1998

	Colorectal Cancer	Prostate Cancer	Hodgkin Lymphoma	Multiple Myeloma	All Leukemias	NHL
Production						
Overall						
Obs/Exp	64/54	44/42	2/3.6	6/8.5	29/20	24/18
SMR	118	106	56	71	146	135
95% CI	91 , 150	77 , 142	7 , 201	26 , 154	98 , 210	86 , 201
Polymerization						
Obs/Exp	22/25	23/20	0/1.4	1/3.8	18/8.8	11/8.0
SMR	89	117	0	26	204	137
95% CI	56 , 135	74 , 175	0 , 260	1 , 146	121 , 322	69 , 246
Coagulation						
Obs/Exp	14/12	9/9.5	0/0.7	0/2.0	10/4.3	4/4.0
SMR	119	95	0	0	231	100
95% CI	65 , 200	43 , 180	0 , 569	0 , 183	111 , 425	27 , 256
Finishing						
Obs/Exp	36/32	21/23	2/2.3	2/5.3	19/12	16/11
SMR	111	90	88	38	156	143
95% CI	78 , 154	55 , 137	11 , 319	5 , 137	94 , 244	82 , 233
Maintenance						
Overall						
Obs/Exp	56/46	29/39	1/2.7	5/7.1	16/17	18/15
SMR	121	75	37	71	95	121
95% CI	91 , 157	50 , 108	1 , 207	23 , 165	54 , 154	72 , 191
Shop						
Obs/Exp	16/11	9/9.4	0/0.7	1/1.7	4/4.3	4/3.8
SMR	142	95	0	57	93	105
95% CI	81 , 231	44 , 181	0 , 530	1 , 320	25 , 238	29 , 268
Field						
Obs/Exp	41/33	21/27	1/1.9	3/5.0	10/12	11/11
SMR	122	77	53	60	84	104
95% CI	88 , 166	48 , 118	1 , 296	12 , 175	40 , 155	52 , 186
Labor						
Overall						
Obs/Exp	38/37	45/39	1/2.2	10/7.3	18/12	10/9.7
SMR	102	115	45	138	151	103
95% CI	72 , 140	84 , 153	1 , 250	66 , 253	89 , 239	50 , 190
Production						
Obs/Exp	12/11	11/12	0/0.7	4/2.1	4/3.3	4/2.5
SMR	113	94	0	189	123	157
95% CI	58 , 198	47 , 168	0 , 547	52 , 483	34 , 315	43 , 403
Maintenance						
Obs/Exp	21/23	31/24	1/1.4	7/4.7	15/7.4	7/6.1
SMR	93	128	74	150	203	115
95% CI	57 , 141	87 , 181	2 , 411	60 , 310	114 , 335	46 , 237
Laboratories						
Obs/Exp	8/12	6/7.1	0/0.8	0/1.9	14/4.3	5/4.3
SMR	69	84	0	0	326	117
95% CI	30 , 136	31 , 184	0 , 445	0 , 200	178 , 546	38 , 274
Other operations						
Obs/Exp	20/24	15/20	2/1.4	4/3.9	6/8.7	4/7.9
SMR	82	77	141	102	69	51
95% CI	50 , 127	43 , 127	17 , 508	28 , 261	25 , 150	14 , 131

never worked in coagulation. Leukemia also was increased among laborers, particularly those in maintenance (SMR = 203, CI = 114, 335); and among laboratory workers, who had a threefold increase in leukemia deaths (SMR = 326, CI = 178, 546). There were no strong or statistically significant associations between work area and NHL, Hodgkin lymphoma, multiple myeloma, or colorectal or prostate cancers.

SMRs for all lymphocytic leukemias and for CLL were elevated more than twofold over expected in production, labor, and laboratory workers (Table 6). Deaths from CLL and CLL–NHL were increased in each of the three subgroups of production. Because of the overlap among employees in these three subgroups, we carried out further mutually exclusive analyses. Subjects employed in polymerization, but never in finishing, had more than the expected number of deaths from CLL (2/0.7) and from CLL–NHL (7/3.5). Subjects employed in finishing, but never in polymerization, had approximately equal numbers of observed and expected deaths from CLL (1/1.1) and had more than the expected number of deaths from CLL–NHL (11/6.8). For myelogenous leukemia, the only statistically significant result was for chronic myelogenous leukemia among laboratory workers (3/0.6).

For the overall study group (1944 through 1998), analyses by time period of hire indicated that more than the expected number of deaths from leukemia occurred among men hired in the 1950s (31/21, SMR = 150, CI = 101, 211) (Table 7). Men hired in the 1940s had 28/30 leukemia deaths (SMR = 93, CI = 62, 134), and men hired in or after 1960 had 12/10 leukemia deaths (SMR = 120, CI = 62, 210). Although men hired in the 1940s had nearly equal observed and expected leukemia deaths overall, the subgroup with 20 to 29 years since hire and 10 or more years worked had a twofold increase (7/3.5, SMR = 202, CI = 81, 416). The increase among men hired in or after 1960 was concentrated in the subgroup with 20 to 29 years since hire and less than 10 years worked (5/1.6, SMR = 313, CI = 101, 729). In ever-hourly workers, the pattern of leukemia mortality by time period of hire was similar to that for all subjects.

ANALYSES OF CUMULATIVE EXPOSURE

Analyses of the relations between mortality from various causes and cumulative exposure to BD, styrene, or DMDTC involved employees from the six plants for which work histories were sufficiently detailed to assess each individual worker's exposure—16,579 subjects with a maximum of 500,174 person-years of observation. (For internal analyses reported in this section, "all subjects" refers to this group of 16,579 workers.)

Internal Analyses of LHC

Internal analyses of mortality from LHC involved 81 decedents with leukemia, 58 with NHL, 27 with multiple myeloma, and 13 with Hodgkin lymphoma.

The group of decedents with leukemia consisted of 68 subjects who had leukemia as the underlying cause of death, 12 with leukemia as a contributing cause of death, and one who died of myelodysplasia but whose medical records indicated that he had acute leukemia of an unspecified cell type.

The decedents with NHL included 43 of 46 subjects who had NHL as the underlying cause of death. We excluded from this group the three men whose underlying cause of death was coded as NHL but whose medical records indicated that they had pancreatic, lung, or head and neck cancer. The NHL group also included seven men with NHL as a contributing cause of death and eight whose medical records indicated that they had both a diagnosis of NHL and a diagnosis of CLL. The latter eight subjects were also counted as cases in the leukemia group.

The multiple myeloma group consisted of the 24 decedents with multiple myeloma as the underlying cause of death and three with it as a contributing cause of death. The Hodgkin lymphoma group included 12 decedents with Hodgkin lymphoma as the underlying cause of death and one whose medical records indicated that he had Hodgkin lymphoma that transformed to leukemia. The latter subject was also in the leukemia group.

Descriptive Results for Exposure Variables The main three indices of cumulative exposure to the agents of interest examined in the internal analyses were BD ppm-years, styrene ppm-years, and DMDTC mg/cm–years (referred to hereafter as DMDTC). Of all subjects employed in the six plants, 77% were exposed to BD, 84% to styrene, and 60% to DMDTC (Table 8). Median cumulative exposure concentrations for all subjects were 54 BD ppm-years, 13 styrene ppm-years, and 250 for DMDTC. For all decedents, the median values were 85 BD ppm-years, 17 styrene ppm-years, and 680 for DMDTC.

Compared with all decedents, subjects with leukemia died younger, were hired later, worked slightly longer, and had median exposure concentrations that were 2.2 times higher for BD ppm-years, 1.9 times higher for styrene ppm-years, and 1.1 times higher for DMDTC (Table 8). Compared with all decedents, NHL decedents had higher median exposure concentrations for BD ppm-years and styrene ppm-years and a slightly lower median concentration for DMDTC. Compared with all decedents, multiple myeloma decedents had a higher median exposure concentration for BD ppm-years, a similar concentration for

Table 6. Observed/Expected Number of Deaths, SMRs, and 95% CIs for Cell Type–Specific Leukemias and CLL–NHL for Workers in SBR-Related Work Area/Job Groups, 1968–1998[a]

	Lymphocytic Leukemia			Myelogenous Leukemia			
	Total	Acute	Chronic (CLL)	Total	Acute	Chronic	CLL–NHL
Production							
Overall							
Obs/Exp	10/4.8	1/0.9	9/3.4	9/7.6	5/4.7	4/2.4	33/19
SMR	208	115	266	118	105	170	173
95% CI	100 , 383	3 , 642	122 , 505	54 , 224	34 , 246	46 , 435	119 , 244
Polymerization							
Obs/Exp	8/2.2	0/0.4	8/1.6	4/3.4	2/2.2	2/1.0	19/8.7
SMR	359	0	497	118	93	202	218
95% CI	155 , 706	0 , 1030	215 , 980	32 , 302	11 , 335	24 , 728	131 , 341
Coagulation							
Obs/Exp	5/1.1	0/0.2	5/0.8	2/1.7	1/1.1	1/0.5	9/4.5
SMR	452	0	607	116	91	188	199
95% CI	147 , 1055	0 , 2053	197 , 1417	14 , 420	2 , 507	5 , 1049	91 , 379
Finishing							
Obs/Exp	7/2.9	0/0.6	7/2.0	7/4.9	5/3.0	2/1.6	23/12
SMR	238	0	344	143	165	128	191
95% CI	96 , 491	0 , 630	138 , 709	57 , 294	54 , 386	15 , 460	121 , 286
Maintenance							
Overall							
Obs/Exp	3/4.2	0/0.7	2/3.0	6/6.2	3/4.0	2/1.8	18/16
SMR	72	0	67	97	76	111	112
95% CI	15 , 211	0 , 571	8 , 241	36 , 211	16 , 222	13 , 400	66 , 177
Shop							
Obs/Exp	1/1.0	0/0.2	0/0.7	1/1.6	0/1.0	1/0.5	3/4.1
SMR	98	0	0	63	0	216	73
95% CI	2 , 545	0 , 2256	0 , 499	2 , 350	0 , 359	5 , 1201	15 , 214
Field							
Obs/Exp	2/3.0	0/0.5	2/2.1	4/4.4	2/2.8	1/1.3	12/11
SMR	68	0	93	92	72	79	105
95% CI	8 , 244	0 , 815	11 , 338	25 , 234	9 , 259	2 , 440	54 , 184
Labor							
Overall							
Obs/Exp	5/2.9	0/0.5	5/2.1	8/4.4	5/2.6	3/1.5	14/10
SMR	173	0	244	181	191	199	134
95% CI	56 , 404	0 , 738	79 , 570	78 , 357	62 , 445	41 , 581	73 , 225
Production							
Obs/Exp	1/0.8	0/0.1	1/0.5	2/1.2	1/0.7	1/0.4	4/2.7
SMR	132	0	185	168	143	250	147
95% CI	3 , 736	0 , 3032	5 , 1031	20 , 608	4 , 795	6 , 1390	40 , 377
Maintenance							
Obs/Exp	4/1.8	0/0.3	4/1.3	6/2.9	5/1.7	1/1.0	11/6.7
SMR	219	0	309	210	295	101	163
95% CI	60 , 562	0 , 1122	84 , 792	77 , 457	96 , 688	3 , 560	82 , 292
Laboratories							
Obs/Exp	4/1.0	0/0.2	4/0.7	6/1.8	2/1.1	3/0.6	9/4.6
SMR	390	0	559	331	177	522	195
95% CI	106 , 999	0 , 1796	152 , 1431	122 , 720	22 , 642	108 , 1526	89 , 369
Other operations							
Obs/Exp	1/2.2	0/0.4	1/1.6	3/3.3	1/2.1	2/1.0	5/8.6
SMR	46	0	64	91	48	197	58
95% CI	1 , 257	0 , 1044	2 , 354	19 , 265	1 , 269	24 , 713	19 , 136

[a] Acute and chronic columns do not sum to the total because the total includes leukemias not specified as acute or chronic.

Table 7. Observed/Expected Leukemia Deaths, SMRs, and 95% CIs by Years Since Hire, Years Worked, and Period of Hire for All Subjects and Ever-Hourly Subjects, 1944–1998

Subgroup by Years Since Hire and Years Worked	Period of Hire					
	All Subjects			Ever-Hourly Subjects		
	1943–1949	1950–1959	1960 or Later	1943–1949	1950–1959	1960 or Later
< 20 since hire and < 10 worked						
Obs/Exp	0/3.1	0/2.1	4/3.4	0/2.8	0/1.8	4/2.4
SMR	0	0	119	0	0	164
95% CI	0 , 118	0 , 173	33 , 306	0 , 132	0 , 208	45 , 420
< 20 since hire and 10+ worked						
Obs/Exp	2/2.0	4/1.8	0/1.3	2/1.8	4/1.6	0/1.1
SMR	102	220	0	113	258	0
95% CI	12 , 367	60 , 566	0 , 275	14 , 408	70 , 661	0 , 335
20–29 since hire and < 10 worked						
Obs/Exp	0/2.3	1/1.2	5/1.6	0/2.0	1/1.0	3/1.1
SMR	0	83	313	0	105	274
95% CI	0 , 160	2 , 464	101 , 729	0 , 182	3 , 586	56 , 797
20–29 since hire and 10+ worked						
Obs/Exp	7/3.5	11/3.3	2/1.7	6/3.1	11/2.8	2/1.4
SMR	202	335	116	193	392	139
95% CI	81 , 416	167 , 600	14 , 418	71 , 420	196 , 703	17 , 502
30+ since hire and < 10 worked						
Obs/Exp	8/6.9	5/3.3	1/0.9	5/5.7	4/2.6	1/0.5
SMR	115	150	112	88	152	176
95% CI	50 , 227	49 , 350	3 , 626	29 , 206	41 , 389	4 , 977
30+ since hire and 10+ worked						
Obs/Exp	11/12	10/9.1	0/1.1	11/11	9/7.7	0/0.9
SMR	88	110	0	100	117	0
95% CI	44 , 158	53 , 203	0 , 345	50 , 179	54 , 222	0 , 424
All subjects						
Obs/Exp	28/30	31/21	12/10	24/26	29/17	10/7.5
SMR	93	150	120	91	167	133
95% CI	62 , 134	101 , 211	62 , 210	58 , 135	112 , 240	64 , 244

Table 8. Number of Exposed Workers and Median Exposure Values for BD ppm-years, Styrene ppm-years, and DMDTC mg/cm–years, for All Subjects, All Decedents, and LHC Decedents from Six Plants[a]

Group	Total *n*	Median Year of Hire	Median Years Worked	Median Age	BD (ppm-years)		Styrene (ppm-years)		DMDTC (mg-years/cm)	
					n > 0 (%)	Median	*n* > 0 (%)	Median	*n* > 0 (%)	Median
All subjects	16,579	1958	12	62	12,814 (77)	54	14,006 (84)	13	9874 (60)	250
All decedents	5703	1948	16	67	4518 (79)	85	4841 (85)	17	2975 (52)	680
All LHC decedents										
All leukemia	81	1951	17	61	71 (88)	185	74 (91)	32	64 (79)	739
Chronic lymphocytic	25	1950	24	63	22 (88)	287	24 (96)	39	19 (76)	976
Acute myelogenous	26	1952	12	61	24 (92)	55	25 (96)	20	23 (88)	344
Chronic myelogenous[b]	16	1951	21	60	15 (94)	89	15 (94)	36	13 (81)	580
Other leukemias	14	1951	17	60	10 (71)	332	10 (71)	61	9 (64)	1398
NHL	58	1950	21	64	47 (81)	139	52 (90)	30	39 (67)	603
Multiple myeloma	27	1951	19	66	23 (85)	123	23 (85)	15	14 (52)	654
Hodgkin lymphoma	13	1951	14	53	6 (46)	55	7 (54)	6	6 (46)	82

[a] These analyses involved only the 16,579 employees from the six plants for which we had sufficiently detailed work histories. Percentages are calculated from this total number of workers. *n* > 0 is the number of workers with exposure higher than 0.

[b] Other leukemias include acute lymphocytic (*n* = 3), unspecified lymphocytic (*n* = 2), unspecified myelogenous (*n* = 3), acute unspecified (*n* = 4), chronic unspecified (*n* = 1), and leukemias not otherwise specified (*n* = 1).

styrene ppm-years, and a lower concentration for DMDTC. Compared with all decedents and to decedents with other forms of LHC, Hodgkin lymphoma decedents had a low median exposure for each of the agents.

The three main exposure variables were correlated (data not shown). Spearman rank correlation coefficients for all subjects were 0.79 for BD and styrene ppm-years, 0.58 for BD ppm-years and DMDTC, and 0.63 for styrene ppm-years and DMDTC; and for the 81 leukemia decedents, they were 0.87 for BD ppm-years and styrene ppm-years, 0.74 for BD ppm-years and DMDTC, and 0.68 for styrene ppm-years and DMDTC.

Additional cumulative exposure indices examined in internal analyses were BD ppm-years due to concentrations ≤ 100 ppm and those due to > 100 ppm; total BD peaks (defined as > 100 ppm); and total styrene peaks (defined as > 50 ppm) (Table 9). Proportions of subjects exposed were 77% for BD ppm-years due to concentrations≤ 100, 70% for BD ppm-years due to concentrations > 100 ppm, 70% for total BD peaks, and 57% for total styrene peaks. Median cumulative exposure values were 18 for BD ppm-years due to concentrations ≤ 100 ppm, 33 for BD ppm-years due to concentrations > 100 ppm, 386 for total BD peaks, and 60 for total styrene peaks for all subjects and were for 27 BD ppm-years due to concentrations ≤ 100 ppm, 53 BD ppm-years due to concentrations > 100 ppm, 521 for total BD peaks, and 66 for total styrene peaks for all decedents.

Compared with all decedents, subjects with leukemia had median exposure that was 2.1 times higher for BD ppm-years due to concentrations ≤ 100 ppm, 1.8 times higher for BD ppm-years due to concentrations > 100 ppm, 1.9 times higher for total BD peaks, and 2.6 times higher for total styrene peaks (Table 9). Compared with all decedents, NHL decedents had slightly higher median exposure for BD ppm-years due to concentrations of both ≤ 100 ppm and > 100 ppm, and had lower median values for total BD peaks and total styrene peaks. Multiple myeloma decedents had relatively high median exposure for BD ppm-years due to concentrations > 100 ppm; median number of styrene peaks was about 60% lower than that for all decedents; and median values for the other indices were not markedly different from those of all decedents. Median values of each of the four exposure indices were lower for Hodgkin lymphoma decedents than for other decedent groups. We did not analyze Hodgkin lymphoma further because of the limited number of decedents with this form of LHC.

Poisson Regression Results Single-agent Poisson regression analyses adjusted for age and years since hire results indicated a positive association between BD ppm-years and leukemia (RRs of 1.0, 1.4, 1.2, 2.9, and 3.7 for exposures of

Table 9. Number of Exposed Workers and Median Exposure Values for BD ppm-years Due to Concentrations ≤ 100 ppm and > 100 ppm, and for Total BD Peaks and Total Styrene Peaks for All Subjects, All Decedents, and LHC Decedents from Six Plants[a]

	BD ppm-years							
	Due to ≤ 100 ppm		Due to > 100 ppm		Total Number of BD Peaks		Total Number of Styrene Peaks	
Group	*n* > 0 (%)	Median	*n* > 0 (%)	Median	*n* > 0 (%)	Median	*n* > 0 (%)	Median
All subjects	12,814 (77)	18	11,622 (70)	33	11,622 (70)	386	9463 (57)	60
All decedents	4518 (79)	27	4039 (71)	53	4039 (71)	521	3552 (62)	66
All LHC decedents								
All leukemia	71 (88)	56	71 (88)	97	71 (88)	965	67 (83)	170
Chronic lymphocytic	22 (88)	74	22 (88)	112	22 (88)	1865	20 (80)	113
Acute myelogenous	24 (92)	18	24 (92)	37	24 (92)	413	23 (88)	170
Chronic myelogenous	15 (94)	51	15 (94)	51	15 (94)	1077	14 (88)	175
Other leukemias[b]	10 (71)	100	10 (71)	237	10 (71)	3300	10 (71)	195
NHL	47 (81)	32	45 (78)	68	45 (78)	466	41 (71)	54
Multiple myeloma	23 (85)	36	19 (70)	117	19 (70)	449	19 (70)	41
Hodgkin lymphoma	6 (46)	8	6 (46)	39	6 (46)	181	5 (38)	52

[a] These analyses involved only the 16,579 employees from the six plants for which we had sufficiently detailed work histories. Percentages are calculated from this total number of workers. *n* > 0 is the number of workers with exposure higher than 0.

[b] Other leukemias include acute lymphocytic (*n* = 3), unspecified lymphocytic (*n* = 2), unspecified myelogenous (*n* = 3), acute unspecified (*n* = 4), chronic unspecified (*n* = 1), and leukemias not otherwise specified (*n* = 1).

