



October 24, 1997

VIA FEDERAL EXPRESS

Dr. Larry G. Hart
Executive Secretary
National Toxicology Program
Report on Carcinogens (MD WC-05)
111 Alexander Drive
Research Triangle Park, NC 27709

**Re: Review of 1,3-Butadiene for NTP's
Biennial Report on Carcinogens**

Dear Dr. Hart:

As we let you know by phone earlier this week, Dr. John F. Acquavella will be speaking for the International Institute of Synthetic Rubber Producers (IISRP) at the Board of Scientific Counselors' meeting on October 30. Enclosed is his full presentation, which he will summarize at the meeting.

Dr. Acquavella will be discussing the human studies of cancer and butadiene. We urge NTP and the Board to scrutinize carefully the epidemiology studies and to consider the inconsistencies and uncertainties in the existing database, as detailed by Dr. Acquavella. None of these inconsistencies and uncertainties are highlighted in the NTP staff write-up, but each is central to assessing whether there is sufficient evidence to reclassify butadiene, and each should be included in the final NTP assessment of the evidence.

As Dr. Acquavella details, the results of the epidemiology studies are not consistent. The Delzell styrene-butadiene rubber (SBR) worker study found a coherent, dose-related association between leukemia and estimated butadiene exposure, but no association with lymphosarcoma/non-Hodgkin's lymphoma (NHL). Previous studies of SBR workers either showed no association with leukemia or were plagued with methodologic problems. In addition, no association of butadiene with leukemia has been found in the studies of monomer workers. Although some subgroups had lymphosarcoma/NHL excesses in the monomer worker studies, there was no lymphosarcoma/NHL excess in the Delzell study, nor was there a dose-response relationship in the monomer worker studies.

Dr. Larry G. Hart
October 24, 1997
Page 2

The issue for NTP and the Board is whether this inconsistent evidence is, as specified in the statute, "sufficient" for listing butadiene as a known carcinogen. NTP and the Board should consider separately the evidence for an association between butadiene exposure and the various lymphatic and hematopoietic cancers. We urge a conclusion that the evidence is insufficient for each type of cancer because of the inconsistencies and weaknesses in the evidence with respect to lymphosarcoma/NHL and because, with respect to leukemia, a single study should not be deemed adequate to reach a statutory determination of "sufficient evidence" of causality.

We especially urge the adoption of a criterion requiring evidence from more than one study in light of an uncertainty in the Delzell study that is directly relevant to the classification determination and that requires further study. Still to be fully explored are possible confounding exposures in styrene-butadiene rubber (SBR) facilities. We thus urge the Board to consider carefully the comments being presented by the Chemical Manufacturers Association Olefins Panel with respect to their on-going research on possible confounding exposures unique to the SBR industry.

As our August 20, 1997, letter to Dr. Jameson noted, IISRP has two on-going projects to shed further light on the Delzell study results: (1) an analysis of the cell types of the leukemia decedents; and (2) a reassessment of the exposure estimation methodology and results. We look forward to a continuing dialogue with NTP and its Board of Scientific Counselors as they review butadiene. As further information becomes available on our research programs, we will forward it.

Sincerely yours,



Richard Killian
IISRP Managing Director

Review of Butadiene Epidemiology as Presented in
NTP's Biennial Report on Carcinogens

October 27, 1997

John F. Acquavella, PhD

**On Behalf of the International Institute
of Synthetic Rubber Producers**

Executive Summary

The National Toxicology Program's (NTP 1997) review for 1,3-butadiene (hereafter butadiene) characterizes the epidemiologic evidence to "have consistently found excess mortality from lymphatic and hematopoietic (LHC) cancers associated with occupational exposure to butadiene." This characterization reflects a selective culling of positive results from the individual studies and neglects significant methodologic issues that have been discussed in a number of published papers (Acquavella 1989, Cole et al. 1993, Acquavella 1996, Himmelstein et al. 1997).

The evidence linking butadiene exposure and cancer is clearly best for leukemia. This conclusion is based on a large, high quality cohort study of styrene butadiene rubber (SBR) workers which found an excess of leukemia and an exposure-response relationship with estimated butadiene exposure (Delzell et al. 1995, Delzell et al. 1996, Macaluso et al. 1996). Earlier cohort studies of (practically) the same SBR workers (Meinhardt et al. 1982, Matanoski et al. 1990) had found essentially null results for leukemia and no indication that mortality increased with duration of employment.¹ Both Meinhardt and colleagues

¹ Meinhardt and colleagues (1982) studied one plant from the Delzell et al. (1995) study (actually it was two contiguous plants at the time of the Meinhardt study), and Matanoski and colleagues (1987 and 1990) studied seven plants later studied by Delzell and colleagues and one additional small plant that could not be included in the latter study.

