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OFFICE OF TOXIC SUBSTANCES
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Attention: Section 8(e) Coordinator

RE: Docket 8(e) HQ-99-14447



BEHQ-99-14447

Dear Sir or Madam:

The International Institute of Synthetic Rubber Producers, Inc. (IISRP) has been sponsoring a cohort mortality study of nearly 18,000 workers employed between 1943 and 1991 at eight styrene butadiene rubber (SBR) plants in the United States and Canada. IISRP reported to EPA on this study and its findings concerning leukemia and exposure to butadiene on a number of occasions including May 19, 1995 and June 26, 1995; the final report was submitted to this office of October 24, 1995.

Over the past three years, additional collection and refinement of exposure information and reanalysis of the mortality data on SBR worker cohort has been conducted by the investigators of the University of Alabama at Birmingham. The initial preliminary results of this work were presented to IISRP on April 19, 1999 and provided to this office on May 10, 1999.

IISRP, on behalf of its member companies and pursuant to TSCA 8 (e) guidelines, set forth below a summary of the report and attaches the final report. These results provide both additional information concerning butadiene and new information concerning dimethylthiocarbamate (DMDTC). This study is a companion study to the *Araluso et al* exposure reassessment of the same cohort. That final report is expected within a couple of weeks and we will send it to you immediately upon receipt.

In summary information on leukemia cell type has now been confirmed using medical records and pathology reports. Reassessment of butadiene and styrene exposure and assessment of DMDTC exposure are complete. A reanalysis based on the new exposure estimates and leukemia cell type information continues to indicate an association between butadiene exposure and leukemia, although no one type of leukemia predominates. The correlation between leukemia and butadiene exposure is present only in workers with exposures above 100 ppm. DMDTC showed an approximately 3-fold increased risk of leukemia, although there was no trend of increasing risk with increasing DMDTC exposure. Non-Hodgkin's lymphoma continued to show no relationship with butadiene exposure (or styrene or DMDTC).

This report has also been sent to Mr. William Farland, Ms. Vanessa Vu, Dr. Apparna Kopikar and the IRIS docket.

Sincerely,
James L. McGraw
James L. McGraw
Managing Director and CEO

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**LYMPHOHEMATOPOIETIC CANCER
AMONG WORKERS EXPOSED TO 1,3-BUTADIENE, STYRENE AND
DIMETHYLDITHIOCARBAMATE IN THE SYNTHETIC RUBBER INDUSTRY**

by

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December 28, 1999

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SUMMARY

This study evaluated relationships between exposure to 1,3-butadiene (BD), styrene (STY) and dimethyldithiocarbamate (DMDTC) and lymphohematopoietic cancer (LHC) among 13130 workers at six North American plants that manufactured synthetic rubber and related products. The purpose was to refine previous research by 1) reviewing BD and STY exposure estimates 2) obtaining medical records pertaining to LHC and 3) assessing potential effect modification and controlling for potential confounding of the BD-leukemia relation by DMDTC.

An in-depth review assessed the original BD and STY estimates developed for our prior research and led to extensive revision of those estimates. In particular, revised BD exposure estimates were considerably higher than previous estimates. Dermal DMDTC exposure estimates were developed using procedures similar to those for BD and STY. We obtained medical records to confirm LHCs identified from death certificates. The final LHC subgroups were 59 leukemias (49 confirmed with medical records), 38 non-Hodgkin's lymphomas (NHLs, 34 confirmed), 21 multiple myelomas (MMs, 16 confirmed) and nine Hodgkin's disease cases (HDs, eight confirmed). Poisson regression procedures estimated relative rates (RRs) for cumulative exposure to BD (ppm-years), STY (ppm-years) and DMDTC (mg-years/cm). We further evaluated BD by partitioning total ppm-years into ppm-years due to exposure below 100 ppm (nonpeak exposure) and ppm-years due to exposure at or above 100 ppm (peak exposure).