0, > 0 to < 33.7, 33.7 to < 184.7, 184.7 to < 425.0, and > 425.0 ppm-years, respectively) (Table 10, Model 1) and between styrene ppm-years and leukemia (RRs of 1.0, 1.3, 1.6, 3.0, and 2.7 for exposures of 0, > 0 to < 8.3, 8.3 to < 31.8, 31.8 to < 61.1, and > 61.1 ppm-years, respectively) (Model 2). DMDTC also was positively associated with leukemia, without a consistent exposure–response (RRs of 1.0, 2.5, 3.0, 4.9, and 2.7 for 0, > 0 to < 185.3, 185.3 to < 739.4, 739.4 to < 1610.3, and > 1610.3 mg/cm–years, respectively) (Model 3). (Hereafter all cumulative exposure ranges are referred to as 0 exposure and quartiles 1, 2, 3, and 4.)

The magnitude of the association between BD ppm-years and leukemia was reduced after adjusting for styrene ppm-years, DMDTC, or both; RRs in the highest BD quartile ranged from 2.2 (CI = 0.9, 5.4) after adjusting for DMDTC (Model 5) to 3.0 (CI = 1.0, 9.2) after adjusting for both styrene and DMDTC (Model 7). The magnitude of the styrene–leukemia association was also reduced after adjusting for BD (Model 4). No association remained between styrene and leukemia after adjusting for DMDTC alone (Model 6) or for both BD and DMDTC (Model 7). The positive association (without exposure–response) between DMDTC and leukemia was also reduced, but not removed, after adjusting for one or both of the other agents.

Analyses that incorporated a 10-year exposure lag yielded results (Table 11) that did not differ materially from those shown in Table 10. For example, in Model 1 (BD ppm-years only), RRs were 1.0, 1.8, 1.7, 3.6, and 3.6, respectively (for BD ppm-years of 0 and quartiles 1, 2, 3, and 4) in comparison to RRs of 1.0, 1.4, 1.2, 2.9, and 3.7 obtained for the same quartiles using data without a 10-year time lag. We used exposure data without time lags in all subsequent analyses.

Total BD peaks and total styrene peaks also were positively associated with leukemia (Table 12). Models that included both BD peaks and styrene peaks (Models 4 and 7) indicated a somewhat stronger relation between styrene peaks and leukemia than between BD peaks and leukemia. We found a moderate association between DMDTC cumulative exposure and leukemia regardless of adjustment for BD peaks, styrene peaks, or both.

Results for partitioned BD ppm-years indicated that leukemia was associated both with BD ppm-years due to concentrations ≤ 100 ppm and with BD ppm-years due to concentrations > 100 ppm, although the latter association was stronger than the former (Table 13). The low number of deaths from leukemia hampered further analyses of these BD exposure variables (Table 14).

Table 10. RRs for Leukemia and BD ppm-years, Styrene ppm-years, and DMDTC mg/cm–years Shown by Model

Exposure	Number of Leukemias	Person-Years	Model Number and Agents Included[a] (RR [95% CI]) Model 1: BD Only	Model 2: Styrene Only	Model 3: DMDTC Only	Model 4: BD + Styrene	Model 5: BD + DMDTC	Model 6: Styrene + DMDTC	Model 7: BD + Styrene + DMDTC
BD (ppm-years)									
0	10	116,471	1.0			1.0	1.0		1.0
> 0 to < 33.7	17	154,443	1.4 (0.7 , 3.1)			1.3 (0.5 , 3.5)	1.1 (0.5 , 2.5)		1.4 (0.5 , 3.9)
33.7 to < 184.7	18	144,109	1.2 (0.6 , 2.7)			0.9 (0.3 , 2.7)	0.8 (0.3 , 1.8)		0.9 (0.3 , 2.6)
184.7 to < 425.0	18	49,411	2.9 (1.4 , 6.4)			2.2 (0.7 , 6.3)	1.7 (0.7 , 4.2)		2.1 (0.7 , 6.2)
425.0+	18	35,741	3.7 (1.7 , 8.0)			2.9 (1.0 , 8.8)	2.2 (0.9 , 5.4)		3.0 (1.0 , 9.2)
Styrene (ppm-years)									
0	7	77,460		1.0		1.0		1.0	1.0
> 0 to < 8.3	18	177,551		1.3 (0.6 , 3.2)		1.2 (0.4 , 3.7)		0.7 (0.3 , 2.0)	0.6 (0.2 , 2.2)
8.3 to < 31.8	19	132,311		1.6 (0.7 , 3.9)		1.4 (0.4 , 4.5)		0.7 (0.3 , 2.1)	0.7 (0.2 , 2.5)
31.8 to < 61.1	18	55,797		3.0 (1.2 , 7.1)		1.9 (0.6 , 6.5)		1.2 (0.4 , 3.5)	0.8 (0.2 , 3.1)
61.1+	19	57,056		2.7 (1.1 , 6.4)		1.3 (0.4 , 4.3)		1.0 (0.3 , 2.9)	0.5 (0.1 , 2.0)
DMDTC (mg/cm–years)									
0	17	206,617			1.0		1.0	1.0	1.0
> 0 to < 185.3	16	128,688			2.5 (1.2 , 5.0)		2.4 (1.2 , 4.8)	2.6 (1.2 , 5.8)	2.6 (1.2 , 5.8)
185.3 to < 739.4	16	77,743			3.0 (1.5 , 5.9)		2.8 (1.3 , 5.8)	2.8 (1.3 , 6.4)	3.1 (1.4 , 7.1)
739.4 to < 1610.3	16	36,178			4.9 (2.5 , 9.7)		3.9 (1.8 , 8.4)	4.6 (2.1 , 10.4)	4.4 (1.9 , 10.2)
1610.3+	16	50,947			2.7 (1.4 , 5.4)		1.8 (0.8 , 4.1)	2.5 (1.1 , 5.7)	2.0 (0.8 , 4.8)

[a] Models included indicator variables for age, years since hire, and exposure quartiles of each agent.

Table 11. RRs for Leukemia and BD ppm-years, Styrene ppm-years, and DMDTC mg/cm–years Lagged 10 Years Shown by Model

Exposure	Number of Leukemias	Person-Years	Model Number and Agents Included[a] (RR [95% CI]) Model 1: BD Only	Model 2: Styrene Only	Model 3: DMDTC Only	Model 4: BD + Styrene	Model 5: BD + DMDTC	Model 6: Styrene + DMDTC	Model 7: BD + Styrene + DMDTC
BD (ppm-years)									
0	11	225,370	1.0			1.0	1.0		1.0
> 0 to < 33.7	19	116,383	1.8 (0.8 , 3.7)			1.6 (0.6 , 4.3)	1.4 (0.7 , 3.1)		1.7 (0.6 , 4.7)
33.7 to < 184.7	21	102,808	1.7 (0.8 , 3.6)			1.2 (0.4 , 3.2)	1.1 (0.5 , 2.4)		1.0 (0.4 , 3.0)
184.7 to < 425.0	17	32,924	3.6 (1.6 , 7.9)			2.4 (0.8 , 7.0)	2.0 (0.8 , 5.0)		2.0 (0.7 , 6.3)
425.0+	13	22,689	3.6 (1.6 , 8.4)			2.7 (0.8 , 8.4)	2.1 (0.8 , 5.3)		2.4 (0.7 , 8.0)
Styrene (ppm-years)									
0	8	193,481		1.0		1.0		1.0	1.0
> 0 to < 8.3	18	139,492		1.5 (0.6 , 3.5)		1.1 (0.4 , 3.5)		1.0 (0.4 , 2.5)	0.7 (0.2 , 2.5)
8.3 to < 31.8	24	93,635		2.4 (1.0 , 5.4)		1.8 (0.6 , 5.6)		1.3 (0.5 , 3.5)	1.1 (0.3 , 3.8)
31.8 to < 61.1	16	37,483		3.4 (1.4 , 8.3)		2.1 (0.6 , 7.1)		1.7 (0.6 , 4.8)	1.1 (0.3 , 4.3)
61.1+	15	36,083		3.0 (1.2 , 7.2)		1.4 (0.4 , 5.0)		1.3 (0.5 , 3.9)	0.7 (0.2 , 2.8)
DMDTC (mg/cm–years)									
0	21	294,335			1.0		1.0	1.0	1.0
> 0 to < 185.3	14	93,129			1.9 (1.0 , 3.8)		1.7 (0.9 , 3.5)	1.7 (0.8 , 3.7)	1.8 (0.8 , 3.8)
185.3 to < 739.4	17	54,103			2.9 (1.5 , 5.6)		2.6 (1.3 , 5.3)	2.5 (1.2 , 5.2)	2.7 (1.2 , 5.7)
739.4 to < 1610.3	14	25,032			4.2 (2.1 , 8.4)		3.3 (1.5 , 7.3)	3.6 (1.6 , 7.8)	3.4 (1.5 , 7.8)
1610.3+	15	33,575			2.7 (1.4 , 5.3)		1.9 (0.9 , 4.3)	2.2 (1.0 , 4.7)	1.9 (0.8 , 4.3)

[a] Models included indicator variables for age, years since hire, and exposure quartiles of each agent.

Table 12. RRs for Leukemia and Total BD Peaks, Total Styrene Peaks, and DMDTC mg/cm–years Shown by Model

Exposure	Number of Leukemias	Person-Years	Model Number and Agents Included[a] (RR [95% CI]) Model 1: BD Only	Model 2: Styrene Only	Model 4: BD + Styrene	Model 5: BD + DMDTC	Model 6: Styrene + DMDTC	Model 7: BD + Styrene + DMDTC
Number of BD peaks								
0	10	150,623	1.0		1.0	1.0		1.0
> 0 to < 255	17	151,029	2.1 (0.9 , 4.5)		1.5 (0.5 , 4.3)	1.5 (0.7 , 3.4)		1.3 (0.4 , 3.8)
255 to < 965	18	94,764	2.7 (1.2 , 5.8)		1.4 (0.5 , 4.2)	1.8 (0.8 , 4.1)		1.1 (0.4 , 3.5)
965 to < 3137	18	65,086	3.3 (1.5 , 7.1)		1.5 (0.5 , 4.7)	2.1 (0.9 , 5.0)		1.2 (0.4 , 3.9)
3137+	18	38,672	4.9 (2.2 , 10.6)		2.0 (0.6 , 6.3)	3.2 (1.3 , 7.9)		1.6 (0.5 , 5.6)
Number of Styrene peaks								
0	14	202,225		1.0	1.0		1.0	1.0
> 0 to < 58	16	151,484		1.5 (0.7 , 3.0)	1.1 (0.4 , 2.9)		1.1 (0.9 , 3.7)	1.0 (0.4 , 2.7)
58 to < 170	17	53,266		3.6 (1.8 , 7.3)	2.6 (1.0 , 7.0)		2.3 (1.0 , 4.5)	2.0 (0.7 , 5.6)
170 to < 699	17	40,653		4.6 (2.3 , 9.4)	3.3 (1.2 , 8.9)		3.3 (1.4 , 6.6)	2.9 (1.0 , 8.2)
699+	17	52,545		4.2 (2.0 , 8.6)	2.8 (1.0 , 7.8)		3.0 (1.4 , 6.4)	2.4 (0.8 , 6.9)
DMDTC (mg/cm–years)								
0	17	206,617				1.0	1.0	1.0
> 0 to < 185.3	16	128,688				2.1 (1.0 , 4.4)	1.8 (0.5 , 2.4)	1.8 (0.9 , 3.7)
185.3 to < 739.4	16	77,743				2.2 (1.0 , 4.6)	2.1 (1.0 , 5.0)	2.0 (0.9 , 4.4)
739.4 to < 1610.3	16	36,178				3.3 (1.5 , 7.0)	3.1 (1.5 , 7.3)	3.0 (1.3 , 6.5)
1610.3+	16	50,947				1.6 (0.7 , 3.5)	1.5 (0.7 , 3.2)	1.4 (0.6 , 3.1)

[a] Models included indicator variables for age, years since hire, and exposure quartiles of each agent. Model 3 is not included to avoid redundancy with Table 10.

Table 13. RRs for Leukemia and BD ppm-years Due to Concentrations > 100 ppm and Concentrations ≤ 100 ppm Shown by Model

Exposure	Number of Leukemias	Person-Years	Model Number and Agents Included[a] (RR [95% CI]) Model 1: BD Only	Model 4: BD + Styrene	Model 5: BD + DMDTC	Model 7: BD + Styrene + DMDTC
Models for BD Concentrations > 100 ppm						
BD (ppm-years due to >100 ppm)[b]						
0	10	151,191	1.0	1.0	1.0	1.0
> 0 to < 16.3	17	122,168	2.6 (1.2 , 5.8)	3.1 (1.2 , 8.2)	2.0 (0.9 , 4.5)	2.8 (1.0 , 7.7)
16.3 to < 96.5	18	131,678	1.9 (0.9 , 4.2)	2.2 (0.8 , 5.7)	1.2 (0.5 , 2.9)	1.7 (0.6 , 4.7)
96.5 to < 247.6	18	53,610	4.0 (1.8 , 8.7)	4.0 (1.5 , 10.7)	2.3 (1.0 , 5.7)	3.0 (1.0 , 8.5)
247.6+	18	41,526	4.6 (2.1 , 10.1)	4.7 (1.7 , 13.0)	2.8 (1.1 , 6.8)	3.7 (1.3 , 11.1)
Styrene (ppm-years)						
0	7	77,460		1.0		1.0
> 0 to < 8.3	18	77,551		0.7 (0.2 , 2.0)		0.4 (0.1 , 1.4)
8.3 to < 31.8	19	32,311		0.7 (0.2 , 2.1)		0.4 (0.1 , 1.4)
31.8 to < 61.1	18	55,797		1.1 (0.4 , 3.4)		0.6 (0.2 , 2.1)
61.1+	19	57,056		0.8 (0.3 , 2.7)		0.4 (0.1 , 1.6)
DMDTC (mg/cm–years)						
0	17	206,617			1.0	1.0
> 0 to < 185.3	16	128,688			2.1 (1.0 , 4.3)	2.5 (1.1 , 5.4)
185.3 to < 739.4	16	77,743			2.4 (1.1 , 5.1)	2.7 (1.2 , 6.1)
739.4 to < 1610.3	16	36,178			3.4 (1.5 , 7.4)	3.9 (1.7 , 9.0)
1610.3+	16	50,947			1.7 (0.8 , 3.9)	2.0 (0.8 , 4.7)
Models for BD Concentrations ≤ 100 ppm						
BD (ppm-years due to ≤100 ppm)[b]						
0	10	116,471	1.0	1.0	1.0	1.0
> 0 to < 7.7	17	125,906	1.8 (0.8 , 3.9)	1.7 (0.6 , 4.6)	1.4 (0.6 , 3.0)	1.8 (0.7 , 5.0)
7.7 to < 56.2	18	167,350	1.2 (0.5 , 2.5)	0.9 (0.3 , 2.5)	0.7 (0.3 , 1.6)	0.8 (0.3 , 2.4)
56.2 to < 124.7	18	49,438	2.9 (1.3 , 6.3)	1.9 (0.6 , 5.4)	1.7 (0.7 , 4.1)	2.0 (0.7 , 5.9)
124.7+	18	41,008	2.9 (1.4 , 6.4)	1.8 (0.6 , 5.5)	1.7 (0.7 , 4.0)	2.0 (0.6 , 6.0)
Styrene (ppm-years)						
0	7	77,460		1.0		1.0
> 0 to < 8.3	18	77,551		1.1 (0.3 , 3.3)		0.5 (0.2 , 1.9)
8.3 to < 31.8	19	32,311		1.4 (0.4 , 4.5)		0.6 (0.2 , 2.3)
31.8 to < 61.1	18	55,797		2.1 (0.6 , 6.9)		0.8 (0.2 , 3.0)
61.1+	19	57,056		1.8 (0.5 , 6.0)		0.6 (0.2 , 2.4)
DMDTC (mg/cm–years)						
0	17	206,617			1.0	1.0
> 0 to < 185.3	16	128,688			2.4 (1.2 , 4.9)	2.7 (1.2 , 6.0)
185.3 to < 739.4	16	77,743			3.0 (1.5 , 6.3)	3.3 (1.5 , 7.4)
739.4 to < 1610.3	16	36,178			4.7 (2.2 , 10.0)	5.2 (2.2 , 11.9)
1610.3+	16	50,947			2.1 (1.0 , 4.6)	2.3 (1.0 , 5.3)

[a] Models included indicator variables for age, years since hire, and exposure quartiles of each agent. Models 2, 3, and 6 are not included to avoid redundancy with Table 10.

[b] BD exposure quartiles are based on the partitioned BD concentrations.

Table 14. RRs for Leukemia and BD ppm-years Due to Concentrations > 100 ppm and ≤ 100 ppm, Cross-Classified[a]

	BD ppm-years Due to Concentrations > 100 ppm[b]			**Overall, for BD ppm-years Due to Concentrations ≤100 ppm**
	0 to < 16.3	16.3 to < 247.6	247.6+	
BD ppm-years Due to Concentrations ≤ 100 ppm[b]				
0 to < 7.7				
Number of leukemias	21	6	None[c]	27
Person-years	211,934	30,336		242,377
RR	1.0	1.9		1.0
95% CI	—	0.8 , 4.7		—
7.7 to < 124.7				
Number of leukemias	6	21	9	36
Person-years	58,633	135,827	22,328	216,788
RR	0.9	1.2	3.1	1.2
95% CI	0.4 , 2.2	0.7 , 2.2	1.4 , 6.7	0.7 , 2.0
124.7+				
Number of leukemias	None[c]	9	9	18
Person-years		19,125	19,091	41,008
RR		2.7	2.4	2.1
95% CI		1.2 , 6.0	1.1 , 5.3	1.2 , 3.9
				$P = 0.44$[d]
Overall, for BD ppm-years Due to Concentrations >100 ppm				
Number of leukemias	27	36	18	
Person-years	273,360	185,288	41,526	
RR	1.0	1.6	2.8	$P = 0.02$[e]
95% CI	—	1.0 , 2.6	1.6 , 5.2	

[a] All RRs were adjusted only for age and years since hire unless otherwise noted.

[b] BD exposure quartiles are based on the partitioned BD concentrations; exposure quartiles 2 and 3 have been combined.

[c] This quartile was not included in the Poisson regression model.

[d] *P* value for trend in BD ppm-years due to concentrations ≤ 100 ppm; adjusted for BD ppm-years due to concentrations > 100 pm, age, and years since hire.

[e] *P* value for trend in BD ppm-years due to concentrations > 100 ppm; adjusted for BD ppm-years due to concentrations ≤ 100 ppm, age, and years since hire.

A model containing a term for each of the partitioned BD ppm-years variables and terms for age and years since hire indicated that a trend of increasing RR with increasing ppm-years was present for BD ppm-years due to concentrations > 100 ppm ($P = 0.02$) (last row of Table 14) and for BD ppm-years due to concentrations ≤ 100 ppm ($P = 0.44$) (rightmost column of Table 14), but was stronger for the former. After controlling for styrene ppm-years and DMDTC, a weak association remained for BD ppm-years due to exposure concentrations > 100 ppm (RRs, 1.0, 1.0, and 1.7), whereas we found no association with BD ppm-years due to exposure concentrations ≤ 100 ppm (RRs, 1.0, 0.7, and 1.0).

To examine possible interactions between BD ppm-years and DMDTC, we formed three groups of the exposure quartiles for each agent: (1) no exposure plus the first quartile (low); (2) the second and third quartiles combined (middle); and (3) the fourth quartile (high). Because of the high correlation between BD ppm-years and DMDTC, the data were limited for evaluating the association between BD ppm-years and leukemia in the group with lowest exposure to DMDTC and vice versa (Table 15). Within the middle and high groups of DMDTC exposure, we noted some suggestion that the leukemia RR increased with increasing to BD ppm-years. The overall association for BD ppm-years and leukemia, adjusted for age, years since

Table 15. RRs for Leukemia and BD ppm-years, and DMDTC mg/cm–years, Cross-Classified[a]

	BD ppm-years			Overall, for DMDTC Unadjusted for BD	Overall, for DMDTC Adjusted for BD
	0 to < 33.7	33.7 to < 425.0[b]	425.0+		
DMDTC mg/cm–years					
0 to < 185.3					
Number of leukemias	23	8	2	33	
Person-years	243,154	81,883	10,268	335,306	
RR	1.0	0.8	1.3	1.0[c]	1.0[c]
95% CI	—	0.3 , 1.7	0.3 , 5.7	—	—
185.3 to < 1610.3[b]					
Number of leukemias	4	20	8	32	
Person-years	25,738	75,337	12,846	113,921	
RR	1.5	2.3	4.7	2.6	2.4
95% CI	0.5 , 4.3	1.3 , 4.3	2.1 , 10.5	1.6 , 4.2	1.4 , 4.1
1610.3+					
Number of leukemias	None[d]	8	8	16	
Person-years		36,299	12,626	50,947	
RR		1.4	3.0	1.9	1.5
95% CI		0.6 , 3.1	1.3 , 6.8	1.1 , 3.5	0.8 , 3.0
				P = 0.06 for Trend	*P* = 0.60 for Trend
Overall for BD Unadjusted for DMDTC					
Number of leukemias	27	36	18		
Person-years	270,914	193,519	35,741	*P* = 0.0003 for Trend	
RR	1.0[c]	1.4	3.0		
95% CI	—	0.9 , 2.3	1.6 , 5.4		
Overall for BD Adjusted for DMDTC					
RR	1.0[c]	1.0	2.1	*P* = 0.003 for Trend	
95% CI	—	0.6 , 1.8	1.0 , 4.2		

[a] All RRs were adjusted for age and years since hire.