(1982) and Matanoski and colleagues (1990) reported elevated leukemia mortality based on very small numbers for a presumably exposed subgroup. But other presumably exposed subgroups in these studies had null or sub-null leukemia results. Various authors have interpreted these results differently (*Acquavella 1996 details the different perspectives*); the proponents of a causal relationship (e.g. *Landrigan 1993*) made unverifiable assumptions about higher exposure potential for the subgroups with positive findings.

As NTP mentions, a nested case control study, based on the larger SBR workers cohort study (*Matanoski et al. 1990*), reported a strong relationship between semi-quantitative estimates of butadiene exposure and leukemia with two separate control groups (*Matanoski et al. 1989 and 1993, Santos-Burgoa et al. 1992*). But the magnitude of the odds ratio (OR) in both instances (approximately 8.0) was so great as to be inconceivable given the overall near null leukemia cohort results (22 observed, 22.9 expected) (*Cole 1990, Cole et al. 1993*). The subsequent moderate exposure response relationship reported by Delzell and colleagues (1995, *Macaluso et al. 1996*), based on detailed quantitative exposure estimates, further questions the validity of the very high ORs from the case control analyses by Matanoski and colleagues. It has also become apparent that 40% of the cases and controls in the case control study came from a plant where more than 2,000 non-SBR workers were included inadvertently in the SBR worker population (*see Himmelstein et al. 1997 for details*).

These major methodologic issues need to be addressed before the results of the case control study can be interpreted at face value.

Thus, other than the study by Delzell and colleagues (1995 and 1996, Macaluso et al. 1996), leukemia results for SBR workers are, at best, equivocal. The study by Delzell and colleagues (1995 and 1996, Macaluso et al. 1996) supersedes those previous studies and rectifies many of the limitations and errors of those earlier studies. The study provides coherent evidence of a causal relationship between butadiene exposure and leukemia including the presence of an exposure response relationship, the finding of elevated leukemia mortality for process groups estimated to have high butadiene exposure, and the finding of elevated mortality, though sometimes slight, at most plants in the study. But, there has not, as yet, been a high quality study which confirms these findings. In fact, several studies of butadiene monomer workers report null results for leukemia (Divine and Hartman 1996, Ward et al. 1995, Cowles et al. 1994). Thus, the major limitation of the butadiene epidemiologic literature from a causal perspective for leukemia is the dependence on one quality positive study.

The available evidence is much weaker for a causal relationship between butadiene and other LHCs. Lymphosarcoma and reticulum cell sarcoma (hereafter lymphosarcoma) have been found to be elevated in one study of monomer workers (Divine and Hartman 1996) and one very small study of workers involved in short lived monomer operations within three multi-purpose

chemical complexes (Ward et al. 1995). On the other hand, lymphosarcoma was not elevated in the SBR cohort which had excess leukemia (Delzell et al. 1995 and 1996) or in several other small studies of butadiene exposed workers (Cowles et al. 1994, Bond et al. 1992, Downs et al. 1993). Further, there was no indication of an exposure response relationship in the larger butadiene monomer worker study for lymphosarcoma or non-Hodgkin's lymphoma (NHL) (Divine and Hartman 1996) or, more importantly, in the SBR workers study where there was a leukemia excess (Delzell et al. 1995). These points deserve consideration in the NTP review. On balance, then, there is insufficient evidence to link butadiene exposure and lymphosarcoma/NHL.

In summary, the epidemiologic literature for butadiene shows variable results for LHCs. The evidence for leukemia is not consistent across studies, though one large study (Delzell et al. 1995 and 1996, Macaluso et al. 1996) provides credible, internally consistent evidence of a relationship with butadiene exposure. The evidence for lymphosarcoma/NHL is not consistent with a causal relationship with butadiene exposure. While two studies show elevated mortality among short term butadiene monomer workers (Divine and Hartman 1996, Ward et al. 1995), the larger study did not find excess mortality for long term exposed workers and there was no exposure response relationship. In addition, none of the SBR workers studies to date provide evidence to suggest a relationship between butadiene and NHL. Accordingly, the butadiene epidemiologic literature should not be

characterized as showing a consistent relationship between butadiene exposure and the various LHCs.

Introduction

Epidemiologic research relevant to butadiene has focused on two industries: the styrene-butadiene rubber (SBR) industry and the butadiene monomer industry. Little is known about historical exposures in these two industries and, in fact, only one study (of SBR workers) estimated historical exposures quantitatively. This makes it difficult to focus attention on the highest exposed workers and affords the opportunity for considerable subjectivity on the part of reviewers. Thus, it is relatively easy to selectively cull results to support a particular viewpoint. However, a comprehensive review seems warranted when a government agency is considering an official change in classification for a chemical or substance. Inconsistencies between studies and uncertainties need to be clearly identified and adjudicated, if possible, in order to develop the most credible conclusion from the available data. Herein, I will describe the inconsistencies and uncertainties that are particularly pertinent.