Vital status was known for 99% of 13130 subjects, and death certificates were retrieved for 98% of 3892 decedents. Proportions of all subjects exposed to the

chemicals of interest were 79% for BD, 85% for STY and 62% for DMDTC. Poisson regression analyses indicated a positive association between BD ppm-years and leukemia (RRs: 1.0, 1.2, 2.0 and 4.1, for exposures of 0, >0-<85.9, 85.9-<392.1 and 392.1+ ppm-years) and between STY ppm-years and leukemia (RRs: 1.0, 1.2, 2.5 and 3.0, for exposures of 0, >0-<23.9, 23.9-<64.4 and 64.4+ ppm-years) after adjusting each set of RRs for age and years since hire. DMDTC mg-years/cm was positively associated with leukemia, without a positive dose-response pattern (RRs: 1.0, 2.1, 4.8 and 3.1, for 0, >0-<555, 555-<1392 and 1392+ mg-years/cm).

Controlling for other exposures reduced the magnitude of the association and the precision of the RR estimates for each of the three chemicals. The associations described above did not appear to be restricted to particular forms of leukemia. NHL displayed weak associations with BD ppm-years and STY ppm-years that were reduced when adjusted for the other exposures. The relation between DMDTC and NHL was weak and irregular. MM was positively associated with BD ppm-years, but the estimates were imprecise. MM was not associated with STY or DMDTC.

Exposures to the three chemicals were highly correlated, and it was not possible to determine whether any one agent was related to the occurrence of leukemia independently from the other two agents. Because there is inadequate evidence to establish that STY is carcinogenic in humans and because there is no evidence that DMDTC is a carcinogen, we interpret the present re-analysis of the UAB study as a confirmation of previously reported results. The new analysis suggests that only exposure to relatively high BD concentrations (100 ppm or more)

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is associated with increased risk of leukemia, and it provides little evidence that BD exposure is related to LHC other than leukemia.

INTRODUCTION

The production of synthetic rubber entails potential exposure to the monomers 1,3-butadiene (BD) and styrene (STY) and to other chemicals used in making styrene-butadiene rubber (SBR) and other synthetic elastomers. The International Agency for Research on Cancer (IARC) has classified BD as a probable human carcinogen, based on sufficient evidence of carcinogenicity in animals but limited evidence in humans (1), and has classified STY as possibly carcinogenic to humans, based on limited evidence of carcinogenicity in experimental animals and on inadequate evidence in humans (2).

Recently, Pyatt, Irons and coworkers reported that sodium dimethyldithiocarbamate (DMDTC), used as a shortstop in synthetic rubber polymerization, is an immune system depressant (3,4). DMDTC is a biologically active amine derivative related to the dithiocarbamates (DTCs), several of which display bone marrow depressant effects leading to reduced counts of peripheral leukocytes and platelets. No epidemiologic information is available on the human health effects of DMDTC. In 1991 IARC judged the available information on certain DTCs, including zinc DMDTC, inadequate for an evaluation of carcinogenicity (5).

In a previous study of North American synthetic rubber industry workers, we assessed mortality patterns during a 47-year period, from 1944 through the end of 1991 (6-8). The workers had lower than expected mortality from all causes combined, from all cancers combined and from most other major causes of death. Leukemia mortality was statistically significantly increased in hourly workers with 10+ years of work in the industry and with 20+ years since hire. This group also had a

slightly, but not statistically significantly, elevated rate of non-Hodgkin's lymphoma (NHL) deaths and had fewer than expected deaths from Hodgkin's disease (HD) and from multiple myeloma (MM).

Other results for leukemia included excesses among workers in plant areas with potentially high BD exposure (polymerization, maintenance labor and laboratory areas); a relative rate (RR) for BD-exposed compared to BD-unexposed workers that increased irregularly with increasing cumulative exposure to BD; and no clear pattern of association with STY (6,7). NHL and MM were not consistently associated with BD or STY (8). HD was not examined in detail because of small numbers. Associations between DMDTC and lymphohematopoietic cancer (LHC) were not assessed.