[b] Exposure quartiles 2 and 3 have been combined.

[c] Referent category.

[d] Person-years excluded from cross-classified analyses.

hire, and DMDTC (last row of Table 15) had a *P* value for trend of 0.003. In the group with the lowest BD exposure, the RR was 1.5 (CI = 0.5, 4.3) for the middle group of DMDTC exposure. The relation between DMDTC and leukemia within the middle and high group of BD ppm-years was irregular. The overall RRs for DMDTC, adjusted for age, years since hire, and BD ppm-years, also displayed an irregular pattern (rightmost column of Table 15), with a *P* value for trend of 0.60. No interaction between the two agents was apparent.

Using an approach similar to that used to examine BD ppm-years and DMDTC, we also evaluated possible interactions between BD and styrene ppm-years (Table 16). Data on the effect of BD ppm-years among subjects with low exposure to styrene ppm-years were largely uninformative. Within the middle and high styrene exposure groups, we noted some suggestion of an increasing leukemia RR with increasing exposure to BD. In the group with the lowest BD exposure, the RR was 1.6 (CI = 0.7, 3.9) for the middle exposure group of styrene. The RR did not increase consistently with increasing

Table 16. RRs for Leukemia and BD ppm-years and Styrene ppm-years, Cross-Classified[a]

	BD ppm-years			Overall, for Styrene Unadjusted for BD	Overall, for Styrene Adjusted for BD
	0 to < 33.7	33.7 to < 425.0[b]	425.0+		
Styrene ppm-years					
0 to < 8.3					
Number of leukemias	20	5	None[c]	25	
Person-years	215,953	37,240		255,011	
RR	1.0[d]	1.2		1.0[d]	1.0[d]
95% CI	—	0.4 , 3.1		—	—
8.3 to < 61.1[b]					
Number of leukemias	7	25	5	37	
Person-years	50,077	128,918	9112	188,107	
RR	1.6	1.6	3.5	1.7	1.5
95% CI	0.7 , 3.9	0.9 , 2.9	1.3 , 9.3	1.0 , 2.8	0.8 , 2.8
61.1+					
Number of leukemias	None[c]	6	13	19	
Person-years		27,362	24,810	57,056	
RR		1.6	3.3	2.2	1.4
95% CI		0.6 , 4.0	1.6 , 6.7	1.2 , 4.0	0.6 , 3.0
				$P = 0.01$ for trend	$P = 0.65$ for trend
Overall, for BD Unadjusted for Styrene					
Number of leukemias	27	36	18		
Person-years	270,914	193,519	35,741	$P = 0.0003$ for trend	
RR	1.0[d]	1.4	3.0		
95% CI	—	0.9 , 2.3	1.6 , 5.4		
Overall, for BD Adjusted for Styrene					
RR	1.0[d]	1.1	2.4	$P = 0.01$ for trend	
95% CI	—	0.6 , 2.1	1.1 , 5.3		

[a] All RRs were adjusted for age and years since hire.

[b] Exposure quartiles 2 and 3 have been combined.

[c] Person-years excluded from cross-classified analyses.

[d] Referent category.

exposure to styrene within the middle and high BD exposure groups. The overall trend was consistent and statistically significant for BD ppm-years adjusted for age, years since hire, and styrene ppm-years ($P = 0.01$, last row of Table 16), but not for styrene ppm-years adjusted for age, years since hire, and BD ppm-years ($P = 0.65$, rightmost column of Table 16).

Analyses of specific forms of leukemia indicated that BD ppm-years was associated positively with chronic lymphocytic, chronic myelogenous, and residual types of leukemia and was not associated with acute myelogenous leukemia (Table 17). The association with BD ppm-years was particularly strong and consistent for chronic myelogenous leukemia (for exposures in the low, middle, and high groups, adjusted for age and years since hire but not for other agents [single-agent model], RRs were 1.0, 2.7, and 7.2; RRs, adjusted for age, years since hire, styrene ppm-years, and DMDTC [multiple-agent model], were 1.0, 2.0, and 7.2), but these results were imprecise. Styrene

Table 17. RRs for Four Types of Leukemia and BD ppm-years, Styrene ppm-years, and DMDTC mg/cm–years Shown by Model Type

Exposure[a]	Number of Leukemias	Person-Years	Single-Agent Models[b]		Multiple-Agent Models[c]	
			RR	95% CI	RR	95% CI
Chronic Lymphocytic Leukemia[d]						
BD (ppm-years)						
< 33.7	7	74,449	1.0		1.0	
33.7 to < 425.0	11	76,798	1.5	0.6 , 4.0	0.9	0.3 , 3.0
425.0+	7	19,146	3.9	1.3 , 11.0	2.7	0.6 , 11.2
Styrene (ppm-years)						
< 8.3	7	72,863	1.0		1.0	
8.3 to < 61.1	11	68,451	1.7	0.7 , 4.4	1.2	0.4 , 3.7
61.1+	7	29,079	2.6	0.9 , 7.3	0.9	0.2 , 3.7
DMDTC (mg/cm–years)						
< 185.3	8	98,743	1.0		1.0	
185.3 to < 1610.3	12	42,981	3.9	1.6 , 9.5	3.5	1.2 , 9.8
1610.3+	5	28,669	2.2	0.7 , 6.6	1.6	0.4 , 5.9
Acute Myelogenous Leukemia						
BD (ppm-years)						
< 33.7	12	270,914	1.0		1.0	
33.7 to < 425.0	12	193,519	1.1	0.5 , 2.5	0.6	0.2 , 1.6
425.0+	2	35,741	0.8	0.2 , 3.6	0.5	0.1 , 3.3
Styrene (ppm-years)						
< 8.3	9	255,011	1.0		1.0	
8.3 to < 61.1	14	188,107	1.9	0.8 , 4.4	2.1	0.8 , 5.8
61.1+	3	57,056	1.0	0.3 , 3.9	1.1	0.2 , 5.6
DMDTC (mg/cm–years)						
< 185.3	13	335,306	1.0		1.0	
185.3 to < 1610.3	9	113,921	2.0	0.8 , 4.6	2.1	0.8 , 5.8
1610.3+	4	50,947	1.3	0.4 , 4.1	1.5	0.4 , 5.4

Table continues next page

[a] Exposure quartiles 2 and 3 have been combined.

[b] Single-agent models included indicator variables for age, years since hire, and exposure categories.

[c] Multiple-agent models included variables for age, years since hire, and exposure categories for each agent in the model.

[d] Models were restricted to ages 40 and older and to 20 or more years since hire (total person-years = 170,392).

[e] Models were restricted to ages 40 and older (total person-years = 338,406).

ppm-years was associated positively with chronic lymphocytic, chronic myelogenous, and other leukemias in single-agent models but was not consistently associated with acute myelogenous leukemia. After adjusting for BD and DMDTC, styrene ppm-years was not strongly or consistently associated with any form of leukemia. DMDTC, unadjusted for BD or styrene, was associated inconsistently (without an exposure–response trend) with chronic lymphocytic (RRs of 1.0, 3.9, 2.2), acute myelogenous (RRs of 1.0, 2.0, 1.3), and chronic myelogenous (RRs of 1.0, 3.9, 2.4) leukemias and was associated consistently with other leukemias (RRs of 1.0, 1.2, 2.5). Adjusting for the other two agents diminished the associations seen for DMDTC.

NHL was associated most strongly with styrene ppm-years, but the data for this agent did not indicate clear trends and were not statistically significant (Table 18, Models 2, 4, 6, and 7). NHL was not associated with BD ppm-years in models that controlled for styrene ppm-years, or DMDTC, or both (Models 4, 5, and 7). RRs for DMDTC were elevated in most exposure quartiles, but we found no trend of increasing RRs with increasing exposure. Analysis

Table 17 (*continued*). RRs for Four Types of Leukemia and BD ppm-years, Styrene ppm-years, and DMDTC mg/cm–years Shown by Model Type

Exposure[a]	Number of Leukemias	Person-Years	Single-Agent Models[b] RR	Single-Agent Models[b] 95% CI	Multiple-Agent Models[c] RR	Multiple-Agent Models[c] 95% CI
Chronic Myelogenous Leukemia[d]						
BD (ppm-years)						
< 33.7	3	166,082	1.0		1.0	
33.7 to < 425.0	8	142,337	2.7	0.7 , 10.4	2.0	0.4 , 10.0
425.0+	5	29,987	7.2	1.7 , 30.5	7.2	1.1 , 47.6
Styrene (ppm-years)						
< 8.3	4	159,976	1.0		1.0	
8.3 to < 61.1	8	131,422	2.1	0.6 , 7.1	1.0	0.2 , 4.1
61.1+	4	47,008	2.7	0.7 , 10.9	0.6	0.1 , 3.5
DMDTC (mg/cm–years)						
< 185.3	5	212,980	1.0		1.0	
185.3 to < 1610.3	8	81,092	3.9	1.3 , 12.1	2.9	0.8 , 10.2
1610.3+	3	44,334	2.4	0.6 , 10.0	1.3	0.3 , 6.6
Other Leukemias[e]						
BD (ppm-years)						
< 33.7	5	166,082	1.0		1.0	
33.7 to < 425.0	5	142,337	1.1	0.3 , 3.9	1.0	0.2 , 5.1
425.0+	4	29,987	4.0	1.0 , 15.0	2.1	0.3 , 16.3
Styrene (ppm-years)						
< 8.3	5	159,976	1.0		1.0	
8.3 to < 61.1	4	131,422	1.0	0.3 , 3.7	0.8	0.2 , 4.4
61.1+	5	47,008	3.2	0.9 , 11.0	1.8	0.3 , 12.4
DMDTC (mg/cm–years)						
< 185.3	7	212,980	1.0		1.0	
185.3 to < 1610.3	3	81,092	1.2	0.3 , 4.7	0.9	0.2 , 4.4
1610.3+	4	44,334	2.5	0.7 , 8.5	1.6	0.3 , 7.6

[a] Exposure quartiles 2 and 3 have been combined.

[b] Single-agent models included indicator variables for age, years since hire, and exposure categories.

[c] Multiple-agent models included variables for age, years since hire, and exposure categories for each agent in the model.

[d] Models were restricted to ages 40 and older and to 20 or more years since hire (total person-years = 170,392).

[e] Models were restricted to ages 40 and older (total person-years = 338,406).

of CLL–NHL yielded results similar to those obtained for NHL; Table 19).

Multiple myeloma was positively associated with BD ppm-years, but not with styrene ppm-years or with DMDTC (Table 20). All of the RRs for BD ppm-years, styrene ppm-years, and DMDTC were statistically imprecise, with CIs that included the null value.

External Analyses of LHCs

In addition to the internal analyses described in the previous section, we compared the mortality rate of subjects in each agent-specific cumulative exposure category to the rate in the general population, adjusting for age, race, and calendar year, and using the SMR as the measure of association. For the most part, the results were similar to those of the internal analyses: an increased rate of leukemia and of NHL among subjects with the highest exposure to BD or styrene ppm-years; and the absence of a consistent exposure–response relation for DMDTC and leukemia and for DMDTC and NHL (Table 21). External analyses of multiple myeloma found essentially no association with BD, styrene, or DMDTC. The highest BD quartile had an SMR of only 158 (5/3.2, CI = 51, 369) for multiple myeloma. For all three agents, most zero exposure groups had SMRs less

Table 18. RRs for NHL and BD ppm-years, Styrene ppm-years, and DMDTC mg/cm–years Shown by Model

Exposure	Number of NHL	Person-Years	Model Number and Agents Included[a] (RR [95% CI])						
			Model 1: BD Only	Model 2: Styrene Only	Model 3: DMDTC Only	Model 4: BD + Styrene	Model 5: BD + DMDTC	Model 6: Styrene + DMDTC	Model 7: BD + Styrene + DMDTC
BD (ppm-years)									
0	11	73,870	1.0			1.0	1.0		1.0
> 0 to < 33.7	16	92,212	1.2 (0.6 , 2.7)			0.9 (0.4 , 2.4)	1.1 (0.5 , 2.4)		1.0 (0.4 , 2.6)
33.7 to < 184.7	10	102,475	0.6 (0.2 , 1.4)			0.4 (0.1 , 1.1)	0.5 (0.2 , 1.2)		0.4 (0.1 , 1.2)
184.7 to < 425.0	12	39,862	1.6 (0.7 , 3.6)			0.8 (0.3 , 2.4)	1.2 (0.4 , 3.1)		0.9 (0.3 , 2.7)
425.0+	9	29,987	1.4 (0.6 , 3.4)			0.7 (0.2 , 2.1)	1.0 (0.4 , 2.9)		0.7 (0.2 , 2.3)
Styrene (ppm-years)									
0	6	53,165		1.0		1.0		1.0	1.0
> 0 to < 8.3	16	106,811		1.4 (0.5 , 3.6)		1.7 (0.5 , 5.6)		1.2 (0.4 , 3.2)	1.4 (0.4 , 4.9)
8.3 to < 31.84	11	88,810		1.1 (0.4 , 2.9)		1.8 (0.5 , 6.3)		0.9 (0.3 , 2.6)	1.3 (0.3 , 5.2)
31.8 to < 61.1	9	42,612		1.5 (0.5 , 4.2)		2.3 (0.6 , 8.7)		1.2 (0.4 , 3.8)	1.7 (0.4 , 7.0)
61.1+	16	47,008		2.3 (0.9 , 5.9)		3.2 (0.9 , 11.2)		1.8 (0.6 , 5.5)	2.3 (0.6 , 9.2)
DMDTC (mg/cm–years)									
0	19	144,095			1.0		1.0	1.0	1.0
> 0 to < 185.3	11	68,885			1.6 (0.8 , 3.4)		1.6 (0.7 , 3.5)	1.5 (0.7 , 3.5)	1.5 (0.6 , 3.3)
185.3 to < 739.4	11	53,278			1.8 (0.8 , 3.7)		2.1 (0.9 , 4.6)	1.5 (0.6 , 3.5)	1.7 (0.7 , 4.0)
739.4 to < 1610.3	4	27,814			1.0 (0.3 , 3.0)		1.1 (0.3 , 3.5)	0.8 (0.3 , 2.7)	0.9 (0.3 , 3.0)
1610.3+	13	44,334			1.7 (0.8 , 3.5)		1.7 (0.7 , 4.1)	1.4 (0.6 , 3.4)	1.5 (0.6 , 3.8)

[a] Models included indicator variables for age, years since hire, and exposure quartiles of each agent. All models were restricted to ages 40 years or older (total person-years = 338,406).

Table 19. RRs for CLL–NHL and BD ppm-years, Styrene ppm-years, and DMDTC mg/cm–years Shown by Model

Exposure	Number of CLL–NHL Combined	Person-Years	Model Number and Agents Included[a] (RR [95% CI])						
			Model 1: BD Only	Model 2: Styrene Only	Model 3: DMDTC Only	Model 4: BD + Styrene	Model 5: BD + DMDTC	Model 6: Styrene + DMDTC	Model 7: BD + Styrene + DMDTC
BD (ppm-years)									
0	12	73,870	1.0			1.0	1.0		1.0
> 0 to < 33.7	18	92,212	1.3 (0.6 , 2.6)			0.8 (0.3 , 2.0)	1.1 (0.5 , 2.4)		0.9 (0.4 , 2.1)
33.7 to < 184.7	14	102,475	0.8 (0.3 , 1.6)			0.5 (0.2 , 1.2)	0.6 (0.2 , 1.3)		0.4 (0.2 , 1.1)
184.7 to < 425.0	17	39,862	2.0 (1.0 , 4.3)			1.1 (0.4 , 2.9)	1.4 (0.6 , 3.3)		1.0 (0.4 , 2.7)
425.0+	14	29,987	2.0 (0.9 , 4.4)			1.0 (0.4 , 2.8)	1.4 (0.6 , 3.4)		0.9 (0.3 , 2.7)
Styrene (ppm-years)									
0	6	53,165		1.0		1.0		1.0	1.0
> 0 to < 8.3	20	106,811		1.7 (0.7 , 4.4)		2.2 (0.7 , 6.8)		1.4 (0.5 , 3.8)	1.9 (0.6 , 6.1)
8.3 to < 31.84	15	88,810		1.5 (0.6 , 3.8)		2.2 (0.7 , 7.1)		1.1 (0.4 , 3.1)	1.7 (0.5 , 6.2)
31.8 to < 61.1	13	42,612		2.2 (0.8 , 5.7)		2.7 (0.8 , 9.2)		1.5 (0.5 , 4.5)	2.0 (0.5 , 7.5)
61.1+	21	47,008		3.0 (1.2 , 7.5)		3.1 (0.9 , 10.3)		2.0 (0.7 , 5.8)	2.2 (0.6 , 8.2)
DMDTC (mg/cm–years)									
0	22	144,095			1.0		1.0	1.0	1.0
> 0 to < 185.3	12	68,885			1.5 (0.7 , 3.0)		1.5 (0.7 , 3.0)	1.3 (0.6 , 2.9)	1.3 (0.6 , 2.7)
185.3 to < 739.4	13	53,278			1.8 (0.9 , 3.5)		1.9 (0.9 , 4.0)	1.4 (0.7 , 3.1)	1.6 (0.7 , 3.6)
739.4 to < 1610.3	11	27,814			2.4 (1.2 , 4.9)		2.3 (1.0 , 5.3)	1.9 (0.8 , 4.3)	2.0 (0.8 , 4.7)
1610.3+	17	44,334			1.9 (1.0 , 3.7)		1.7 (0.8 , 3.7)	1.6 (0.7 , 3.4)	1.5 (0.7 , 3.3)

[a] Models included indicator variables for age, years since hire, and exposure quartiles of each agent. All models were restricted to ages 40 years or older (total person-years = 338,406).

Table 20. RRs for Multiple Myeloma and BD ppm-years, Styrene ppm-years, and DMDTC mg/cm–years Shown by Model

Exposure	Number of Multiple Myelomas	Person-Years	Model Number and Agents Included[a] (RR [95% CI]) Model 1: BD Only	Model 2: Styrene Only	Model 3: DMDTC Only	Model 4: BD + Styrene	Model 5: BD + DMDTC	Model 6: Styrene + DMDTC	Model 7: BD + Styrene + DMDTC
BD (ppm-years)									
0	4	73,870	1.0			1.0	1.0		1.0
> 0 to < 33.7	6	92,212	1.3 (0.4 , 4.7)			1.8 (0.3 , 11.4)	1.4 (0.4 , 5.0)		1.8 (0.3 , 10.9)
33.7 to < 184.7	8	102,475	1.4 (0.4 , 4.7)			3.3 (0.6 , 19.8)	1.7 (0.5 , 5.9)		3.7 (0.6 , 21.6)
184.7 to < 425.0	2	39,862	0.8 (0.1 , 4.4)			1.8 (0.2 , 16.1)	1.1 (0.2 , 6.8)		2.0 (0.2 , 17.8)
425.0+	7	29,987	3.5 (1.0 , 11.9)			5.7 (0.8 , 39.9)	4.7 (1.2 , 18.9)		6.2 (0.9 , 43.2)
Styrene (ppm-years)									
0	4	53,165		1.0		1.0		1.0	1.0
> 0 to < 8.3	10	106,811		1.4 (0.4 , 4.4)		0.7 (0.1 , 4.1)		1.5 (0.4 , 5.0)	0.8 (0.1 , 4.6)
8.3 to < 31.84	3	88,810		0.5 (0.1 , 2.1)		0.2 (0.0 , 1.5)		0.5 (0.1 , 2.6)	0.2 (0.0 , 1.7)
31.8 to < 61.1	2	42,612		0.6 (0.1 , 3.3)		0.2 (0.0 , 2.0)		0.7 (0.1 , 4.3)	0.3 (0.0 , 2.5)
61.1+	8	47,008		2.0 (0.6 , 6.6)		0.6 (0.1 , 4.1)		2.3 (0.5 , 9.9)	0.8 (0.1 , 5.7)
DMDTC (mg/cm–years)									
0	13	144,095			1.0		1.0	1.0	1.0
> 0 to < 185.3	4	68,885			0.9 (0.3 , 2.9)		0.8 (0.3 , 2.6)	0.9 (0.3 , 3.0)	1.0 (0.3 , 3.3)
185.3 to < 739.4	3	53,278			0.8 (0.2 , 2.8)		0.6 (0.2 , 2.3)	0.7 (0.2 , 2.7)	0.6 (0.2 , 2.5)
739.4 to < 1610.3	2	27,814			0.8 (0.2 , 3.6)		0.6 (0.1 , 2.7)	0.7 (0.1 , 3.3)	0.5 (0.1 , 2.8)
1610.3+	5	44,334			1.1 (0.4 , 3.1)		0.7 (0.2 , 2.2)	1.0 (0.3 , 3.5)	0.8 (0.2 , 2.7)

[a] Models included indicator variables for age, years since hire, and exposure quartiles of each agent. All models were restricted to ages 40 years or older (total person-years = 338,406).