The exposure estimation approach used in the above study was controversial and unvalidated. Therefore, we undertook a comprehensive review and revision of the procedures. At the same time, another group of investigators developed DMDTC exposure estimates. In addition, we attempted to document all LHCs and deaths from other blood diseases with medical records. In this report, we used the revised BD and STY exposure estimates in Poisson regression models to examine associations between BD, STY and various forms of LHC among workers in the synthetic rubber industry. We also assessed the relation between DMDTC and LHC. We did not extend the follow-up period, 1944-1991, of our previous study.

METHODS

Subject Identification

Elsewhere, we have described in detail the procedures used to identify the subjects, to develop work histories, to estimate exposure to BD, STY and DMDC and to obtain information on vital status and causes of death (6-8). In brief, plant records provided personal and job history information on 17964 men who had worked for at least one year at any of eight synthetic rubber plants, seven in the United States (US) and one in Canada. Personnel records from two of the study plants did not contain work area/job assignment information of sufficient specificity for quantitative exposure estimation. Thus, the present study excludes the 1354 men who worked at these two plants. Other exclusions were 12 duplicate records of men who had worked at more than one study plant (in previous reports, for each of these 12 subjects we inadvertently counted the work history pertaining to each plant as a separate subject in some analyses) and 3468 men who died or were lost to follow-up before reaching 40 years of age or 10 years since hire (see *Analysis*, below). The present study thus included 13130 subjects.

Job histories

Job histories identified 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 classified each of the 8281 unique work area/job title combinations into one of 308 work area/job groups. Each group consisted of processes and jobs considered to be similar with respect to its component tasks and exposure potential.

Exposure estimation

The exposure estimation procedures that were initially developed at UAB and were revised during the present project are described in detail in a companion paper (9). Briefly, we developed quantitative estimates of BD and STY exposure by: 1) identifying for each work area/job group at a plant, historical changes in specific tasks entailing exposure; 2) using mathematical models to calculate plant-, work area/job group- and time-specific average exposures; and 3) linking the resulting estimates with each subject's work history to obtain cumulative exposure estimates.

To develop information on work area/job groups and on historical changes in exposure potential within each group, we conducted in-depth walk-through surveys at each plant, 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 title groups. The interviews provided information on process layout, equipment and material flow, process operations, job titles of workers employed in routine operations or maintenance/cleanup, potential exposure sources and exposure control systems.

We identified tasks that may be associated with exposure, task-specific determinants of exposure (equipment used, duration and frequency of the task, work practices, presence of exposure reduction mechanisms) and identified historical changes in the work area/job title group with respect to exposure determinants.

Next, we determined how a worker would be exposed while performing each task entailing exposure and specified a procedure to calculate the exposure level for a particular exposure scenario. We considered three different exposure scenarios:

1) background exposure resulting from work in buildings, 2) background exposure resulting from work in open areas and 3) exposure originating from a point source of monomer emissions.

For background exposure due to work in buildings, we computed the exposure level using a dilution ventilation formula. The determinants of air concentration in this model were the generation rate (e.g., 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 time unit.

For background exposure due to work in open areas such as a tank farm, we developed a subjective estimate of the exposure level, assuming that exposure was present throughout the work shift at levels higher than in offices or outside the plant.

To calculate exposure originating from a point source, such as exposure during minor maintenance of a pump or during latex sampling from a reactor, we used a near-field air dispersion model. In this model the determinants of air concentrations were the monomer 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 (e.g., the approximate amount of unstripped latex purged plus the sample size for a reactor sample during batch polymerization) and on chemical parameters such as vapor pressure of the chemical and the evaporation surface. Interviews and direct observations provided information on distance. We used three air velocities: 4.4 m/sec for work in open air, on

elevated structures; 2.2 m/sec for work in open air at ground level; and 1.1 m/sec for work in semi-enclosed areas.