Table 21. Observed/Expected Deaths, SMRs, and 95% CIs for All Leukemias, NHL, and Multiple Myeloma and BD ppm-years, Styrene ppm-years, and DMDTC mg/cm–years, 1944–1998

	All Leukemias			NHL			Multiple Myeloma		
Exposure	Obs/Exp	SMR	95% CI	Obs/Exp	SMR	95% CI	Obs/Exp	SMR	95% CI
BD (ppm-years)									
0	9/12.1	75	34 , 142	6/10.5	57	21 , 124	3/5.1	58	12 , 171
> 0 to < 33.7	16/14.1	113	65 , 184	12/12.6	95	49 , 167	6/5.8	104	38 , 226
33.7 to < 184.7	17/17.1	99	58 , 159	8/15.1	53	23 , 105	8/7.5	106	46 , 209
184.7 to < 425.0	12/7.1	169	87 , 295	11/6.2	177	89 , 317	2/3.5	58	7 , 209
425.0+	14/5.7	246	134 , 412	9/4.9	185	85 , 352	5/3.2	158	51 , 369
Styrene (ppm-years)									
0	7/8.9	79	32 , 163	3/7.9	38	8 , 112	3/3.8	79	32 , 163
> 0 to < 8.3	16/17.0	94	54 , 153	11/14.9	74	37 , 132	10/7.0	144	69 , 265
8.3 to < 31.84	15/14.3	105	59 , 173	9/12.6	71	33 , 135	3/6.2	49	10 , 143
31.8 to < 61.1	14/7.5	187	102 , 313	9/6.7	134	61 , 255	2/3.5	58	7 , 208
61.1+	16/8.4	191	109 , 310	14/7.1	197	108 , 331	6/4.7	127	47 , 276
DMDTC (mg/cm–years)									
0	16/26.2	61	35 , 99	13/22.0	59	31 , 101	12/11.2	107	55 , 187
> 0 to < 185.3	15/9.1	165	92 , 272	8/8.6	93	40 , 183	4/3.8	106	29 , 271
185.3 to < 739.4	13/7.4	176	94 , 300	9/6.9	130	60 , 248	3/3.4	89	18 , 260
739.4 to < 1610.3	13/4.7	277	148 , 474	3/4.2	72	15 , 211	1/2.2	45	1 , 252
1610.3+	11/8.7	127	63 , 227	13/7.5	127	63 , 227	4/4.5	89	24 , 228

than 100 for leukemia, NHL, and multiple myeloma. NHL had the lowest SMR for subjects with no exposure to styrene (SMR = 38, CI = 8, 112).

Results of external analyses for specific forms of leukemia were also consistent with those of internal analyses (Table 22). The number of deaths from chronic myelogenous leukemia and from CLL was higher than expected in the highest BD and styrene exposure quartiles. For DMDTC, intermediate (quartiles 2 and 3 combined) cumulative exposure had the greatest increase for each of these two forms of leukemia.

Internal Analyses of Lymphoid and Myeloid Neoplasms

Results of single- and multiple-agent models indicated that all three agents were, at most, associated weakly with lymphoid neoplasms (Table 23). For myeloid neoplasms, the exposure–response relation was most consistent for BD. All results were statistically imprecise.

Internal Analyses of Other Cancers

Additional internal analyses examined relations between BD ppm-years, styrene ppm-years, and DMDTC and mortality rates from colorectal and prostate cancer. These analyses included 198 colorectal cancers (181 cases coded as the underlying cause and 17 as a contributing cause of death) and 181 prostate cancers (142 cases coded as the underlying cause and 39 as a contributing cause of death)

Colorectal cancer decedents exposed to each agent had median values of 73 BD ppm-years, 14 styrene ppm-years, and 657 DMDTC mg/cm–years. Poisson regression modeling did not find consistent association for any of the three agents (Table 24).

Prostate cancer decedents exposed to each agent had median values of 93 BD ppm-years, 24 styrene ppm-years, and 914 DMDTC mg/cm–years. Results of Poisson regression models indicated that BD, styrene, and DMDTC were not associated consistently with prostate cancer (Models 1, 2, and 3 in Table 25).

Table 22. Observed/Expected Deaths, SMRs, and 95% CIs for Three Leukemias and NHL and BD ppm-years, Styrene ppm-years, and DMDTC mg/cm–years, 1968–1998

	Acute Myelogenous Leukemia			Chronic Myelogenous Leukemia			CLL			CLL–NHL		
Exposure	Obs/ Exp	SMR	95% CI	Obs/ Exp	SMR	95% CI	Obs/ Exp	SMR	95% CI	Obs/ Exp	SMR	95% CI
BD (ppm-years)												
0	9/5.9	153	70 , 290	3/2.9	105	22 , 307	4/4.2	94	26 , 242	6/11	55	20 , 120
> 0 to < 33.7										14/13	110	60 , 184
33.7 to < 184.7	4/5.5	73	20 , 187	5/2.6	196	64 , 458	7/4.3	162	65 , 334	11/16	70	35 , 125
184.7 to < 425.0										13/6.7	194	103 , 331
425.0+	0/1.3	0	0 , 277	3/0.6	476	98 , 1391	4/1.1	355	97 , 908	13/5.5	238	126 , 406
Styrene (ppm-years)												
0	7/5.7	122	49 , 252	4/2.7	147	40 , 376	3/3.2	93	19 , 272	2/8.1	25	3 , 89
> 0 to < 8.3										13/15	86	46 , 148
8.3 to < 31.84	5/5.1	99	32 , 231	5/2.4	209	68 , 488	7/3.9	181	73 , 374	12/13	91	47 , 159
31.8 to < 61.1										12/7.4	162	84 , 283
61.1+	1/1.9	52	1 , 290	2/0.9	215	26 , 775	5/1.6	310	101 , 724	18/7.9	229	136 , 362
DMDTC (mg/cm–years)												
0	9/7.8	116	53 , 220	6/3.7	163	60 , 356	4/5.8	69	19 , 177	15/22	67	38 , 111
> 0 to < 185.3										7/9.0	78	31 , 161
185.3 to < 739.4	2/2.8	70	9 , 254	3/1.4	211	44 , 618	8/2.1	379	164 , 747	11/7.2	152	76 , 272
739.4 to < 1610.3										8/4.4	180	78 , 355
1610.3+	2/2.1	96	12 , 347	2/1.0	208	25 , 750	3/1.8	168	35 , 491	16/8.7	185	106 , 301

UNCERTAINTY ANALYSES OF BD EXPOSURE AND LEUKEMIA

The uncertainty analyses of 1000 alternative data sets of BD exposure estimates examined the distribution of leukemia RR estimates in each of the four quartiles of BD ppm-years used in the main analyses (> 0 to < 33.7, 33.7 to < 184.7, 184.7 to < 425.0, and > 425.0 ppm-years). As described earlier (Statistical Methods and Data Analysis / Uncertainty Analyses), we obtained the distribution of RRs for a particular quartile of BD ppm-years by allowing the criterion for computing cumulative exposure (percentile of BD exposure estimates specific to the combination of plant and work area/job group) to vary at random within the uncertainty ranges obtained through the exposure estimation procedures.

Leukemia RRs from the lowest quartile of BD ppm-years (quartile 1) ranged from 1.2 to 1.8 (Table 26). In remaining quartiles of BD ppm-years, the ranges of RRs were 1.1 to 2.2 for quartile 2; 1.2 to 3.8 for quartile 3; and 2.4 to 4.3 for quartile 4. The RR median values indicated a positive association between BD ppm-years and leukemia with RRs of 1.0, 1.5, 1.6, 2.6, and 3.3, respectively, for 0 exposure and quartiles 1, 2, 3, and 4.

Among the 1000 data sets used for uncertainty analyses, 473 indicated a regular exposure–response relation between BD ppm-years and leukemia (data not shown), in that the RR from each quartile of BD ppm-years was greater than the RR for the next lower quartile (a monotonic pattern; one in which each value is greater than or equal to the previous one). Among the 473 data sets that indicated exposure–response, the median change in RR between adjacent exposure quartiles was 20% between quartiles 1 and 2, 41% between quartiles 2 and 3, and 35% between quartiles 3 and 4.

Table 23. RRs for Lymphoid and Myeloid Neoplasms and BD ppm-years, Styrene ppm-years, and DMDTC mg/cm–years Shown by Model Type

Exposure	Number of Leukemias	Person-Years	Single-Agent Models[a]		Multiple-Agent Models[b]	
			RR	95% CI	RR	95% CI
Lymphoid Neoplasms[c]						
BD (ppm-years)						
0	24	116,471	1.0		1.0	
> 0 to < 33.7	28	154,443	1.0	0.6 , 1.7	0.9	0.5 , 2.0
33.7 to < 184.7	25	144,109	0.7	0.4 , 1.2	0.7	0.3 , 1.6
184.7 to < 425.0	21	49,410	1.4	0.8 , 2.5	1.3	0.6 , 3.1
425.0+	22	35,741	1.8	1.0 , 3.2	1.5	0.6 , 3.8
Styrene (ppm-years)						
0	17	77,460	1.0		1.0	
> 0 to < 8.3	36	177,551	1.1	0.6 , 2.0	1.1	0.5 , 2.4
8.3 to < 31.8	20	132,311	0.7	0.4 , 1.4	0.7	0.3 , 1.7
31.8 to < 61.1	17	55,797	1.1	0.6 , 2.2	0.8	0.3 , 2.3
61.1+	30	57,056	1.7	0.9 , 3.1	1.0	0.4 , 2.7
DMDTC (mg/cm–years)						
0	44	206,617	1.0		1.0	
> 0 to < 185.3	21	128,688	1.3	0.8 , 2.2	1.3	0.7 , 2.4
185.3 to < 739.4	17	77,743	1.2	0.7 , 2.1	1.3	0.7 , 2.4
739.4 to < 1610.3	16	36,178	1.9	1.0 , 3.3	1.7	0.9 , 3.4
1610.3+	22	50,947	1.4	0.8 , 2.3	1.2	0.6 , 2.3
Myeloid Neoplasms[d]						
BD (ppm-years)[e]						
0	6	116,471	1.0		1.0	
> 0 to < 33.7	13	154,443				
33.7 to < 184.7 1	15	144,109	1.2	0.6 , 2.5	0.8	0.3 , 1.7
184.7 to < 425.0	11	49,410	2.0	1.0 , 4.3	1.6	0.6 , 4.1
425.0+	11	35,741	2.5	1.2 , 5.3	2.4	0.9 , 6.8
Styrene (ppm-years)[e]						
0	5	77,460	1.0		1.0	
> 0 to < 8.3	11	177,551				
8.3 to < 31.8	17	132,311	1.8	0.9 , 3.3	1.8	0.8 , 4.0
31.8 to < 61.1	13	55,797	2.6	1.2 , 5.5	1.8	0.7 , 4.6
61.1+	10	57,056	1.8	0.8 , 3.9	0.6	0.3 , 2.5
DMDTC (mg/cm–years)[e]						
0	12	206,617	1.0		1.0	
> 0 to < 185.3	14	128,688				
185.3 to < 739.4	13	77,743	2.1	1.1 , 4.1	1.9	0.9 , 3.9
739.4 to < 1610.3	7	36,178	1.9	0.8 , 4.4	1.5	0.6 , 3.7
1610.3+	10	50,947	1.5	0.7 , 3.1	0.9	0.4 , 2.1

[a] Single-agent models included indicator variables for age, years since hire, and exposure quartiles.

[b] Multiple-agent models included variables for age, years since hire, and exposure quartiles of each agent in the model.

[c] Lymphoid neoplasms included lymphocytic leukemia and NHL combined (n = 81), Hodgkin lymphoma (n = 12), and multiple myeloma (n = 27).

[d] Myeloid neoplasms included myeloid and monocytic leukemias combined (n = 44), erythroleukemia (n = 1), myelofibrosis and myelodysplasia combined (n = 7), polycythemia vera (n = 2), and myeloproliferative disease (n = 2).

[e] Referent category consists of zero exposure and the first quartile.

Table 24. RRs for Colorectal Cancer and BD ppm-years, Styrene ppm-years, and DMDTC mg/cm–years Shown by Model

Exposure	Number of Colorectal Cancers	Person-Years	Model Number and Agents Included[a] (RR [95% CI]) Model 1: BD Only	Model 2: Styrene Only	Model 3: DMDTC Only	Model 4: BD + Styrene	Model 5: BD + DMDTC	Model 6: Styrene + DMDTC	Model 7: BD + Styrene + DMDTC
BD (ppm-years)									
0	40	116,471	1.0			1.0	1.0		1.0
> 0 to < 33.7	52	154,443	1.1 (0.7 , 1.7)			1.1 (0.6 , 1.9)	1.1 (0.8 , 1.7)		1.0 (0.6 , 1.8)
33.7 to < 184.7	68	144,109	1.2 (0.8 , 1.7)			1.1 (0.6 , 2.0)	1.1 (0.7 , 1.7)		1.1 (0.6 , 1.9)
184.7 to < 425.0	22	49,411	0.9 (0.5 , 1.4)			0.8 (0.4 , 1.7)	0.8 (0.4 , 1.4)		0.7 (0.4 , 1.5)
425.0+	16	35,741	0.8 (0.4 , 1.4)			0.6 (0.3 , 1.4)	0.7 (0.4 , 1.3)		0.6 (0.3 , 1.3)
Styrene (ppm-years)									
0	29	77,460		1.0		1.0		1.0	1.0
> 0 to < 8.3	63	77,551		1.2 (0.8 , 1.8)		1.1 (0.6 , 2.0)		1.2 (0.8 , 2.0)	1.2 (0.6 , 2.2)
8.3 to < 31.84	58	32,311		1.2 (0.8 , 1.9)		1.2 (0.6 , 2.2)		1.3 (0.8 , 2.1)	1.2 (0.6 , 2.4)
31.8 to < 61.1	14	55,797		0.6 (0.3 , 1.0)		0.6 (0.3 , 1.3)		0.6 (0.3 , 1.1)	0.6 (0.3 , 1.4)
61.1+	34	57,056		1.1 (0.7 , 1.9)		1.4 (0.7 , 2.8)		1.2 (0.7 , 2.1)	1.5 (0.7 , 3.2)
DMDTC (mg/cm–years)									
0	95	206,617			1.0		1.0	1.0	1.0
> 0 to < 185.3	27	128,688			0.8 (0.5 , 1.3)		0.8 (0.5 , 1.3)	0.8 (0.5 , 1.3)	0.8 (0.5 , 1.3)
185.3 to < 739.4	27	77,743			1.0 (0.6 , 1.5)		1.0 (0.6 , 1.5)	1.0 (0.6 , 1.6)	1.0 (0.6 , 1.5)
739.4 to < 1610.3	15	36,178			0.8 (0.5 , 1.4)		0.9 (0.5 , 1.7)	0.8 (0.5 , 1.5)	0.9 (0.5 , 1.6)
1610.3+	34	50,947			1.0 (0.7 , 1.5)		1.2 (0.8 , 2.0)	1.0 (0.7 , 1.6)	1.2 (0.7 , 1.9)

[a] Models included indicator variables for age, years since hire, and exposure quartiles of each agent.

Table 25. RRs for Prostate Cancer and BD ppm-years, Styrene ppm-years, and DMDTC mg/cm–years Shown by Model

Exposure	Number of Prostate Cancers	Person-Years	Model Number and Agents Included[a] (RR [95% CI])						
			Model 1: BD Only	Model 2: Styrene Only	Model 3: DMDTC Only	Model 4: BD + Styrene	Model 5: BD + DMDTC	Model 6: Styrene + DMDTC	Model 7: BD + Styrene + DMDTC
BD (ppm-years)									
0	35	44,828	1.0			1.0	1.0		1.0
> 0 to < 33.7	40	52,506	1.1 (0.7 , 1.7)			1.8 (0.9 , 3.5)	1.1 (0.7 , 1.8)		1.7 (0.9 , 3.4)
33.7 to < 184.7	57	65,270	1.1 (0.7 , 1.7)			1.6 (0.8 , 3.1)	1.2 (0.8 , 1.9)		1.6 (0.8 , 3.1)
184.7 to < 425.0	23	27,872	0.9 (0.5 , 1.5)			1.3 (0.6 , 2.7)	1.0 (0.6 , 1.9)		1.4 (0.6 , 3.0)
425.0+	26	21,853	1.1 (0.6 , 1.8)			1.5 (0.7 , 3.3)	1.2 (0.7 , 2.2)		1.7 (0.8 , 3.6)
Styrene (ppm-years)									
0	32	33,399		1.0		1.0		1.0	1.0
> 0 to < 8.3	39	62,670		0.7 (0.4 , 1.1)		0.5 (0.2 , 0.9)		0.7 (0.4 , 1.2)	0.5 (0.2 , 1.0)
8.3 to < 31.84	51	53,910		1.0 (0.6 , 1.6)		0.7 (0.3 , 1.4)		1.1 (0.7 , 1.8)	0.7 (0.4 , 1.5)
31.8 to < 61.1	24	28,626		0.8 (0.5 , 1.3)		0.6 (0.3 , 1.2)		0.9 (0.5 , 1.6)	0.6 (0.3 , 1.3)
61.1+	35	33,722		0.8 (0.5 , 1.3)		0.6 (0.3 , 1.2)		0.9 (0.5 , 1.6)	0.6 (0.3 , 1.3)
DMDTC (mg/cm–years)									
0	94	93,522			1.0		1.0	1.0	1.0
> 0 to < 185.3	19	35,428			0.8 (0.5 , 1.3)		0.8 (0.5 , 1.3)	0.8 (0.5 , 1.4)	0.9 (0.5 , 1.5)
185.3 to < 739.4	22	31,674			1.0 (0.6 , 1.6)		1.0 (0.6 , 1.6)	1.0 (0.6 , 1.7)	1.0 (0.6 , 1.7)
739.4 to < 1610.3	13	18,832			0.8 (0.4 , 1.4)		0.7 (0.4 , 1.4)	0.8 (0.4 , 1.5)	0.8 (0.4 , 1.5)
1610.3+	33	32,872			0.9 (0.6 , 1.3)		0.8 (0.5 , 1.3)	0.8 (0.5 , 1.3)	0.8 (0.5 , 1.4)

[a] Models included indicator variables for age, years since hire, race, and exposure quartiles of each agent. All models were restricted to ages 50 years and older (total person-years = 212,327).

Of the 1000 data sets, in quartile 1 of BD ppm-years, 25% of the RRs had a value of 1.4, the same value as in the main analysis (Figure 1 and Table 27); 8% of the RRs were less than 1.4, and 67% of the RRs were greater than 1.4. In quartile 2, only 1% of the RRs had the same value as in the main analysis (RR = 1.2); almost all (99%) of the RRs were greater than 1.2, whereas less than 1% had a value lower than 1.2. This pattern suggests that we underestimated the RR for quartile 2 of BD ppm-years in the main analysis. In both quartiles 3 and 4, the majority of RRs were less than the corresponding RR from the main analysis, which indicates that we may have overestimated the RRs for these quartiles of BD ppm-years.

In 166 (31%) of the 527 data sets that did not display a monotonic exposure–response pattern, the lack of monotonicity was due to the fact that two or more adjacent exposure quartiles had the same RR (Table 28). In 79 data sets, the RR from exposure quartile 4 was less than the RR from quartile 3. In 44 data sets, the RR from quartile 3 was less than the RR from quartile 2. In 199 data sets, the RR from quartile 2 was less than the RR from quartile 1. In 38 data sets, the RR from quartile 4 was less than the RR from quartile 3, and the RR from quartile 2 was less than the RR from quartile 1.

Figure 1 can be interpreted as a probability distribution that describes our uncertainty in RR point estimates due to uncertainty in exposure estimation. Given our assumptions in the uncertainty analyses about the exposure estimation parameters and given our analysis assumptions, the point estimate of the RR for quartile 1 of BD ppm-years is most likely to be about 1.5; it is unlikely to be less than 1.2 or greater than 1.9. The RR for quartile 2 is most likely to be about 1.5 to 1.8; it is unlikely to be less than 1.1 or greater than 2.0. The RR for quartile 3 is most likely to be about 2.1 to 3.0; it is unlikely to be less than 1.5 or greater than 3.4. The RR for quartile 4 is likely to be about 2.9 to 3.7; it is unlikely to be less than 2.5 or greater than 4.2.