We compiled task-specific exposure estimates into a task-exposure matrix and developed algorithms to combine task-specific estimates with background estimates to obtain exposure estimates for each work area/job group in a particular plant. These algorithms considered for each task comprising each work area/job title group, the frequency and duration of the task during an eight-hour work shift. For each work area/job group, we estimated both the eight-hour time-weighted average (TWA) exposure intensity (in ppm) for BD and STY and the annual number of peaks for BD and for STY (i.e., any 15-minute time interval during which average exposure during the interval exceeded 100 ppm for BD or 50 ppm for STY). In addition, we partitioned the eight-hour TWA for BD and STY into exposure at or above the peak level and exposure below the peak level. We linked exposure estimates for each work area/job group with the work histories of individual workers and computed final lifetime cumulative exposure indices. The latter computation involved multiplying the plant- and calendar year-specific amount of time a worker spent in each work area/job group by the exposure estimate for that work area/job group and calendar year category, and summing over all work area/job title groups and years covered by a subject's employment history to obtain cumulative exposure indices, including: 1) BD and STY total ppm-years, 2) BD ppm-years due to exposure below the peak level, 3) BD ppm-years due to exposure at or above the peak level; 4) STY ppm-years due to exposure below the peak level, 5) STY ppm-years due to exposure at or above the peak level; 6) the total number of BD peaks; and 7) the total number of STY peaks.

We conducted an extensive review of exposure estimation procedures for BD and STY and refined the original exposure estimates. The review did not scrutinize benzene in detail because exposure to this chemical was judged to have been low and was unassociated with LHC in previous study analyses. In the review process, a panel of industry and nonindustry experts in industrial hygiene and chemical engineering reached a consensus about factors that are crucial to consider in estimating historical monomer exposures. Consensus development involved comprehensively reviewing the assumptions we had made in estimating exposure at the study plants; compiling a list of questions on assumptions about exposure determinants to be addressed to knowledgeable personnel at each plant; reviewing responses to these questions; and specifying ranges of credible values for exposure determinants. We also revisited all study plants to interview key engineering and process personnel and to obtain additional documentation on work practices, operations and engineering controls. Finally, we carried out a systematic survey of air speeds at specific locations within each plant, to provide realistic input for the near field dispersion models.

Two consultants who participated in the review of the BD and STY estimates developed DMDTC exposure estimates (9). Using an approach similar to that used for BD and STY, they identified plant-specific exposure sources and determinants of exposure (including dermal absorption) and estimated task-specific exposure in various time periods. The dermal DMDTC exposure estimation procedure yielded: 1) an estimate of the concentration of DMDTC in the solution wetting the skin of the exposed worker (in mg/cm^3); 2) an estimate of the skin surface exposed (in cm^2); and

3) an estimate of the frequency and duration of exposure. Thus, the exposure intensity was estimated in $(\text{mg}/\text{cm}^3) \times (\text{cm}^2) = \text{mg}/\text{cm}$. We reviewed the DMDTC exposure data, derived work area/job group- and time-specific average DMDTC exposure intensities (eight-hour TWAs, in mg/cm) and linked these estimates with subjects' work histories to obtain cumulative exposure estimates ($\text{mg}\text{-years}/\text{cm}$), again using procedures similar to those used for BD and STY.

We developed the original BD and STY exposure estimates without knowledge of particular LHC decedents and without knowing LHC decedents' work areas or jobs. However, at the time of the BD and STY exposure estimation review and at the time of the DMDTC exposure estimation, detailed information was available on the plant areas and jobs in which the LHC decedents worked. Thus, although our review of the exposure estimation procedures was systematic and was carried out for all tasks and jobs, the potential for inadvertent bias may have been higher for these estimates than for the original BD and STY estimates.

Vital status and cause of death determination

Information on subjects' vital status as of the end of 1991 came from plant records, from individual tracing and from record linkages with various national and private agencies, including the National Death Index (NDI) and the Social Security Administration Death Master File. Cause of death information came from death certificates (US decedents) and from Statistics Canada (Canadian decedents). For US decedents, nosologists coded the underlying cause of death and other causes mentioned on subjects' death certificates using codes from the Ninth Revision of the International Classification of Diseases (ICD) and coding rules in effect at the time of

death. Statistics Canada data used the ICD revision in effect at the time of death. We attempted to retrieve and review medical records and pathology material pertaining to all subjects whose death certificate mentioned LHC or another blood disorder as a cause of death. For analysis, we included as LHC decedents: 1) those subjects whose medical records confirmed that they had LHC and 2) those subjects whose death certificate indicated that they had LHC as the underlying or a contributing cause of death but whose medical records were unavailable. We classified group 1 according to the form of LHC indicated by the medical record review and group 2 according to the form of LHC indicated on the death certificate.

Analysis

The epidemiologic analysis compared the LHC mortality rate of subjects in a particular chemical exposure category with the rate of unexposed cohort members. We computed mortality rates for all leukemia, for chronic lymphocytic leukemia (CLL), for acute myelogenous leukemia (AML), for chronic myelogenous leukemia (CML), for other forms of leukemia (see table 1 for specific diagnoses), for NHL and for MM. The all-leukemia and NHL categories included subjects whose medical records indicated that they had both CLL and NHL. The number of HD decedents was too small for satisfactory modelling of mortality rates.

No leukemia or NHL decedent died before reaching 40 years of age or before the tenth anniversary of hire. Because we controlled for age and time since hire, person-year accumulation began on the date of reaching 40 years of age, the date of reaching 10 years since hire, the date of accumulating one year of employment or the date of reaching a particular exposure level, whichever was latest, and ended on the

date of leaving a particular exposure category, the death date, the date of loss to follow up or December 31 1991, whichever was earliest.

We used Poisson regression procedures to obtain the maximum likelihood RR for the group in a particular agent/exposure category compared to the group unexposed or having low exposure to that agent. The regression models included indicator terms for all exposure variables and covariates. Models for each agent (BD, STY or DMDTC) included terms for that agent and for age (40-49, 50-59, 60-69, 70-79, 80+) and years since hire (10-19, 20-29, 30+), and some models also included terms for one or both of the other chemicals. Agent exposure indices analyzed in this report were BD and STY ppm-years, DMDTC mg-years/cm, total BD peaks, total STY peaks, BD ppm-years due to exposure to intensities below 100 ppm and BD ppm-years due to exposure to intensities at or above 100 ppm. In most models, we specified exposure categories for each agent as tertiles among exposed leukemia decedents. Some analyses of leukemia also considered exposure categories based on quartiles or quintiles among exposed leukemia decedents. Also, in some analyses we lagged cumulative exposure by five or by 10 years. This procedure makes the assumption that exposure occurring within 10 before death from LHC is etiologically irrelevant.

RESULTS

Vital status was known for over 99% of subjects, and death certificates information was available for 3813 (98%) of 3892 decedents. We obtained medical records for 48 of the 58 leukemia decedents identified from death certificates and for 27 of 31 NHLs, 7 of 8 HDs, 16 of 21 MMs and 7 of 8 other blood disorders. Medical

record review found that one subject whose death certificate indicated NHL actually had pancreatic cancer. All other medical records confirmed an LHC. The records of eight subjects mentioned both leukemia (CLL) and NHL, and we counted these eight as observed events in analyses both of leukemia and of NHL. The records of one subject mentioned both leukemia (unspecified myelogenous) and HD, and we counted this subject as an observed event in analyses of leukemia. One man with a death certificate diagnosis of myelodysplasia had medical records indicating acute unspecified leukemia and was included in leukemia analyses. The final LHC subgroups consisted of 59 leukemias (49 confirmed), 38 NHLs (34 confirmed), 21 MMs (16 confirmed) and nine HDs (eight confirmed).

Proportions of all subjects exposed to the chemicals of interest (cumulative exposure based on TWAs) were 79% for BD, 85% for STY and 62% for DMDTC (table 1). Proportions exposed were generally somewhat higher among leukemia, NHL and MM decedents than among all subjects or all decedents and lower among HD decedents.