Table 26. Leukemia and BD ppm-years: Summary of RRs from Uncertainty Analyses of 1000 Alternative Data Sets of Exposure Estimates

	RR			
BD Exposure (ppm-years)[a]	Minimum	Maximum	Mean	Median
0	1.0	1.0	1.0	1.0
> 0 to < 33.7	1.2	1.8	1.5	1.5
33.7 to < 184.7	1.1	2.2	1.6	1.6
184.7 to < 425.0	1.2	3.8	2.6	2.6
425.0+	2.4	4.3	3.3	3.3

[a] The uncertainty analyses used the same quartiles of BD exposure were used in the main analyses.

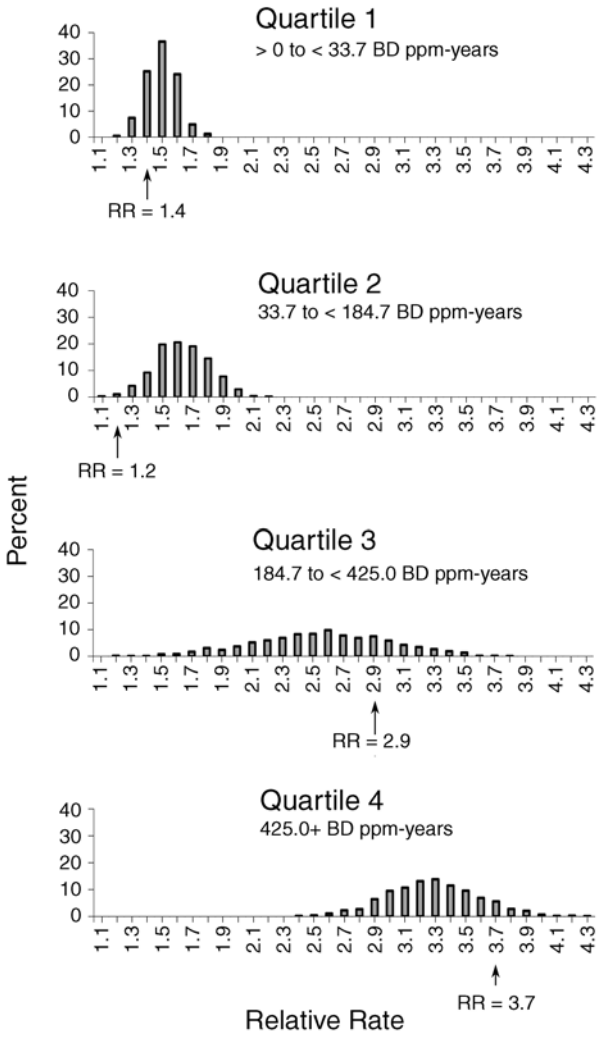

Figure 1. Distribution of leukemia RRs from the Poisson regression models applied to the 1000 datasets used in uncertainty analyses (shown by quartile of cumulative BD exposure). The specific RR (with vertical arrow) in each panel is from the main analysis.

Table 27. Leukemia and BD ppm-years: Distribution of RRs from Uncertainty Analyses (Poisson Regression Models) of 1000 Alternative Data Sets of Exposure Estimates[a]

RR	Observations	% of 1000
BD (ppm-years) > 0 to < 33.7		
1.2	5	0.5
1.3	74	7.4
1.4[b]	252	25.2
1.5	366	36.6
1.6	241	24.1
1.7	49	4.9
1.8	13	1.3
BD (ppm-years) 33.7 to <184.7		
1.1	3	0.3
1.2[b]	11	1.1
1.3	42	4.2
1.4	92	9.2
1.5	198	19.8
1.6	206	20.6
1.7	191	19.1
1.8	145	14.5
1.9	77	7.7
2.0	29	2.9
2.1	4	0.4
2.2	2	0.2
BD (ppm-years) 184.7 to <425.0		
1.2	2	0.2
1.3	1	0.1
1.4	1	0.1
1.5	8	0.8
1.6	9	0.9
1.7	17	1.7
1.8	31	3.1
1.9	24	2.4
2.0	37	3.7
2.1	52	5.2
2.2	60	6.0
2.3	69	6.9
2.4	83	8.3
2.5	84	8.4
2.6	98	9.8

Table continues next column

Table 27 (*continued*). Leukemia and BD: Distribution of RRs from Uncertainty Analyses (Poisson Regressioin Models) of 1000 Alternative Data Sets of Exposure Estimates[a]

RR	Observations	% of 1000
BD (ppm-years) 184.7 to <425.0 (*continued*)		
2.7	78	7.8
2.8	69	6.9
2.9[b]	75	7.5
3.0	59	5.9
3.1	43	4.3
3.2	35	3.5
3.3	27	2.7
3.4	19	1.9
3.5	14	1.4
3.6	2	0.2
3.7	2	0.2
3.8	1	0.1
BD (ppm-years) 425.0+		
2.4	2	0.2
2.5	4	0.4
2.6	11	1.1
2.7	23	2.3
2.8	27	2.7
2.9	64	6.4
3.0	95	9.5
3.1	107	10.7
3.2	131	13.1
3.3	138	13.8
3.4	115	11.5
3.5	96	9.6
3.6	69	6.9
3.7[b]	56	5.6
3.8	28	2.8
3.9	21	2.1
4.0	7	0.7
4.1	2	0.2
4.2	3	0.3
4.3	1	0.1

[a] The uncertainty analyses used the same quartiles of cumulative exposure to BD as were used in the main analyses. The model for each Poisson regression included BD ppm-years, age, and years since hire.

[b] Quartile-specific RR from main analysis.

Table 28. Data Sets That Displayed a Nonmonotonic Dose–Response Pattern Shown by Type of Pattern

Nonmonotonic Pattern[a]	n
$RR_2 = RR_1$	116
$RR_3 = RR_2$	19
$RR_3 = RR_2 = RR_1$	1
$RR_4 = RR_3$	20
$RR_4 = RR_3$ and $RR_2 = RR_1$	10
$RR_4 < RR_3$	59
$RR_4 < RR_3$ and $RR_2 = RR_1$	20
$RR_3 < RR_2$	43
$RR_3 < RR_2 = RR_1$	1
$RR_2 < RR_1$	182
$RR_4 = RR_3$ and $RR_2 < RR_1$	17
$RR_4 < RR_3$ and $RR_2 < RR_1$	38
$RR_3 < RR_2 < RR_1$	1

[a] Only the 527 data sets that did not display monotonicity were used for this analysis. Subscripted numbers indicate the quartiles of cumulative BD exposure in ppm-years used for the main analyses: Quartile 1 is > 0 to 33.7; quartile 2 is 33.7 to < 184.7; quartile 3 is 184.7 to < 425.0; and quartile 4 is 425.0+.

DISCUSSION AND CONCLUSIONS

The research described in this report extended the study of a large group of synthetic rubber industry employees by 7 years and included extensive analyses of mortality patterns. This study increased the information available from our previous study by 83,401 (18% increase) person-years of follow-up, 1,578 (34%) total deaths, 492 (44%) total cancer deaths, 20 (39%) leukemia deaths, 20 (61%) NHL deaths, and 6 (30%) multiple myeloma deaths. The current study carried out several analyses that had not been done previously: an evaluation of mortality from specific forms of leukemia; and an assessment of uncertainty (which stems from possible errors in exposure estimates) pertaining to the relation between BD and leukemia.

The subjects had an overall mortality rate 14% lower than expected on the basis of state or provincial general population rates, and their mortality rate from all cancers combined was 8% lower than expected. Subjects' rates of death from circulatory, nonmalignant respiratory, digestive, and genitourinary diseases and from external causes (ie, accidents, homicides, and suicides) also were lower than expected. These deficits tended to diminish as years since hire increased. This suggests that any confounding effect due to hiring relatively healthy people into the industry gradually disappeared. Although mortality rates from some causes were lower than expected, this group of workers overall and in certain subgroups had more than expected deaths from several forms of cancer, including leukemia, NHL, multiple myeloma, and cancers of the colorectum and prostate.

LEUKEMIA

The total group of 17,924 subjects had 16% more than expected deaths from leukemia. Despite the fact that this increase was small and was not limited to a single form of leukemia, several other results suggest a causal relation between employment in the synthetic rubber industry and leukemia.

The overall increase in leukemia was concentrated in long-term hourly workers, and particularly in men who had worked in SBR-related polymerization, coagulation, maintenance labor, and laboratory jobs. In each of these work groups, the possibility for exposure to agents of interest was relatively high. It is reasonable to assume that ever-hourly workers, because of their more direct participation in plant operations, had a higher possibility for exposure to chemicals in the workplace than did never-hourly workers. Polymerization and laboratory jobs entailed regular exposure to BD and styrene monomers and some exposure to DMDTC. Coagulation workers could have been exposed to all three agents, particularly when monomer stripping and recovery operations were inefficient. Maintenance laborers also could have had high exposure during reactor vessel and other cleaning operations. In contrast, ever-hourly workers in finishing, skilled maintenance, and other plant areas such as warehouses, utilities, and offices had less possibility for regular exposure to BD, although some field maintenance operations may have entailed high exposure to monomers.

Reinforcing the results by work area, analyses of cumulative exposure to BD, styrene, and DMDTC indicated that leukemia was positively associated with these agents. All indices of exposure to BD were positively associated with leukemia, and evidence of exposure–response persisted for some BD exposure indices after controlling for possible confounding by the other two agents. The relation between BD and leukemia appeared to be somewhat stronger for exposure to BD concentrations above 100 ppm than for exposure to lower concentrations. The results of uncertainty analyses supported the presence of a positive relation between BD ppm-years and leukemia.

The magnitude of the leukemia RRs tended to be greater for DMDTC than for BD or styrene. The association between DMDTC and leukemia was still present after adjusting for BD and styrene, but we found no evidence of exposure–response for DMDTC in any analysis. The positive

association between styrene ppm-years and leukemia also did not display a regular exposure–response pattern and was weak after adjusting for BD. However, BD, styrene, and DMDTC exposures were correlated, and it was difficult to separate the effect of one agent from the effects of the other two agents. Our results, taken alone, do not rule out an independent causal role for DMDTC or styrene because for both of these agents we observed an RR of about 1.5 for moderate exposure in the group with low exposure to BD.

Data on specific forms of leukemia were difficult to interpret because of imprecision due to small numbers of subjects and because of diagnostic uncertainty that persisted despite efforts to review medical records. Deaths from CLL were higher in all work areas (polymerization, coagulation, maintenance labor, and laboratories) that had possibly high exposure to BD, styrene, and DMDTC. This form of leukemia was positively associated most consistently, but weakly, with BD; we found no clear evidence of an association with styrene or DMDTC after controlling for the effects of BD.

Mortality from chronic myelogenous leukemia was substantially elevated only for laboratory workers; analyses for workers in other areas were based on very small numbers of subjects. Chronic myelogenous leukemia was more strongly and consistently associated with exposure to BD than were other forms of leukemia; and chronic myelogenous leukemia was, for the most part, unrelated to styrene or DMDTC in analyses that controlled for BD.

Analyses of mortality from acute myelogenous leukemia by work area were imprecise because of small numbers of decedents. This form of leukemia did not appear to be associated consistently with BD, styrene, or DMDTC. However, little confidence can be placed on results for acute myelogenous leukemia because, of the 10 decedents with incomplete information on the specific form of leukemia, 7 could have been acute myelogenous leukemia: 4 of the 10 were acute but unspecified as lymphocytic or myelogenous, and 3 were myelogenous but unspecified as acute or chronic.

Assuming that exposures in the synthetic rubber industry cause leukemia, it is of interest that patterns of increased leukemia mortality categorized by years since hire and years worked varied to some extent according to the specific form of leukemia. Chronic myelogenous leukemia and CLL accounted largely for the overall increase in leukemia mortality in the subgroup with 20 to 29 years since hire and 10 or more years worked. Acute myelogenous leukemia and other leukemias were also higher in this subgroup, but the latter results were based on small numbers of decedents. Mortality from CLL, but not from chronic myelogenous leukemia, was elevated both in the subgroup with 20 to 29 years since hire and 10 or more years worked and in subgroups with 30 or more years since hire, a pattern that may reflect the fact that survival is longer for CLL than for acute or chronic myelogenous leukemias. If exposures in the synthetic rubber industry cause CLL and chronic myelogenous leukemia, the induction period appears to be 20 or more years. An increased mortality rate for acute myelogenous leukemia occurred in the relatively short-term employees with less than 20 years since hire. This increase could be due to chance or to confounding. It is also possible that the acute myelogenous leukemia has a shorter induction time than CLL or chronic myelogenous leukemia.

Our results for BD and leukemia were reasonably consistent with those reported by Santos-Burgoa and colleagues (1992), by Matanoski and associates (1997), and in our earlier publications (Delzell et al 1996, 2001; Macaluso et al 1996). The increases in leukemia that we observed in the overall subject group (16%) and in the subgroup of ever-hourly workers (23%) were similar to the leukemia SMR of 129 found in a recent study of BD monomer production workers (Divine and Hartman 2001). That investigation reported patterns of leukemia mortality by years worked and job category that suggested that the small increase was not due to occupational exposure. However, direct estimates of BD exposure were not available for analysis.

Studies of reinforced-plastics workers, who were exposed to styrene concentrations much higher than levels typically found in the synthetic rubber industry and who were not exposed to BD, have not reported any consistent relation with leukemia (Nicholson et al 1978; Hodgson and Jones 1985; Bond et al 1992; Kogevinas et al 1993, 1994; Coggon 1994; Kolstad et al 1994, 1995). Matanoski and coworkers (1997) did not find that styrene was associated with leukemia in their analyses.

Our results for DMDTC and leukemia were inconclusive. Differential exposure misclassification might have produced a spuriously positive overall association between DMDTC and leukemia. Exposure estimation procedures for DMDTC were developed after considerable information was available on the pattern of leukemia mortality by work area and by BD and styrene exposure levels among the subjects in our study, whereas the basic BD and styrene exposure estimation methods were developed before these results were known. On the other hand, the absence of a consistent exposure–response trend for DMDTC could have been due to nondifferential misclassification of person-years and leukemias by level of DMDTC or to confounding by other agents; both of these problems could dampen a true exposure–response relation. It also is possible that the absence of a consistent trend was due to a

nonlinear exposure–response relation between DMDTC and leukemia or to lack of a biologically meaningful range of DMDTC exposures among the subjects classified as exposed in our study. Available biological information is not adequate to determine if DMDTC is a human carcinogen. No other epidemiologic study has investigated the relation between this chemical and leukemia, NHL, or multiple myeloma. However, because DMDTC is an immune system depressant, it is plausible that it could increase the risk of NHL and some leukemias (Melbye and Trichopoulos 2002).

Our present results are consistent with a causal relation between BD and leukemia. However, the data do not preclude an etiologic role for styrene or DMDTC. Furthermore, the mechanism by which BD could cause leukemia in humans is not understood, and research on exposure to BD and biomarkers of genotoxicity in humans has not yielded consistently positive results (Albertini et al 2003). Thus, the currently available scientific evidence may not be sufficient to conclude that BD causes leukemia in humans.

NHL, MULTIPLE MYELOMA, AND HODGKIN LYMPHOMA

In our study, NHL was associated with styrene and DMDTC, but RRs for this disease did not display a consistent exposure–response relation with either agent. The rather uniformly elevated RRs among subjects exposed to styrene or DMDTC in part reflected a much lower mortality rate for NHL among unexposed subjects compared with external referent populations. For CLL–NHL, results were similar to those for NHL.

Matanoski and coworkers (1997), in an investigation that included many of the same subjects as in our study, also reported a positive association between styrene and NHL. However, their findings and those from the present study are inconsistent with other research. Notably, studies of occupational groups exposed to concentrations of styrene higher than those found in the synthetic rubber industry have not reported any consistent increase in NHL deaths or incident cases (Nicholson et al 1978; Hodgson and Jones 1985; Bond et al 1992; Kogevinas et al 1993, 1994; Coggon 1994; Kolstad et al 1994, 1995; Matanoski et al 1997).

Internal analyses from our study suggested a positive relation between the highest level of BD ppm-years and multiple myeloma. However, SMR analyses indicated that the increased death rate from this cancer (5/3.2 deaths) in the high BD exposure group was not meaningful, and we found no evidence of exposure–response. Our analyses by work area/job group provided little internal support for a causal relation between BD exposure or synthetic rubber industry employment and multiple myeloma.

Matanoski and associates (1997) reported that multiple myeloma was associated with BD in a study that included many of the subjects in our study. Divine and Hartman (2001) found slightly more than expected deaths from multiple myeloma among BD production workers, but as with that study's results for leukemia, the data on multiple myeloma were too sparse and too internally inconsistent to provide any substantial support for a causal interpretation. Data on styrene and DMDTC from the present study were consistent with the absence of any association with multiple myeloma.

Our study included only 13 subjects with Hodgkin lymphoma. This number was too small for detailed analyses of associations with cumulative exposure to agents, but median values of various agent exposure indices suggested that Hodgkin lymphoma decedents had relatively low exposure.

COLORECTAL CANCER AND PROSTATE CANCER

Some subgroups of synthetic rubber industry workers had more that expected deaths from colorectal and prostate cancers. Colorectal cancer was not associated with any of the three agents of interest. Prostate cancer was positively associated with BD in some analyses, but we found no evidence of a consistent exposure–response trend. Chance or uncontrolled confounding by nonoccupational risk factors for these two cancers could be responsible for the patterns that we observed.

STRENGTHS AND LIMITATIONS

The subjects included in our study constituted a large group with many years of follow-up, and we were able to obtain reasonably complete vital status information. The current study added considerably to the amount of information available for assessing mortality patterns and used expanded and refined exposure estimates compared with those used in our previous study of this worker group.

Problems with historical exposure estimation may have affected the measurement of all associations between the agents and diseases studied. Work histories sometimes did not fully specify subjects' work areas; our exposure estimation procedures were based on models that required many assumptions; and the resulting estimates lacked comprehensive validation. Errors in exposure measurement could have distorted exposure–response relations and could have led to residual confounding in analyses that estimated the effect of one agent by adjusting for the effects of other agents. The uncertainty analysis was designed to provide insight into the impact of these limitations but was carried out only for BD ppm-years and leukemia.

For some LHC decedents, confirming the diagnoses via medical records was not possible, and this was another limitation. We obtained medical records for many of these decedents and used the records to determine diagnoses for internal analyses. However, our analyses of specific forms of leukemia, and particularly of acute leukemias, could still have been distorted by disease misclassification. These analyses also were hampered by small numbers of subjects.

Our combination of CLL with NHL in some analyses was unconventional and was done because CLL is considered to be the same disease as small lymphocytic lymphoma, a rare form of NHL (Harris et al 1999). The NHLs in our study, whether or not they are combined with the CLLs, probably represent a pathologically, clinically, and etiologically heterogeneous set of diseases, and any true association of BD, styrene, or DMDTC with a small subset of these diseases could have been obscured. This limitation also applies to our analysis of lymphoid and myeloid neoplasms.

We did not have information on possible nonoccupational confounders or on chemicals other than BD, styrene, and DMDTC used in the synthetic rubber industry. The associations that we observed could, thus, have been due to confounding by unidentified and unmeasured factors. As noted previously, the high correlation among the agents of interest was another limitation of the study that made identification of independent associations difficult.

Our results are limited in their possible use for quantitative risk assessments. This stems from (1) our use of categorical, rather than continuous, exposure variables that included at most five exposure categories (0 exposure and 4 quartiles) in the Poisson regression analyses; (2) imprecision in the data for specific forms of leukemia; and (3) the likelihood of exposure misclassification. Moreover, the results may not be strong enough to warrant a causal interpretation of any of the observed associations between the agents of interest and leukemia or other LHCs.

CONCLUSIONS

The study found that some subgroups of synthetic rubber industry workers had an increased mortality rate from leukemia that probably was due to workplace exposure. Uncertainty remains about the specific agent or agents responsible for the increase. BD was most consistently associated with all leukemias combined and with chronic myelogenous leukemia. Styrene was not clearly associated with all leukemias combined or with specific forms of leukemia after controlling for BD, DMDTC, or both. DMDTC was associated with all leukemias combined and with most specific forms of leukemia, but without evidence of exposure–response. Styrene and DMDTC, but not BD, were associated with NHL and with CLL–NHL, but these associations did not display consistent exposure–response trends and were due in part to lower than expected numbers of deaths among unexposed subjects in comparison with external referent populations. There were no internally or externally consistent and persuasive results indicating that exposure to BD, styrene, or DMDTC causes multiple myeloma. Some subgroups of synthetic rubber industry workers had more than expected deaths from colorectal cancer and prostate cancer; however, these increases did not appear to be related to occupational exposure in the industry.