Median cumulative exposure values were 68.1 ppm-years for BD, 18.8 ppm-years for STY and 372 mg-years/cm for DMDTC for all subjects and were higher (85.2 ppm-years for BD, 21.1 ppm-years for STY and 828 mg-years/cm for DMDTC) for all decedents (table 1). Compared to all decedents, subjects with leukemia were younger at death, were hired later, worked slightly longer and had median exposure values that were 2.6 times higher for BD, 2.0 times higher for STY and 1.3 times higher for DMDTC. NHL decedents also had higher median exposure values for BD, STY and DMDTC than did all decedents, but these differences were not as great as

for leukemias compared to all decedents. MM decedents, compared to all decedents, had higher median BD ppm-years, similar median STY ppm-years and lower DMDTC mg-years/cm.

Foisson regression analyses using unlagged exposure estimates indicated a consistent positive association between BD ppm-years and leukemia (RRs: 1.0, 1.2, 2.0 and 4.1, respectively, for exposures of 0, >0-<85.9, 85.9-<392.1 and 392.1+ ppm-years) and between STY ppm-years and leukemia (RRs: 1.0, 1.2, 2.5 and 3.0, respectively, for exposures of 0, >0-<23.9, 23.9-<64.4 and 64.4+ ppm-years) after adjusting the RRs pertaining to each chemical for age and years since hire (table 2). For both BD and STY ppm-years, the confidence interval (CI) of RR excluded the null value only for the highest exposure category. DMDTC mg-years/cm was positively associated with leukemia. This association did not display a positive dose-response trend (RRs: 1.0, 2.1, 4.8 and 3.1, respectively, for 0, >0-<555, 555-<1392 and 1392+ mg-years/cm), but the RR for each tertile of exposure was statistically significantly elevated. In analyses that controlled only for age and years since hire, BD total peaks and STY total peaks also were positively associated with leukemia, but neither exposure index displayed a consistent dose-response pattern, i.e., an RR that increased consistently with increasing exposure level.

After adjusting for STY ppm-years and DMDTC, as well as for age and years since hire, there was a weak positive association between BD ppm-years and leukemia (RRs: 1.0, 1.2, 1.3 and 2.9, respectively, for 0, >0-<85.9, 85.9-<392.1 and 392.1+ BD ppm-years; all CIs included the null) (table 3). STY was unassociated with leukemia after adjusting RRs for BD ppm-years and DMDTC. The positive

association, without dose-response, remained for DMDTC after adjusting for BD ppm-years and STY ppm-years in addition to age and years since hire (RRs: 1.0, 2.1, 4.3, 2.2, respectively, for 0, >0-<555, 555-<1392 and 1392+ mg-years/cm). Analyses that incorporated a five-year or a 10-year exposure lag yielded results similar to those described above (table 4). Neither BD total peaks nor STY total peaks was strongly or consistently associated with leukemia after adjusting for other exposures (table 5).

Analyses of partitioned BD ppm-years indicated that the overall association between BD ppm-years and leukemia, unadjusted for STY ppm-years or DMDTC, was attributable entirely to an effect of BD ppm-years due to exposure intensities ≥ 100 ppm, whereas BD ppm-years due to exposure intensities < 100 ppm was not associated with leukemia (table 6). After controlling for DMDTC, none of the RRs for BD ppm-years due to exposure intensities ≥ 100 ppm was statistically significant. Results were similar in models that included BD ppm-years due to exposure intensities ≥ 100 ppm but not BD ppm-years due to exposure intensities < 100 ppm and in models of BD ppm-years due to exposure intensities ≥ 100 ppm that were based on lagged exposures (data not shown).