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APPENDIX A. Illustration of Exposure Estimation

INTRODUCTION

To illustrate how we estimated exposure, we have selected one subject's work history with all of its combinations of work area/job group and calendar year and all of the corresponding BD estimates used in our main analyses. We then selected one combination of work area/job group and calendar year from the subject's work history; for that one combination, we describe below how we (1) derived BD estimates for one of the tasks that comprise that work area/job group in that calendar year, and (2) calculated the BD estimates for the selected combination using data from all the component tasks within that year. Finally, we summarize below how we derived the subject's cumulative BD exposure estimates for one of the uncertainty analysis data sets.

OVERVIEW OF ONE SUBJECT'S WORK HISTORY AND BD CUMULATIVE EXPOSURE ESTIMATES

The subject we selected worked at plant 4 for 28 years. His work history consisted of 38 segments, each generated at the end of a calendar year or at the point when the subject had a change in job title during a calendar year (Table A.1). A change in job title did not necessarily correspond to a change in work area/job group. Each segment of the work history included data on the start and end dates of the segment, the work area/job group, the number of days in the segment, the estimated 8-hour TWA BD exposure concentration (in ppm), and the estimated cumulative BD exposure (in ppm-years) as of the end of that segment. The BD exposure estimates displayed in Table A.1 came from the JEM used in the main analysis. That is, each estimate corresponds to the mean of the approximate probability distribution of BD concentration estimates for the combination of plant, work area/job group, and calendar year. The subject's cumulative BD exposure was 1144 ppm-years.

DERIVATION OF BD EXPOSURE ESTIMATE FOR ONE OF THE TASKS THAT COMPRISE ONE WORK AREA/JOB GROUP

Work area/job group 817, in which the subject worked longest (1948 through 1971), is recovery in SBR polymerization. It includes compressor house and high solids recovery operations; it consists of five tasks that entail exposure to BD (Table A.2). We selected task 305 (minor maintenance of recovery compressor house) to illustrate how we estimated task-specific BD exposure concentrations.

Sidebar 1 describes task 305, its exposure scenario, and the parameters used to calculate the distribution of BD

SIDEBAR 1. DESCRIPTION OF TASK 305, AN EXPOSURE SCENARIO, AND THE PARAMETERS USED TO ESTIMATE BD EXPOSURE

Inspection and maintenance of the recovery compressors involves inspecting the area for compressor leaks and preparing the compressor for repair by a mechanic or pipefitter.

Exposure is a function of the compressor leak rate. The leak rate for compressors was determined to be 20-30 lbs per day. The compressors leaked liquid that was approximately 90% butadiene.

The average wind speed values (lower and upper limit) for this task across all plants was used. We assumed that, during the inspection, the operator maintained an average distance of 1 m from any one of the four compressor seals. The lower and upper limits (LL and UL) were calculated based on the theory that the probability that the operator stood directly in the plume was 0.125 (LL) to 0.25 (UL) of standing directly in the plume.

Exposure Scenario

Point source emission of butadiene. During the time period 1943–1983, compressors leaked a water/butadiene mixture at a rate of 20-30 lbs/day; 90% of this mixture was butadiene; thus 18-27 lbs of butadiene were lost from each seal per compressor per day.

Parameters

BD Emission Rate (Q)

LL = 18 lb/day × 454 g/lb × 1 day/24 hr × 1 hr/3600 sec
= 0.09458 g/sec

UL = 27 lb/day × 454 g/lb × 1 day/24 hr × 1 hr/3600 sec
= 0.141875 g/sec

Duration of Task (minutes)

LL = 10
UL = 20

Duration of Exposure (minutes)

LL = 10
UL = 20

Frequency of Task = 4 times/shift

Distance of the Operator = 1 m

Wind Speed (m/sec)

LL = 1.44
UL = 0.42

(The UL is lower than LL because a lower wind speed results in a higher exposure.)

Probability of Operator Standing Directly in the Plume

LL = 0.125
UL = 0.25

Table A.1. Work History of One Subject from Plant 4 with BD Exposure Concentrations and ppm-years Used in the Main Analyses and in Dataset 70 of Uncertainty Analyses

				Main Analyses		Uncertainty Analyses	
Work Area/Job Group[a]	Start Date	End Date	Elapsed Days	BD 8-Hour TWA (ppm)	Cumulative BD (ppm-years)	BD 8-Hour TWA (ppm)	Cumulative BD (ppm-years)
812	08/27/1943	09/24/1943	28	36.0066	2.76	18.5570	1.42
812	09/24/1943	12/31/1943	98	36.0066	12.42	18.5570	6.40
812	12/31/1943	01/23/1944	23	36.2725	14.71	18.5622	7.57
812	01/23/1944	10/01/1944	252	36.2725	39.73	18.5622	20.38
817	10/01/1944	12/31/1944	91	43.1242	50.48	25.3114	26.68
816	12/31/1944	12/12/1945	346	42.9674	91.18	16.4205	42.24
816	12/12/1945	12/31/1945	19	42.9674	93.41	16.4205	43.09
816	12/31/1945	01/06/1946	6	42.5815	94.11	16.4347	43.36
816	01/06/1946	12/31/1946	359	42.5815	135.97	16.4347	59.52
816	12/31/1946	12/31/1947	365	42.7788	178.72	16.4499	75.96
816	12/31/1947	10/31/1948	305	37.3081	209.87	16.6307	89.84
817	10/31/1948	12/31/1948	61	43.1242	217.07	25.3126	94.07
817	12/31/1948	12/31/1949	365	43.1242	260.17	25.3045	119.36
817	12/31/1949	10/22/1950	295	43.1242	295.00	25.3120	139.80
817	10/22/1950	12/31/1950	70	43.1242	303.26	25.3120	144.65
817	12/31/1950	12/31/1951	365	43.1242	346.36	25.3614	169.20
817	12/31/1951	12/31/1952	366	43.1242	389.57	25.3120	195.36
817	12/31/1952	12/31/1953	365	43.1242	432.66	25.3366	220.68
817	12/31/1953	12/31/1954	365	43.1242	475.76	25.3100	245.97
817	12/31/1954	12/31/1955	365	43.1242	518.85	25.3139	271.27
817	12/31/1955	12/31/1956	366	43.1242	562.06	25.3084	296.63
817	12/31/1956	12/31/1957	365	43.1242	605.16	25.3092	321.92
817	12/31/1957	12/31/1958	365	43.1242	648.25	25.3137	347.22
817	12/31/1958	12/31/1959	365	43.1242	691.35	25.3126	372.51
817	12/31/1959	12/31/1960	366	40.4189	731.85	23.7432	396.30
817	12/31/1960	12/31/1961	365	40.4189	772.24	23.7102	415.00
817	12/31/1961	12/31/1962	365	40.4189	812.63	23.7005	443.68
817	12/31/1962	03/14/1963	74	40.4189	820.82	23.6767	448.41
817	04/30/1963	12/31/1963	245	40.4189	847.93	23.6767	464.30
817	12/31/1963	12/31/1964	366	40.4189	888.44	23.7113	488.06
817	12/31/1964	12/31/1965	365	40.4189	928.83	23.6885	511.73
817	12/31/1965	12/31/1966	365	40.4189	969.22	23.6767	535.39
817	12/31/1966	12/31/1967	365	40.4189	1009.61	23.6888	559.06
817	12/31/1967	12/31/1968	366	40.4189	1050.11	23.6718	582.78
817	12/31/1968	10/31/1969	304	40.4189	1083.75	23.7432	602.54
817	10/31/1969	12/31/1969	61	40.4189	1090.50	23.7432	606.51
817	12/31/1969	12/31/1970	365	40.4189	1130.89	23.6718	630.16
817	12/31/1970	04/29/1971	120	40.4189	1144.17	23.7115	637.89

[a] Work area/job group 812 = polymerization operative, unspecified; 816 = polymerization reactor recovery; 817 = recovery in SBR polymerization.

concentration estimates for the task during the time period 1943 through 1983. No BD exposure occurred in task 305 after 1983 at plant 4.

Table A.2. Component Tasks That Entailed BD Exposure in Work Area/Job Group 817 at Plant 4[a]

Task Number	Task Name
301	Recovery area background
303	Water draw-off from vacuum pumps
305	Minor maintenance of recovery compressor house
312	Drain water from butadiene decanter (recycle tanks)
315	Minor maintenance of butadiene pumps

[a] Work area/job group 817 = recovery in SBR polymerization, which includes compressor house and high solids recovery operations.

BD exposure for task 305 occurred if an operator stood in the plume generated by leaking compressors (exposure scenario, point source of emissions). The probability of nonzero exposure for an operator in task 305 (ie, the probability that an operator stood in the emission plume) ranged from 0.125 to 0.25. Because the maximum probability of exposure was low, many of the exposure estimates in the probability distribution had a value of zero (Figure A.1). The task had seven exposure parameters relevant to calculating estimates under nonzero exposure conditions. Six of these could vary in value. For the distance of the operator from the emission source, we assumed an average of 1 m. For frequency of the task, we assumed that the lower limit, the upper limit, and the actual number were all four times per shift. We used the point source emissions exposure scenario and the parameter estimates listed in Sidebar 1 to estimate the distribution of nonzero values of the BD partial TWA for task 305, as shown in Sidebar 2, and obtained a lower limit of 18.1886 ppm and an upper limit of 187.0889 ppm. The full data set of estimates consisted of 3000 observations. From the complete approximate probability distribution, we

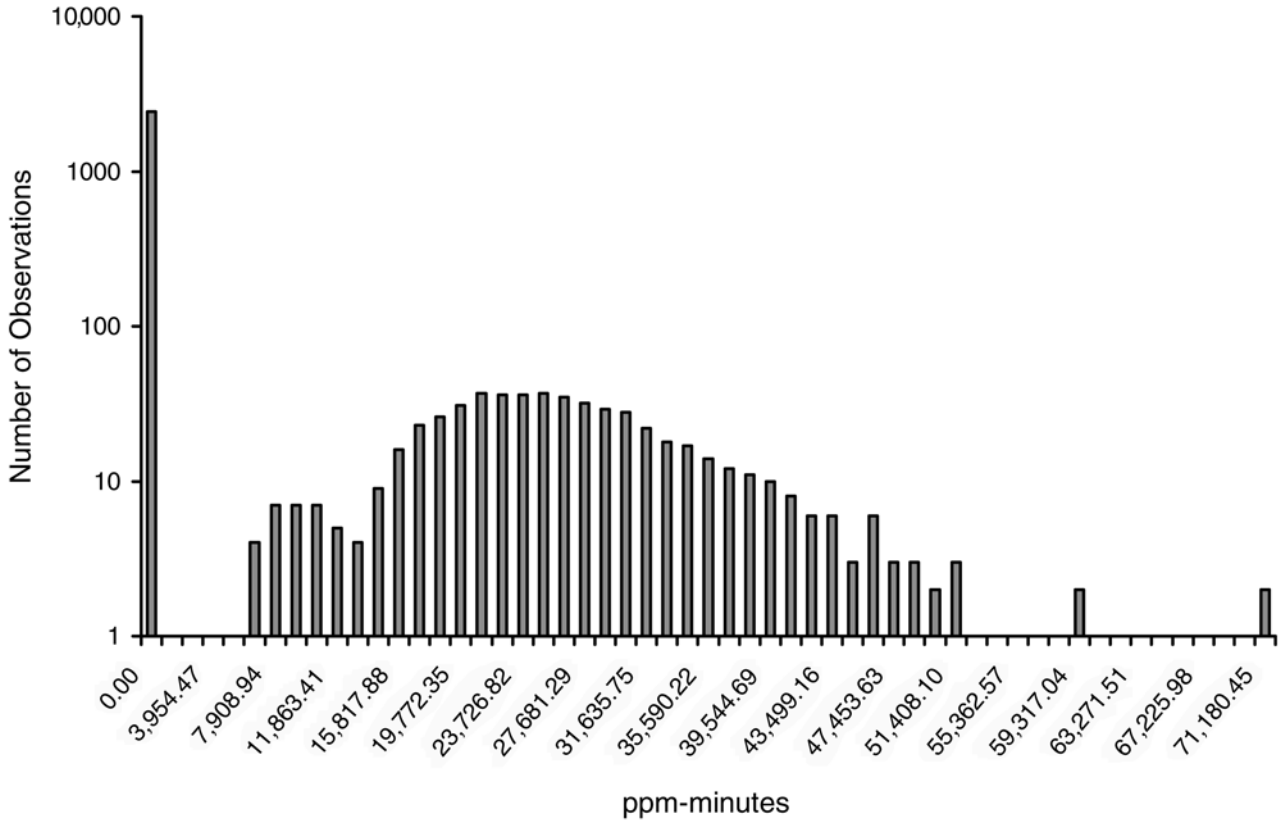

Figure A.1. Distribution of BD ppm-minutes for task 305 at plant 4, 1943–1983.

SIDEBAR 2. EXPOSURE ESTIMATION MODEL AND CALCULATION OF LOWER AND UPPER LIMITS OF NONZERO BD PARTIAL TWA FOR TASK 305

The concentration of exposure that originates from a point source was calculated using a near-field air dispersion model that estimates a worker's exposure to gases and vapors that leak from pumps and valves:

$$E_{ppm} = 1000 \times 24.45 \times Q/(MW \times 0.136 \times D^{1.84} \times u),$$

where E_{ppm} is the estimated air concentration of BD (in ppm) in the plume that originates from the emission source; Q is the BD emission rate (LL = 0.09458; UL = 0.141875 g/sec); MW is the molecular weight of BD (54.1); D is the distance of the operator from the emission source (1 m); and u is the air speed across the dispersion field (LL = 1.44, UL = 0.42 m/sec). The constants in the denominator of the model are dispersion coefficients from the Gaussian model for predicting downwind concentrations due to dispersion of a gas or vapor.

Information from interviews indicated that duration of task 305 ranged from 10 minutes to 20 minutes, with an exposure frequency of four times per shift. The partial 8-hour TWA was calculated as the point source exposure (E_{ppm}) multiplied by the duration and frequency of the task and then divided by 480 (the number of minutes in an 8-hour shift).

The probability of an operator standing directly in the plume and having an exposure greater than zero ranged from 0.125 to 0.25. If the operator was not directly in the plume, exposure would have been equal to zero. Therefore, the majority of exposure estimates for task 305 had a value of zero (see Figure A.1).

Calculation of Nonzero Exposure Values

Lower Levels

Point source exposure if operator was in the emission plume:

$$E_{ppm} = (1000 \times 24.45 \times 0.09458) / (54.1 \times 0.136 \times 1^{1.84} \times 1.44)$$
$$= 218.2627$$

Partial TWA (ppm) if operator was in the emission plume for task 305:

$$= [E_{ppm}\ (LL) \times \text{duration (LL)} \times \text{frequency (LL)}] / 480$$
$$= (218.2627 \times 10 \times 4) / 480$$
$$= 18.1886$$

Upper Levels

Point source exposure if operator was in the emission plume:

$$E_{ppm} = (1000 \times 24.45 \times 0.141875) / (54.1 \times 0.136 \times 1^{1.84} \times 0.42)$$
$$= 1122.5334$$

Partial TWA (ppm) if operator was in the emission plume for task 305:

$$= [E_{ppm}\ (UL) \times \text{duration (UL)} \times \text{frequency (UL)}] / 480$$
$$= (1122.5334 \times 20 \times 4) / 480$$
$$= 187.0889$$

selected 99 percentile values of the BD exposure concentration estimates for task 305 at plant 4 during the period 1943 through 1983 (Sidebar 3). The first 80 percentiles had a BD exposure concentration of 0 because of the high probability of zero exposure in task 305.

DERIVATION OF BD EXPOSURE ESTIMATES FOR WORK AREA/JOB GROUP 817 FROM COMPONENT TASKS

We combined the approximate probability distributions of the five component tasks (shown in Table A.2) to obtain the final approximate probability distribution of the 8-hour TWA exposure concentration for work area/job group 817 (Sidebar 4). To do this, we (1) selected 100 points from each of the approximate probability distributions of exposure concentration for the first two component tasks (tasks 301 and 303), each point corresponding to the midpoint of the range of ppm-minutes of exposures that comprised each percentile; (2) created a new distribution of every possible combination of these exposure concentrations (100 × 100 = 10,000 possible combinations); (3) computed the sum of ppm-minutes of exposure for each combination; and (4) sorted the 10,000 resulting sums from the lowest to the highest. From that distribution we selected 100 new points of the approximate probability distribution of ppm-minutes of exposure attributable to the first two component tasks. We then combined those values with 100 selected points of the approximate probability distribution of the third component task, created a distribution of all possible combinations of exposure concentrations, and selected 100 new percentile points of the exposure concentration attributed to the first three tasks. We repeated this process for each of the remaining two component tasks of work area/job group 817. At its completion, this procedure yielded a data set with 10,000 observations corresponding to the approximate probability distribution of the cumulative exposure (ppm-minutes) of BD for work area/job group 817 during a specified calendar year. The arithmetic mean of this distribution, divided by 480 minutes in a work shift, is the BD

SIDEBAR 3. DISTRIBUTION OF BD PPM-MINUTES FOR TASK 305 AT PLANT 4 FOR 1943–1983

We computed an approximate probability distribution of the BD exposure concentration for task 305 by assuming that each parameter in the exposure model followed a triangular distribution with a mode at the midpoint between the LLs and ULs. To do this, we identified the 1st, 2nd, ..., 99th percentile of this distribution and computed the exposure concentration for all possible combinations of parameter quantiles (ie, for the approximate joint distribution of the exposure parameters). We evaluated the resulting empirical distribution of exposure estimates to find the approximate 1st, 2nd, ..., 99th percentile of the specific exposure concentration estimate for each task and time period.

Results

Percentile of Probability Distribution	BD Exposure (ppm-minutes)
1–80	0
81	5,866.33
82	12,203.21
83	17,268.85
84	18,717.13
85	19,896.17
86	20,910.66
87	21,850.47
88	22,790.27
89	23,681.70
90	24,669.88
91	25,609.69
92	26,594.45
93	27,721.00
94	28,984.96
95	30,450.26
96	32,126.42
97	34,454.32
98	37,932.57
99	45,111.79

concentration that we used as the 8-hour TWA of BD exposure in the main analyses.

We used the entire percentile distribution of BD TWAs created for work area/job groups to create the 1000 data sets used for uncertainty analyses. To obtain each data set, we randomly selected a percentile for each work area/job group in a particular plant and chose for that work area/job group the set of BD concentrations corresponding to that percentile (ie, for a given work area/job group in a given plant, we used the same percentile *for all years* to select BD concentrations). We compiled 1000 JEMs containing BD concentrations selected according to each set of randomly selected percentiles, linked the 1000 JEMs to subjects' work histories, and recalculated all subjects' cumulative exposures to BD for each iteration. Table A.1 displays the work history and exposure estimates of our sample subject from data set 70 of the 1000 data sets used for uncertainty analyses. In data set 70, the BD ppm 8-hour TWA for work area/job group 817 in 1950 was based on the 25th percentile of the approximate probability distribution of exposure concentrations for work area/job group 817.

SIDEBAR 4. COMBINATION OF TASK-SPECIFIC BD EXPOSURE ESTIMATES TO OBTAIN THE DISTRIBUTION OF 8-HOUR TWA ESTIMATES FOR WORK AREA/JOB GROUP 817 AT PLANT 4 DURING 1950

As described in the text, we used the five component tasks that entailed BD exposure for work area/job group 817, to compute the approximate probability distribution of the 8-hour TWA exposure concentration.

DISTRIBUTION OF ESTIMATES: Selected Values of the Approximate Probability Distribution of BD

Percentile of Probability Distribution	BD Exposure (ppm-minutes)	Percentile of Probability Distribution	BD Exposure (ppm-minutes)
5	9,213.70	60	16,382.51
10	10,208.70	65	17,295.72
15	10,920.08	70	18,323.38
20	11,557.11	75	19,912.71
25	12,149.74	80	23,472.45
30	12,718.85	85	33,112.75
35	13,283.74	90	38,563.94
40	13,788.17	95	45,231.64
45	14,415.39	Minimum	5,435.93
50	15,007.26	Mean	20,699.60
55	15,666.86	Maximum	130,474.33

Calculation of BD 8-Hour TWA Used in the Main Analyses

TWA (ppm)

= mean of approximate probability distribution / 480 minutes

= 20699.60 / 480

= 43.1242

Calculation of BD 8-Hour TWA for Data Set 70 Used in the Uncertainty Analyses

In the 70th of the 1000 data sets created for the uncertainty analyses, we randomly selected the 25th percentile of the approximate probability distribution of BD exposure concentration.

TWA (ppm)

= 25th percentile value of approximate probability distribution / 480 minutes in an 8-hour workshift

= 12149.74 / 480

= 25.3120

APPENDIX B. Percentage of Agreement for Underlying Cause of Death Codes Between Previous and Current Studies for Decedents, 1944–1991

Cause of Death	Previous Study (*n*)	Current Study (*n*)	Agreement (%)
All cancers	776	753	97
Buccal cavity and pharynx	10	10	100
Esophagus	12	12	100
Stomach	28	28	100
Colorectum	86	86	100
Liver	11	11	100
Pancreas	30	29	97
Larynx	14	14	100
Lung	307	300	98
Prostate	68	68	100
Bladder	15	15	100
Kidney	18	18	100
Central nervous system	18	18	100
LHC	78	75	96
NHL	22	22	100
Hodgkin lymphoma	6	6	100
Leukemia	40	37	93
Multiple myeloma	10	10	100
Other cancers	71	61	86
Benign neoplasms	9	8	89
Blood disorders	10	10	100
Mental disorders	8	6	75
Allergic, endocrine, and metabolic disease	55	54	98
Nervous system disease	35	5	100
Circulatory disease	1665	1642	99
Nonmalignant respiratory disease	183	76	96
Digestive disease	111	102	92
Genitourinary disease	45	41	91
External cause	273	263	96
Other known	90	87	97
Unknown	122	113	93

APPENDIX C. Cause of Death Categories (ICD Codes) Analyzed and Sources Used to Obtain Comparison Rates for Each Category Shown by Time Periods of ICD Revisions

Cause of Death	ICD 5 1944–1948	ICD 6 and 7[a] 1949–1967	ICD 8[a] 1968–1978	ICD 9 1979+
All cancers	45–57	140–205	140–209	140–208
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Buccal cavity and pharynx	45	140–148	140–149	140–149
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Esophagus	46a	150	150	150
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Stomach	46b	151	151	151
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Colorectum	46d,e	153–154	153–154	153–154
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Liver	46f	155	155, 156	155, 156
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Pancreas	46g	157	157	157
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Larynx	47a	161	161	161
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Lung	47b,c,d	162, 163	162	162
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Prostate	51b	177	185	185
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Bladder	52b	181	188,1899	188,1893,1894, 1898,1899
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Kidney	52a	180	1890,1891,1892	1890,1891,1892
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Brain	54	193	191	191
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
All LHCs	—	200–205	200–209	200–208
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
NHL	55e	200, 202	200, 202	200, 202
	OCMAP	OCMAP	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario

Table continues next page

[a] Ontario cause of death categories were based on ICD 7 for 1958–1968 and on ICD 8 for 1969–1978.

APPENDIX C (*continued*). Cause of Death Categories (ICD Codes) Analyzed and Sources Used to Obtain Comparison Rates for Each Category Shown by Time Periods of ICD Revisions

Cause of Death	ICD 5 1944–48	ICD 6 and 7 1949–1967 (1950–1968 for Ontario)[a]	ICD 8 1968–1978 (1969–1978 for Ontario)[a]	ICD 9 1979+
All Cancers (*continued*)				
All LHCs (*continued*)				
Hodgkin lymphoma	—	201	201	201
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Leukemia	74	204	204–207	204–208
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Multiple myeloma	55e	203	203	203
	OCMAP	OCMAP	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Other cancers	—	165,191,197–199	171,1730–1734, 1736–1739, 195–199	171,173, 195–199
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Benign neoplasms	—	210–239	210–239	210–239
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Blood disorders	72–76	290–299	280–289	280–289
	USDR	USDR 1949, OCMAP 1950–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Mental disorders	84	300–326	290–315	290–319
	USDR	USDR 1949–1959, OCMAP 1960–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Allergic, endocrine, and metabolic disease	58–71	240, 242–289	240–279	240–279
	USDR	USDR 1949–1959, OCMAP 1960–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Nervous system disease	80–89	340–398	320–389	320–389
	USDR	USDR 1949–1959, OCMAP 1960–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Circulatory disease	90–103	330–334, 400–468	390–458	390–459
	USDR	USDR 1949–1959, OCMAP 1960–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Nonmalignant respiratory disease	104–114	241, 470–527	460–519	460–519
	USDR	USDR 1949–1959, OCMAP 1960–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Digestive disease	115–129	530–587	520–577	520–579
	USDR	USDR 1949–1959, OCMAP 1960–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
Genitourinary disease	130–139	590–637	580–629	580–629
	USDR	USDR 1949–1959, OCMAP 1960–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario
External causes	163–198	800–999	800–999	800–999
	USDR	USDR 1949–1959, OCMAP 1960–1967	OCMAP	OCMAP
	—	Ontario 1950–1968	Ontario 1969–1978	Ontario

[a] Ontario cause of death categories were based on ICD 7 for 1958–1968 and on ICD 8 for 1969–1978.

APPENDIX D. HEI Quality Assurance Audit Statement

The conduct of this study was subjected to periodic, independent audits by a team from Hoover Consultants. This team consisted of auditors with experience in toxicology and epidemiology and a practicing, board-certified, physician epidemiologist. The audits included in-process monitoring of study activities for conformance to the study protocol and examination of records and supporting data. The dates of each audit are listed below with the phase of the study examined.

Written reports of each inspection were provided to the Director of Science of the Health Effects Institute, who transmitted these findings to the Principal Investigator. These quality assurance audits demonstrated the study was conducted by a well-coordinated, experienced team according to the study protocol and standard operating procedures. The report appears to be an accurate representation of the study.

QUALITY ASSURANCE AUDITS

Date and Phase of Study Audited

July 17–18, 2000

The audit team conducted an audit of this study, which began in September 1999. A random sample of the most raw form of the data from 50 subjects (0.28%) from the eight original manufacturing plants was audited against database printouts. Since only five deaths occurred in this sample, an additional 100 death certificates were randomly selected. All of the death certificates and medical records were examined for the 49 subjects identified at the time as having lymphohematopoietic cancer. The audit team was provided with a detailed description of the development, documentation, and implementation of the exposure determinations by plant, year, and job classification. The uncertainty analysis was described to assess factors associated with possible under- or overestimation of exposures.

June 15–16, 2004

An audit was conducted of the final report of this study. This audit included subjects from the original update and subjects from the external analysis of specific forms of leukemia and of decedent medical records who had been previously diagnosed with lymphohematopoietic cancer. Data from 50 subjects from the US were sampled at random (approximately 0.4%). Canadian subjects were excluded from the 50-subject sample because it was not possible to audit the record linkage done by the Canadian government. Printouts of data from these subjects were obtained and audited against the most raw form of printed records. Dates of death were verified against available documents such as the death certificate, National Death Index (NDI), Pension Board Inc (PBI), and/or Social Security Administration records. All of the death certificates and medical records were examined for the 54 subjects identified between 1992 and 1998 who had lymphohematopoietic cancer. Vital status determinations were audited for all 50 subjects in the sample and an additional 10 subjects were selected at random when an error was noted.

B Kristin Hoover, Audit Coordinator

Hoover Consultants

APPENDICES AVAILABLE ON REQUEST

The following materials may be requested by contacting the Health Effects Institute at Charlestown Navy Yard, 120 Second Avenue, Boston MA 02129-4533, +1-617-886-9330, fax +1-617-886-9335, or email (*pubs@healtheffects.org*). Please give (1) the first author, full title, and number of the Research Report and (2) the title of appendix requested. Appendix E is available only as a paper copy; Appendix F appears with the report on the HEI website *www.healtheffects.org*.

APPENDIX E. A Retrospective Assessment of Exposure to Dimethyldithiocarbamate in Styrene Butadiene Rubber Plants

APPENDIX F. Random Selection of Percentiles and Creation of 1000 Datasets for Uncertainty Analysis of Butadiene and Leukemia

ABOUT THE AUTHORS

Elizabeth Delzell, the Principal Investigator for the project, has an ScD from Harvard University. She is professor of epidemiology in the Department of Epidemiology, School of Public Health, at the University of Alabama at Birmingham. Her primary research interests include occupational, environmental, and cancer epidemiology, as well as pharmacoepidemiology.

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John Graff was the project manager for this research while he was a doctoral candidate at the University of Alabama at Birmingham. He is now assistant professor of Oncology and Family Medicine at the Wayne State University School of Medicine and the chief of Cancer Surveillance Research at the Karmanos Cancer Institute. His research interests include cancer registry–based investigations of mesothelioma, breast, and oral cancers; occupational and environmental asbestos exposure; and other occupational and environmental carcinogens.

Maurizio Macaluso holds a Doctor of Medicine and Surgery degree (1979) from the University of Palermo, Italy, and a Doctor of Public Health degree in epidemiology (1991) from the University of Alabama at Birmingham. He was professor of epidemiology at the University of Alabama School of Public Health when the research was carried out. Presently he is senior research scientist and chief of the Women's Health and Fertility Branch in the Division of Reproductive Health at the Centers for Disease Control and Prevention in Atlanta, Georgia. His research interests include epidemiologic research methods, surveillance systems, reproductive health, cancer epidemiology, and occupational epidemiology.

George Maldonado, the methodological consultant for this project, has a PhD from the University of California, Los Angeles. He is associate professor at the University of Minnesota School of Public Health, Division of Environmental Health Sciences. His primary research interest is the design, analysis, and interpretation of epidemiologic studies.

Robert Matthews has a BS degree in computer science from the University of Alabama at Birmingham, where he is senior systems analyst in the Department of Epidemiology. He specializes in SAS users groups that deal with technical programming issues. His research includes exposure to butadiene and other chemicals in the synthetic rubber industry, exposure assessment and mortality for workers in the semiconductor industry, and mortality among hourly and salaried workers in the motor vehicle industry.

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Delzell E, Sathiakumar N, Graff J, Matthews R. 2005. Styrene and ischemic heart disease mortality among synthetic rubber industry workers. J Occup Environ Med 47(12):1235–1243.

Graff JJ, Sathiakumar N, Macaluso M, Maldonado G, Matthews R, Delzell E. 2005. Chemical exposures in the synthetic rubber industry and lymphohematopoietic cancer mortality. J Occup Environ Med 47(9):916–932.

Sathiakumar N, Graff JJ, Macaluso M, Maldonado G, Matthews R, Delzell E. 2005. An updated study of mortality among North American synthetic rubber industry workers. Occup Environ Med 62(12)822–829.

ABBREVIATIONS AND OTHER TERMS

BD	1,3-butadiene
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMDB	Canadian Mortality Data Base
DMDTC	dimethyldithiocarbamate
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IRS	Internal Revenue Service
JEM	job–exposure matrix
LHC	lymphohematopoietic cancer
NCHS	National Center for Health Statistics (US)
NDI	National Death Index (US)
NHL	non-Hodgkin lymphoma
OCMAP	Occupational Cohort Mortality Analysis Program
PY	person-years [in tables]
RR	relative rate
SBR	styrene-butadiene rubber
SMR	standardized mortality ratio
SSA	Social Security Administration (US)
TWA	time-weighted average
USDR	US Death Rate

Research Report 132, *An Updated Study of Mortality Among North American Synthetic Rubber Industry Workers,* E Delzell et al

INTRODUCTION

1,3-Butadiene (BD)* is a volatile organic compound used in the production of synthetic rubber since the 1930s. Industrial emissions contribute to its outdoor presence in some urban areas; however, BD is also emitted in automotive exhaust and this source accounts for the preponderance of emissions in the US and for much of the human exposure.

Concern about the toxicity of BD was first raised in the 1980s, when cancer studies showed an association between BD exposure and tumor development at many sites in laboratory rats and mice (Huff et al 1985; Irons et al 1986a,b; Melnick et al 1988, 1990). Early epidemiologic studies also suggested an increased risk of cancers of the lymphatic and blood-forming systems (lymphohematopoietic cancers [LHCs]) in BD-exposed workers (Meinhardt et al 1982; Matanoski and Schwartz 1987; Matanoski et al 1990). Later studies suggested an increased risk of chronic leukemia in workers in the styrene-butadiene rubber (SBR) industry who had been exposed to BD over many years (Delzell et al 1996), but the effects of exposure to other chemicals used in combination with BD had not been determined. Thus it was not possible to determine which chemical or combination of chemicals was responsible for the effects being identified.

Given the uncertainties in understanding the cancer risks for exposed workers, risk assessments have generally relied on data from animal studies. Certain problems are inherent in these assessments, however: first, the carcinogenic potency of BD appears to vary between rats and mice, perhaps due to differences in the way the compound is metabolized (Health Effects Institute 2000); and second because of the omnipresent uncertainties of interspecies extrapolation from rodents to humans.

Thus, it is not surprising that international agencies that have evaluated the data have reached varying conclusions about the carcinogenicity of BD. The International Agency for Research on Cancer (1999) classified BD as "probably carcinogenic to humans" (a Group 2A carcinogen). The Canadian Ministers of Environment and Health have labeled BD as "toxic" and as "highly likely to be carcinogenic in humans" (Health Canada 1998). The US Environmental Protection Agency (EPA 1998a) and the US National Toxicology Program's Annual Report on Carcinogens (1998) both classify BD as a "known human carcinogen".

Since the mid-1990s, HEI has funded research on the health effects of BD. The general goals of the research have been to (1) explore the reactivity and mutagenicity of BD metabolites to elucidate the mechanisms of BD carcinogenicity; and (2) identify biomarkers of exposure, dose, and metabolism and then validate them in an exposed human population.

The Institute realized the importance of strengthening epidemiologic research on the carcinogenicity of butadiene to establish a firmer context for mechanistic work and biomarker development (referred to as transitional epidemiology). In 1999, HEI funded an extension of a major epidemiologic study by Dr Elizabeth Delzell (University of Alabama) and her colleagues. The study updated the earlier follow-up of mortality (Delzell et al 1996) in the largest occupational group exposed to butadiene: 18,000 men employed in the production of SBR in eight North American plants. The study also examined the possible contribution to mortality of exposure to other compounds in the work environment.†

REGULATORY AND SCIENTIFIC BACKGROUND

BD is one of a large group of toxic or possibly toxic compounds emitted from mobile, stationary, and area sources. In the United States, unlike ozone and particulate matter, air toxics are not regulated under the National Ambient Air Quality Standards but under separate provisions of the

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

† Dr Delzell's 2-year study, "An Updated Study of Mortality Among North American Synthetic Rubber Workers", began in May 1999. Total expenditures were $445,511. The draft Investigators' Report from Delzell and colleagues was received for review in November 2001; the HEI Health Review Committee requested additional analyses. Those were completed and a revised report was received in January 2003; it was accepted for publication in October 2004. During the review process, the Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and in the Review Committee's Commentary.

Clean Air Act, which was most recently amended in 1990 (US Congress 1991). Section 112 lists 188 pollutants or chemical groups as "air pollutants of a hazardous or toxic nature". It defines them as a compound or group of compounds "to which no ambient air standard is applicable and that . . . causes, or contributes to, air pollution which may reasonably be anticipated to result in an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness."

In addition, the Act requires that a strategy be implemented for substantially reducing the public health risk posed by exposure to hazardous air toxics from all stationary sources, including a 75% reduction in cancer risk attributed to these toxic air pollutants. The Act focuses on cancer reduction because the EPA assumes that there is no threshold level in the dose–response relation between air toxics exposure concentrations and cancer effects; thus the low concentrations of these air toxics would most readily affect cancer development (EPA 1986, 1996).

Five of the 188 hazardous air pollutants are also listed in Sections 202 and 211 of the Clean Air Act Amendments as mobile-source toxic air pollutants. These are defined as the aggregate emissions of acetaldehyde, benzene, BD, formaldehyde, and polycyclic organic matter (a class of chemicals that includes polycyclic aromatic hydrocarbons). Mobile-source air toxics may contribute 21% to 42% of all urban air toxics (EPA 1998a,b).

Mobile sources account for most of the BD emitted in the United States and for much of the human exposure (although side-stream cigarette smoke may contribute substantially to indoor concentrations in some environments; Health Effects Institute 1993). Emissions tend to be greater from vehicles with more than two axles (Sapkota and Buckley 2003). BD levels in ambient air are generally 1 to 10 ppb, about 1000-fold less than occupational exposure levels (International Agency for Research on Cancer 1992; Health Effects Institute 1993).

Acute toxicity is observed in people and laboratory animals only when they are exposed to high concentrations of BD. For this reason, BD was long considered to be relatively benign and the occupational exposure limit was set at 1000 ppm as an 8-hour time-weighted average (TWA). The limit was based on irritation of mucous membranes and narcosis at high exposure levels (US Occupational Safety and Health Administration 1990).

In the 1980s, however, a series of toxicologic experiments led scientists to reconsider this view. One study showed that inhalation of 1000 ppm BD produced tumors in multiple organs in male and female Sprague-Dawley rats (Hazleton Laboratories Europe 1981). In another study, differences in tumor development were observed between rats and B6C3F1 mice. The mice were shown to be much more sensitive: Tumors occurred in multiple organs after exposure to 625 ppm BD, the lowest concentration tested in that study (US National Toxicology Program 1984). In a follow-up study (1993), inhaled BD caused tumors in mice at exposure concentrations as low as 6.25 ppm and heart hemangiosarcomas at concentrations as low as 20 ppm. Tumors were found in multiple organs after exposure to 625 ppm BD. On the basis of these results, occupational exposure limits were reduced to 1 ppm BD as an 8-hour TWA (Occupational Safety and Health Administration 1996).

Epidemiologic studies of workers exposed to BD have reported increased mortality from LHCs, but the specific cancers varied among studies. Because workers in some industries were exposed to other possible leukemogens, the possibility that those other compounds were responsible for the increased mortality could not be excluded (for example, Meinhardt et al 1982; Matanoski and Schwartz 1987). More recent studies reported that, compared with expected rates of mortality from leukemia in the general population, mortality from chronic leukemia was higher in long-term SBR industry workers 25 years after beginning employment in jobs with BD exposure (Delzell et al 1996). Furthermore, a higher rate of lymphosarcoma was observed in workers exposed for a short duration to high concentrations in BD monomer production. However, no increase in mortality from chronic leukemia was observed in these workers (Divine and Hartman 1996).

The apparent discrepancies among the results of the epidemiologic studies discussed above may reflect (1) the lower TWA BD concentrations in the monomer facilities, (2) the smaller number of monomer workers included in the analysis, or (3) the presence of styrene or some other confounding substance (such as the stopping agent dimethyldithiocarbamate [DMDTC]) in the rubber-production facilities. The International Agency for Research on Cancer (2002) recently classified styrene as "possibly carcinogenic to humans" (Group 2B) based on "limited evidence" from both animal experiments and epidemiologic studies; however, the US National Toxicology Program's Report on Carcinogens (1998) does not list styrene as a human carcinogen. The carcinogenicity of DMDTC has been hypothesized on the basis of computer simulations (Bird et al 2001), but experimental evidence regarding this is lacking. Simultaneous exposure to DMDTC and BD has been reported to affect the metabolism of BD in both mice and rats, although Green and associates (2001) have noted that the "nature and full significance" of their own findings were unclear. No epidemiologic studies of the carcinogenicity of DMDTC have been conducted except for the current and previous studies of this cohort of workers in the SBR industry.

The EPA has conducted several quantitative cancer risk assessments of BD since the mid-1980s. Its first estimate, obtained using tumor data from mice (the more sensitive rodent species), gave 2.5×10^{-1} per ppm BD as a 95% upper bound. This can be interpreted as 250 cancer deaths among 1000 people continuously exposed for their entire lives to 1 ppm BD (Bayard et al 1985). In 1998 the EPA reported a much lower quantitative cancer risk assessment of BD using data from SBR workers and retrospective exposure estimates developed from work history records (Delzell et al 1995). At that time, the best estimate of human lifetime extra cancer risk was 9×10^{-3} per ppm BD, or 9 cancer deaths among 1000 people exposed continuously for their entire lives to 1 ppm BD (EPA 1998b). The EPA's most recent quantitative risk estimate applies the leukemia relative risk for male synthetic rubber workers exposed to BD (Delzell et al 1995) to US leukemia incidence rates and obtains a lifetime leukemia incidence risk of 4×10^{-3} per ppm. This incidence risk is then multiplied by 2 to account for the possibility, suggested by experiments in rodents, that exposure to BD increases the risk of breast cancer in women. Incorporating this additional possible risk results in an estimated lifetime cancer risk for the general population of 8×10^{-3} per ppm BD (EPA 2002). In presenting its most recent risk estimates, the EPA discussed eight sources of uncertainty; these include the statistical models used to extrapolate the epidemiologic results to the US population, the dose metric, and the estimates of occupational exposure themselves. The EPA was particularly concerned about the last source of uncertainty: "Nondifferential exposure misclassification would tend to bias estimates of effect toward the null, resulting in an underestimate of risk. Differential misclassification could bias results in either direction" (EPA 2002).