Further Poisson regression modelling indicated that the association between BD ppm-years and leukemia was reduced in magnitude after adjusting singly, either for STY ppm-years or for DMDTC mg-years/cm (table 7). The RRs for STY ppm-years also were reduced, but remained above the null, after controlling either for BD ppm-years or for DMDTC; however, controlling simultaneously for BD ppm-years and DMDTC changed the direction of the association between STY ppm-years and

leukemia, from positive to inverse. Adjusting DMDTC RRs for BD ppm-years, STY ppm-years or both reduced the magnitude of the association. In all models containing two or three of the exposure variables, the results were imprecise, and the only statistically significant RR was for the second tertile of DMDTC exposure. Analyses based on quartiles of exposure (table 8) or quintiles of exposure (table 9) yielded results similar to those of analyses based on tertiles.

To examine possible interaction between BD ppm-years and DMDTC, we formed three exposure categories for each variable, specified as 1) no exposure plus the first quintile, 2) the second and third quintiles combined and 3) the fourth and fifth quintiles combined. 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 among the group with lowest exposure to DMDTC and vice-versa.

Within the middle and high categories of DMDTC, there was some suggestion that the leukemia RR increased with increasing BD ppm-years, although the dose-response pattern was weak (table 10). The marginal RRs for leukemia, adjusted for age, years since hire and DMDTC, were 1.0 for <38.8 BD ppm-years (referent category), 1.1 (95% CI, 0.5-2.2) for 38.8-<313.8 BD ppm-years and 2.4 (CI, 1.1-5.2) for 313.8+ BD ppm-years.

The relation between DMDTC and leukemia within the middle category of BD ppm-years was irregular. Within the highest category of BD ppm-years the leukemia RR increased with increasing DMDTC, but the dose-response pattern was weak. RRs were 1.0, 4.3 (CI, 1.4-12.9) and 4.7 (CI, 2.3-9.8) for <348, 348-<1236 and 1236+ mg-years/cm. The marginal RRs for leukemia, adjusted for age, years since hire and

BD ppm-years, were 1.0 for <348 mg-years/cm DMDTC, 3.1 (CI, 1.6-6.1) for 348- <1236 mg-years/cm DMDTC and 1.9 (CI, 0.9-4.0) for 1236+ mg-years/cm. No interaction between the two exposures was apparent.

We also examined possible interaction between BD and STY ppm-years, using an approach similar to that used for BD ppm-years and DMDTC (table 11). Data on the effect of BD among subjects with low exposure to STY were largely uninformative. There was some suggestion that the leukemia RR increased with increasing exposure to BD within the middle and high STY exposure categories. The RR appeared to increase with increasing exposure to STY only within the high BD exposure category. The marginal associations (BD, adjusted for STY; STY, adjusted for BD) were consistent both for BD and for STY but were not statistically significant.

The overall associations with BD, STY and DMDTC were not clearly restricted to particular forms of leukemia (tables 12 and 13). However, sparse data made in-depth analyses of exposures in relation to specific subgroups of leukemias largely uninformative.

NHL displayed weak associations with BD ppm-years and STY ppm-years that were reduced when adjusted for the other exposures (table 14). The relation between DMDTC and NHL was weak and irregular. MM was positively associated with BD ppm-years, particularly in analyses that controlled for STY ppm-years and DMDTC, but all of the RRs for BD ppm-years and MM were statistically imprecise and included the null value (table 15). STY ppm-years and DMDTC did not appear to be associated with MM.

DISCUSSION

This study found that leukemia was positively and statistically significantly associated with BD ppm-years in analyses that did not control for STY ppm-years or for DMDTC. Controlling for either of the latter two exposures reduced the magnitude of the association for BD and increased the imprecision of the RR estimates. Similar results were observed for STY ppm-years and for DMDTC, although the association between STY and leukemia disappeared completely after adjusting for the other two agents.

The three exposures were highly correlated, and it was, therefore, difficult to determine which ones are truly related to the occurrence of leukemia and, consequently, which ones might act as confounders. Both BD ppm-years and STY ppm-years displayed a consistent dose-response pattern in single exposure models, but for each chemical this pattern was weakened in analyses that controlled for the other agent. Further adjustment for DMDTC did not substantially alter the data for BD (also adjusted for STY), but did have a marked impact on the RRs for STY (also adjusted for BD), changing its association with leukemia from positive to inverse.

BD is an established animal carcinogen (1, 11-20), but results from studies of BD monomer production workers contradict the hypothesis of a causal link between BD and leukemia (21-26). The contradictory epidemiologic data are rather sparse and do not include an evaluation of quantitative BD exposure estimates (21-26) but nonetheless suggest that BD alone might not be sufficient to cause leukemia in humans. The results of the present study do not clarify this possibility, as few data were available on the effect of BD in groups with low exposure to STY or low exposure to DMDTC. If BD is carcinogenic, our data suggest that in humans

exposure to high BD intensity levels (in the present analysis, above 100 ppm) may be of more etiologic importance than lower levels of exposure. While the data are consistent with the presence of a threshold of effect, uncertainty about the validity of the quantitative BD exposure estimates precludes making a definite statement that exposure levels below 100 ppm are safe. Additional analyses based on credibility ranges developed for the BD exposure estimates and a systematic evaluation of alternative exposure thresholds may clarify this issue. Our data also suggest that the effect of BD is not limited to a specific form of leukemia, although our evaluation of this issue was hampered by missing data on the histologic classification of some of the leukemia cases and by statistical imprecision.

The health effects of STY have been evaluated extensively among workers with exposure levels presumably considerably higher than in the subjects of the present study (27-36). These investigations reported increases in leukemia, NHL and/or other LHC in some subgroups of workers, but the pertinent results were difficult to interpret because of small numbers of observed and expected deaths, because of a lack of consistent duration-response patterns and because of methodologic limitations regarding exposure assessment and control of confounding by other chemicals present in the occupational settings that were studied. On balance, STY in the absence of BD does not appear to cause leukemia. The present study supports this observation and cannot disentangle a possible effect of STY from a possible effect of BD among persons exposed to both chemicals.

DMDTC, although positively associated with leukemia, did not display dose-response. This pattern has several alternative interpretations: 1) DMDTC is a cause

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of leukemia, but exposure to this chemical was inadequately estimated in the present study, with measurement bias dampening a true dose-response; 2) DMDTC is a cause of leukemia, with the biological response approximately equal in all of the exposure categories that we examined; or 3) the apparent relationship between DMDTC and leukemia is noncausal, with a systematic measurement bias having produced rather a strong, but spurious, association in each of the nonzero exposure categories that we evaluated. We have little information to support or refute any of these interpretations. Although DMDTC is an immune system depressant (4), there is no evidence that this chemical is carcinogenic. Elucidation of the human health effects of DMDTC will require epidemiologic investigation in other exposed groups.

The present study found little evidence to support or refute an association between BD, STY or DMDTC and NHL or MM. RRs for NHL were elevated in several exposure categories of BD, STY and DMDTC, but results were imprecise, even in analyses that assessed a single agent at a time. The data on MM indicated a positive association with high exposure to BD ppm-years, but again the data were unpersuasive because of imprecision.

Matanoski et al., investigating a cohort that contained many of the same subjects included in our study but using different exposure estimation procedures, reported that STY was positively associated with NHL and with MM but not with leukemia (37). Our results do not support the findings of Matanoski et al. for STY and NHL or MM.

In summary, we obtained medical records of deceased synthetic rubber industry workers with LHC and blood disorders, used extensively revised BD and

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STY exposure estimates to reassess relations between these agents and LHC and evaluated DMDTC as a possible cause of leukemia and as a possible confounder and effect modifier of the BD-leukemia association. Medical records substantiated a high proportion of LHC decedents. Analyses based on the revised BD and STY exposure data confirmed a positive association between BD and leukemia. Both STY and DMDTC also were positively related to leukemia, and one or both may have partially confounded the association with BD. However, neither the present study nor other research provides compelling evidence that STY and DMDTC are leukemogens. Thus, their role as confounders of the association between BD and leukemia remains uncertain. This study did not find any clear association between the BD, STY or DMDTC and NHL or MM.

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