TECHNICAL EVALUATION

SPECIFIC AIMS

The overall aim of the study was to expand and reevaluate an earlier epidemiologic study (conducted by the same investigators) on mortality among North American SBR workers, the largest group of BD-exposed subjects studied to date. The study had three objectives:

1. to determine if occupational factors such as time period of hire, duration of employment, years since hire, and work area/job group are associated with mortality from specific causes among this group of workers;
2. to evaluate the relation of quantitative estimates of exposure to BD, styrene, or DMDTC with deaths from leukemia and other LHCs; and
3. to evaluate the relation of exposure to BD or to styrene with deaths from selected cancers other than LHCs.

APPROACH

Population and Outcomes

The original cohort study of North American SBR workers was a retrospective evaluation of mortality among men who had worked at least 1 year in any of eight plants (seven in the United States and one in Ontario, Canada) from 1944 through 1991 (Delzell et al 1996; Macaluso et al 1996; Sathiakumar et al 1998). The current cohort study covers the period from 1944 through 1998 and includes 540,586 person-years of follow-up, 18% more than the original study. Cancer mortality was the principal outcome studied; leukemia, non-Hodgkin lymphoma, and other LHCs were of particular interest.

In the original study, 4665 workers were identified as having died before 1992. Another 12,565 were presumed alive, and 734 were categorized as lost to follow-up. In the current analysis, a modified standardized protocol (more extensive than that for the original study) was used to update vital status information through 1998 about subjects that had been classified as living or lost to follow-up in the original study. Vital status was established for 97% of the cohort (see Table 1 in the Investigators' Report). A total of 6237 deaths were recorded between 1944 and 1998; of these, 75% occurred between 1944 and 1991 and 25% between 1992 and 1998. This information was obtained from death certificates for US decedents and the Canadian Mortality Data Base for Canadian decedents. Cause-of-death information was obtained for 98% of decedents.

In the original study (covering 1944 through 1991), the investigators attempted to obtain medical records for all 127 death certificates that mentioned LHC or a blood disorder. A pathologist reviewed those records to confirm the cause of death stated on the death certificates. Subsequent supplemental funding from HEI supported a similar review of medical records and death certificates that listed LHCs since 1992.

Exposure Assessment

Exposures were estimated using both qualitative and quantitative methods. Qualitative estimates used data obtained from work records and included such factors as time period of hire, duration of employment, years since hire, type of employment (ever-hourly or never-hourly),

job categories (production, maintenance, labor, laboratories, and other), and job subgroups (polymerization, coagulation, finishing, shop maintenance, field maintenance, production labor, and maintenance labor).

Quantitative estimates of exposure to BD and styrene were derived from two sources and are documented in the Investigators' Report Appendix E (available on request). The first was an in-depth analysis of sources of exposure associated with the tasks that made up each job during specific time periods in each plant. The second was a mathematical model used to calculate exposure concentrations in ppm. The mathematical model estimated background exposure from work in buildings and in open areas (eg, tank farms) and from exposures originating from point sources in work areas. The point-source model used estimates of emission rates from possible sources of exposure (obtained during interviews with workers) and dispersion models to calculate a worker's breathing-zone exposure. The model was not validated with actual industrial hygiene measurements.

The models for BD exposure required estimating several parameters; the estimates for each parameter contain considerable uncertainty about the true numeric values. A probability distribution of BD exposures was estimated by allowing the parameters to take on a range of plausible values. For the primary analyses, the mean of this distribution was used as the exposure estimate for each work area/job group category in each time period and plant. Cumulative exposure was computed for each worker by multiplying the estimated exposure concentration in each of his work area/job groups by the number of days he worked in each and by summing the resulting quantities over all of his jobs. The results were expressed in units of ppm-years.

Skin contact was the most important route of exposure to DMDTC, which was used in an aqueous solution. Cumulative exposure was calculated for each worker by computing the product of the DMDTC concentration in the solution, the area of exposed skin, and the duration of exposure. The results for cumulative exposure were expressed in units of mg/cm–years.

DATA ANALYSIS

The investigators estimated the effects of exposure to BD using the two approaches of external and internal analyses. They also conducted sensitivity analyses to quantify the uncertainty of cumulative exposure to BD in their model-based estimates.

In the external analyses, the investigators compared the observed mortality rate of the workers with the expected mortality rate according to mortality in the general population (ie, the male general population of each state in which a US plant was located and of Ontario for the Canadian plant). An estimated relative rate of mortality for the workers, called a standardized mortality ratio (SMR), was calculated as the ratio of the observed rate to the expected rate. SMRs (and 95% confidence intervals [CIs]) were calculated by cause of death for all subjects combined and for subgroups defined by various employment factors (eg, plant, work area/job group, duration of employment, time since hire) and by time periods of follow-up (1944 through 1991, 1992 through 1998, and 1944 through 1998). The external analyses included specific forms of leukemia and a combined category consisting of chronic lymphocytic leukemia and non-Hodgkin lymphoma.

Internal analyses, using Poisson regression models, compared mortality rates of exposed subgroups with those for unexposed groups of workers. Outcomes assessed included all leukemias, four subtypes of leukemia, non-Hodgkin lymphoma, multiple myeloma, and other causes of death. Cumulative exposure estimates for BD, styrene, and DMDTC (in ppm-years for BD and styrene and in mg/cm–years for DMDTC) were derived from mathematical models and used in regression analyses as the measures of exposure. Exposure was then categorized in different ways: For example, they divided the number of all leukemia decedents into quartiles and determined the range of cumulative exposure that matched each quartile (referred to as exposure quartiles). A similar procedure was used to define categories of peak exposure. A relative rate for each exposure quartile was estimated. (The relative rate for a given exposure quartile is the mortality rate for the quartile divided by the mortality rate for the referent group [zero or low exposure].) Relative rate estimates for each of the agents of interest (BD, styrene, and DMDTC) were estimated in a model that included possible confounders (such as age); in some analyses, exposures to the other agents of interest were also included as confounders.

In the set of uncertainty analyses, the estimated probability distribution of BD exposure (described at the end of the Exposure Assessment section above) was used to provide a range of plausible exposure estimates for each work area/job group. Similarly, variations in the duration of exposure and in exposure concentration were incorporated. Using this approach, the authors simulated 1000 datasets, each of which was analyzed in the same manner as the original BD exposure estimates. Conclusions drawn from the analyses of these datasets (Table 26 and Figure 1) are consistent with the conclusions from the main analyses of the effects of cumulative exposure to BD on the relative rate of mortality from leukemia. The uncertainty analyses

were also conducted for BD to assess the potential impact of exposure estimation error on calculated relative rates for leukemia (Figure 1). (The results in Table 26 are unadjusted for DMDTC or styrene; thus they should be compared with the results of Model 1 in Table 11. Although further analyses with adjustments for styrene and DMDTC could be envisioned, the computational burden would be rather high and the results would likely be difficult to interpret.)

RESULTS

External Analyses

External analyses of the cohort for the entire study period (1944 through 1998) found higher than expected deaths from certain forms of LHCs, colorectal cancer, and prostate cancer; for all causes of death combined and for all other specific forms of cancer, mortality rates were lower than expected (Table 2). This result can perhaps be explained as reflecting the "healthy worker effect", which is a common result of analyses of occupational cohorts because they selectively include individuals who are healthier than the general population.

For LHCs, leukemia had the highest ratio of observed-to-expected number of deaths (71/61; SMR = 116; 95% CI = 91, 147; Table 3). It was also higher in comparisons between several identifiable subgroups (such as ever-hourly vs never-hourly workers) as well as in the subgroups for years since hire and duration of employment in the ever-hourly workers. The SMR for leukemia was approximately the same for 1992 through 1998 (117) as for the earlier period 1944 through 1991 (116; Table 2). The observed leukemia increase was concentrated in the hourly workers (Tables 3 and 4), in selected work-area subgroups (polymerization, coagulation, maintenance, labor, and laboratory operations; Tables 5 and 6), in workers with 20 to 29 years since hire, and in workers with 10 or more years of employment (Table 7). Limiting the analyses to deaths from 1968 through 1998 resulted in higher SMRs for leukemia and for specific forms of leukemia for various exposure metrics (Tables 4–6). For example, SMRs for leukemia were high in production workers (SMR = 204; 95% CI = 121, 322), maintenance laborers (SMR = 203; 95% CI = 114, 335), and laboratory workers (SMR = 326; 95% CI = 178, 546).

Internal Analyses

Using Poisson regression models, internal analyses revealed associations between mortality rates from leukemia and cumulative exposures to BD, styrene, and DMDTC (Table 10). The single-agent models estimated the effects of each agent without adjusting for the other two. These results suggest that, after adjusting for age and years since hire, each compound independently affected rates of death from leukemia; furthermore, the relative rates were generally higher with higher cumulative exposures. However, exposures to BD, styrene, and DMDTC were correlated with each other (correlation coefficients from 0.58 to 0.87). In models that included exposure to the other two agents, only BD and DMDTC retained their association with increased leukemia mortality.

The most apparent increasing trend in the relative rate for leukemia occurred with exposure to BD (Table 15). No clear association was found between any of the three agents and non-Hodgkin lymphoma, multiple myeloma, or colorectal cancer. In models that controlled for styrene, BD exposure was positively associated with prostate cancer, but little evidence supported a direct relation with increasing cumulative exposure.

The investigators also explored the sensitivity of the results to different groupings of LHCs (Table 21). In accordance with recent World Health Organization recommendations, the investigators created two broad categories of neoplasms, those of lymphoid or of myeloid origin (Harris et al 2000). These groupings were examined with the same internal analyses of cumulative exposure to each of the three agents in both single- and multiple-agent models. The investigators observed weak associations between each broad group and all three agents in both models. However, the relative rates increased with cumulative exposure to BD in both models, particularly for the group of myeloid neoplasms.

DISCUSSION

This study expanded and reassessed the epidemiologic evidence for a relation between BD exposures and cancer in the largest cohort of BD-exposed workers in the world: styrene-butadiene rubber workers. To date, it provides not only the most extensive epidemiologic assessment of (1) the association between BD and leukemia and other LHCs, and (2) an extensive assessment of a possible link between LHCs and BD in the presence of two other chemicals associated with the SBR industry—styrene and DMDTC. The study was carefully thought out and successfully executed. The investigators followed the original study population (Delzell et al 1996; Macaluso et al 1996; Sathiakumar et al 1998b) and applied carefully constructed protocols to update the retrospective assessment of workers' exposures.

The investigators concluded that employment in the SBR industry is causally related to leukemia, but that it is uncertain which agent or agents were responsible for the associations found in this population. External and

internal analyses showed an increased mortality relative rate for leukemia. Although the SMRs in the external analyses for leukemia for the whole study period (1944 through 1998) were not estimated with great precision, they were consistently higher for worker subgroups thought to have higher exposures and for groups of workers with longer periods of employment. For some time periods, such as 1968 through 1998, SMRs for leukemia were clearly elevated.

The investigators conclusions concerning the association between employment in the industry and an increased mortality rate from leukemia are well founded and carefully documented. Furthermore, we believe that this study provides stronger evidence than previous studies for the carcinogenicity of BD in particular:

- This worker group was followed longer than any other, which provides the highest number of person-years of observation.
- Strong efforts were made to validate the medical diagnoses to substantiate the recorded causes of death.
- The effort to estimate retrospectively the exposure to BD and other agents in the workplace was extensive and detailed.

An analysis of BD that controlled for the possibly carcinogenic coexposures to styrene and DMDTC produced the most important result of the investigation: the clear and consistent exposure–response relation observed between cumulative exposure to BD and mortality from leukemia. The results from a χ^2 test for a linear trend in the relative rates for BD exposure (adjusted for DMDTC, $P = 0.003$) support the presence of a linear increase in the relative rate of leukemia mortality with increasing cumulative exposure to BD (Table 15). Cumulative exposure to BD was also associated with mortality rates in the broader grouping of LHCs, albeit more weakly; this relation also appeared to increase directly with cumulative exposure.

Coexposure to DMDTC did not account for the observed association of BD with LHCs. The results do suggest an independent association between DMDTC and LHCs. The investigators concluded, however, that because the leukemia relative rates do not consistently increase with increasing cumulative exposure to DMDTC, the results do not support a causal interpretation. The leukemia relative rates for DMDTC (Tables 10 and 15) appear to vary directly with cumulative exposure; however the highest relative rate observed is in the third quartile of cumulative exposure and a lower relative rate is seen in the highest quartile (Table 10). These results suggest that a direct relation may be present between cumulative exposure to DMDTC and leukemia mortality, but a formal test for the presence of a (linear) trend in the increased relative rate was not conducted. A trend test was performed using the results shown in Table 15; for this analysis, the four nonzero exposure quartiles defined in Table 10 were collapsed into three. No evidence of a linear trend was found, although the regrouping of exposure quartiles may have introduced additional uncertainty.[‡] The authors reported $P = 0.60$ for trend in the leukemia relative rate from a regression model that controlled for BD exposure.

The association of styrene with leukemia seen in single-agent models was not observed in multiple-agent models that included BD and DMDTC. Thus the current analysis does not provide evidence that styrene is a leukemogen, which is consistent with the results of another study of styrene-exposed workers in the boatbuilding industry (Ruder et al 2004).

In any observational study that involves workplace exposure to multiple chemical agents, it is difficult to identify a specific agent as being responsible for the observed effects. The major limitation in this study is that the exposure assessment conducted was retrospective and that those results were used in both the external and internal analyses. It is clear that the investigators applied considerable effort in estimating the cumulative exposures of workers. The exposure models were quite comprehensive in that they considered important parameters (eg, background levels and emissions rates from specific production processes). However, these estimates were largely constructed using subjective information gathered from walking through the plants and interviewing knowledgeable employees. The information gathered from these interviews and the resulting estimates were not validated using actual industrial hygiene measurements.

The investigators also note that errors in the estimation of exposure to the three agents could have led to residual confounding in the multivariate analyses and produced distorted estimates of the agent-specific exposure–response relations. Depending on the extent of the estimating errors for each pollutant and how those errors might be correlated, effects of DMDTC could, in theory, have been erroneously attributed to BD. However, such a pattern of correlated errors is not apparent in the data, and we conclude that the estimated BD relative rate for leukemia is unlikely to be explained by a concomitant increase in exposure to DMDTC (or styrene).

[‡] The DMDTC exposure groupings used in Table 15 may have obscured any linear trend that is arguably more apparent in the groupings used in Table 10. It is not unusual to observe a relative rate in the highest exposure quartile that is lower than those for lower exposures. Such relations may occur for a variety of toxicologic reasons or because extreme exposure estimates may be more highly subject to bias or misclassification. For example, workers in jobs with the potential for the highest exposure may be more likely to wear personal protective equipment and thus reduce their actual exposure.

Validating the exposure model estimates with industrial hygiene data gathered from the SBR industry over the last several years would strengthen the results of this investigation. The importance of this validation cannot be overstated because exposure estimates are frequently a major source of uncertainty when the observed associations are interpreted or used in quantitative risk assessments.

To address the importance of validation and the uncertainties inherent in exposure estimates, two studies have been conducted by investigators at the University of Alabama. The first study (Macaluso et al 2004) was very limited, based on only two small studies of BD and styrene exposures in the SBR industry conducted by US National Institute of Occupational Safety and Health (NIOSH). This study observed that exposure levels estimated from models in the two NIOSH studies were significantly higher than the measured levels. For most job groups, estimated BD exposure levels were about 2 times the mean measured levels, but were 6.5 times the measured levels for the job of tank farm operator. Overestimations of styrene exposures were even higher: Model estimates for the job group of recovery operator, for example, were 9 times higher than measured levels (Table VIII in Macaluso et al 2004). The authors suggested that technical sampling problems in the two NIOSH studies contributed to possible systematic negative biases in the data, which may have led to higher than actual estimates. Regardless, it seems unlikely that these sampling problems could result in overestimation by such large margins.

A second study (Sathiakumar et al 2006) was undertaken by Dr Delzell and her associates simultaneously with the project reported in this Research Report and the results have recently been accepted for publication. It used a set of about 9000 BD and 6000 styrene measurements from a large industrial facility that produces synthetic rubber and chemicals in Sarnia, Ontario to evaluate the accuracy of the exposure estimation methods used in the current study. Those results could shed considerable light on the quantitative estimates of BD exposure that were used in the present research.

It is reassuring that the main finding from this study (the exposure–response relation between cumulative exposure to BD and leukemia) appears to be supported by the uncertainty analyses performed even without an extensive validation of the exposure estimates. In retrospect, this should not be too surprising; the analysis by quartiles of exposure was designed to be relatively insensitive to the estimated values of BD. The method for establishing the probability distribution of BD exposures used in the uncertainty analyses is carefully detailed in Investigators' Report Appendix A and seems reasonable; but to our knowledge, the statistical properties of the method have not been investigated. (A different sampling method was used to establish a probability distribution for DMDTC exposures [Appendix E; available on request].) It is possible that the method used for BD may oversample from the extremes of the distribution. But the distribution is determined only by varying the parameters in the exposure model and does not consider the form of the model itself; therefore it may not fully capture the true variability in exposure. Although it was clearly beyond the scope of this study, investigating the statistical properties of the model for uncertainty analyses would be of interest.

Although the current study strengthens the evidence for the carcinogenicity of BD, a fundamental question remains: How does this investigation enhance the ability to conduct a quantitative risk assessment that could identify what concentration of BD above background exposure is safe?

As discussed above, the exposure levels estimated in this study were based on extensive onsite observations and interviews combined with mathematical modeling (Macaluso et al 2004). Although these methods are the state of the art for determining exposure estimates, using the results from these methods is limited by the absence of quantitative exposure measurements. This limitation has been noted in the literature, and caution has been advised in using such exposure estimates for quantitative risk assessment and for setting and enforcing standards (Schneider 2002; Spear 2002).

Grouping subjects according to exposure level, as these investigators have done, is an effective means of reducing (though not completely controlling) the potential biases that result from measurement error. As a result, it is likely that the relative ranking of exposures among the groups used in the analyses is reasonably accurate and leads us to conclude that the study provides additional evidence of BD carcinogenicity.

The quantitative levels derived from these procedures are, however, much more uncertain. The evidence provided by Macaluso and colleagues (2004) is quite limited, but suggests that these BD exposure estimates could be two- to sixfold too high, which would further undermine the validity of the estimated levels. If further validation efforts confirm that estimated exposure concentrations are higher than measured exposures, the quantified risks calculated using the estimated concentrations would actually be associated with the lower measured concentrations of exposure.

The more extensive study by Sathiakumar and colleagues (2006) will hopefully provide much needed additional evidence concerning the accuracy of the BD

exposure estimates used in the current Delzell study. If the Sathiakumar study provides a high degree of assurance that the estimates used are accurate, then the present study by Delzell and associates will provide a very substantial basis for quantitative risk assessment of BD exposure related to leukemia. In the absence of such quantitative validation, a quantitative risk assessment using the estimated concentrations as guides to safe levels of exposure would produce highly uncertain results. Furthermore, even in the presence of validated quantitative estimates, the possible influence of exposure measurement errors must be considered.

SUMMARY AND CONCLUSIONS

This investigation conducted by Delzell and associates strengthens the epidemiologic evidence for the carcinogenicity of BD. In particular, it indicates that cumulative occupational exposure to BD may increase the relative rate of mortality from LHCs (in particular leukemia) and that this elevation is heightened as cumulative exposure increases. These results persist even when workplace exposures to other putative carcinogens, such as styrene and DMDTC, are accounted for. The investigation addressed more definitively than earlier studies of this cohort the possibility that the observed relative rates associated with BD exposure may actually reflect exposure to styrene or DMDTC.

This study provides some evidence of an association of leukemia mortality with occupational exposure to DMDTC. The evidence, however, was not as strong as that linking BD with leukemia because it did not support a linear increase in relative rate with cumulative exposure to DMDTC. The critical finding for both the validity and generalizability of these results is that the BD relative rates remain elevated when exposure to DMDTC is accounted for. To the extent that DMDTC continues to be used in the SBR industry or elsewhere, further research may be indicated.

The quantitative interpretation of these results faces serious limitations, especially in their application to risk assessments in other occupational or general populations. The relative ranking of the exposures of cohort members appears to be reasonably accurate; nevertheless, because the estimated exposure levels lack validation by actual workplace measurements, they are a source of considerable uncertainty. The limited evidence available to date suggests that the BD exposure estimates used in the current study may be too high. If so, the risks calculated using these estimates could actually be associated with lower measured concentrations of exposure. Fortunately, a more comprehensive exposure assessment using industrial hygiene measurements has been conducted and the results have recently been accepted for publication. They may provide a needed degree of assurance that the estimates used in the analyses from the current investigation are accurate. With that assurance, this study will provide a firm basis for quantitative risk assessment of BD in relation to leukemia—although the effects of exposure measurement error would need to be taken into account. Without such validation, quantitative risk assessment using these estimated exposure levels would be highly uncertain.

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