SBR worker studies

The two initial SBR cohort studies (*Meinhardt et al. 1982, Matanoski and Schwartz 1987*) included all 10 SBR plants which were still in operation in 1976. Nine of the plants were built during World War II as a joint government/industry program critical to the War effort. According to the Occupational Safety and Health Administration (OSHA) "At that time the federal government undertook to construct 15 plants all of which had similar design and all of which were committed to the manufacture

of styrene BD rubber." (OSHA 1990). Thus, the SBR studies address a somewhat unique research situation whereby all but one of the plants were contemporaneous and had similar initial design and environmental characteristics.

The initial SBR workers study, by Meinhardt and colleagues (1982), evaluated mortality patterns from 1943-1976 for 2,756 non-administrative white male workers employed at least six months at two SBR plants (Plants A & B). The study was initiated in response to two leukemia deaths among former employees of these plants, though neither of the employees met the employment duration criterion for inclusion in the study. Exposure measurements (8 hour time weighted averages (TWA)) taken as part of the study averaged 1.2 ppm in plant A based on 41 samples and 13.5 ppm for plant B based on 47 samples.²

Mortality analyses by Meinhardt and colleagues (1982) found 56 cancer deaths (versus 78.1 expected) and 11 LHC deaths (versus 8.3 expected). For specific LHCs, there were 6 observed and 3.5 expected leukemias, 4 observed and 2.4 expected lymphosarcomas, and there were no deaths and 1.1 expected in the category "other lymphatic cancers."³

² It is unlikely that this is a good representation of historical exposures at the two plants. There is reason to believe that historical exposures did not differ greatly across plants due to similarities in design and operation, especially during the early (presumably high exposure) years of the SBR industry. Current monitoring data should be considered a questionable basis for comparing historical exposures.

³ Other lymphatic cancers is a non-specific LHC category which includes primarily NHL (other than those specified under the

Analyses of LHC mortality rates by plant showed variable findings. Rates were elevated for workers in plant A, but not for workers in plant B. In plant A, all 9 LHC deaths occurred in a subgroup of 600 men who had worked during the period 1943-1945. The authors highlighted this finding because the period 1943-45 corresponded to production of SBR by a hot batch polymerization process which was presumed to involve higher butadiene exposures, at least during polymerization, than later processes.⁴ There were 5 leukemia deaths in this subgroup versus 1.8 expected (standardized mortality ratio (SMR) = 2.8, 95% confidence interval (CI) 0.9-6.5), 3 lymphosarcoma deaths versus 1.3 expected (SMR = 2.2, 95% CI 0.5-6.5), and no deaths from other lymphatic cancers versus 0.6 expected. In plant B, from 1950-76⁵, there were 2 deaths from LHCs versus 2.6 expected (SMR = 0.8, 95% CI 0.1-2.8); 1 was a leukemia death versus 1.0 expected (SMR = 1.0, 95% CI 0-5.6).

The authors detailed characteristics of the leukemias at both plants. Two review articles (*Acquavella 1989, Cole et al. 1993*)

rubric lymphosarcoma/ reticulosarcoma) and multiple myeloma.

⁴ In fact, hot batch polymerization at plant A continued well past 1945 as determined during a detailed industrial hygiene review and exposure estimation by Delzell and colleagues (*Delzell E. personal communication*).

⁵ Plant B operated from 1943-47 and closed until 1950. At that time, it was reopened and has operated to the present day. Complete personnel records could not be located for the 1943-47 period, so cohort enumeration and mortality analyses began in 1950.

noted that two of the five leukemia decedents from plant A and the one leukemia decedent from plant B had very limited SBR employment (0.6, 1.5, and 0.8 years, respectively) and extremely short intervals from first employment until death (3, 3, and 4 years, respectively). These short "induction-survival" times were characterized by Cole et al. (1993) as insufficient for the leukemias to be related to SBR employment. This premise is supported by findings from the much larger SBR workers study by Matanoski et al. (1989) where the interval from first employment till death for leukemia decedents ranged from 15-38 years for those hired 1943-49 - a period which includes the hot batch polymerization years.

Both plants studied by Meinhardt and colleagues (1982) are included in the recent study by Delzell and colleagues (1995 and 1996). The latter study has much longer follow-up and more detailed evaluation of work histories and exposures. It makes sense, therefore, to refer to the more recent study for findings relative to these SBR workers. But, in retrospect, the findings by Meinhardt and colleagues (1982), per se, provide little evidence of a relationship between butadiene exposure and leukemia.

Matanoski and colleagues

Matanoski and Schwartz (1987, updated as Matanoski et al. 1990) conducted a cohort study which included 12,110 workers employed at least 1 year from 8 SBR plants, 7 in the U.S. and 1 in Canada. The Canadian SBR plant, in Sarnia, Ontario, was unlike

the U.S. plants in that it was part of a large multi-purpose petrochemical facility. Over the years, the facility housed units devoted to SBR, styrene and butadiene monomer production, alkylbenzenes, polybutadiene rubber, butyl rubber, polystyrene, and other operations.

Matanoski and colleagues (1988, 1990) appear to have incorrectly enumerated the SBR workforce of the Canadian plant. According to the 1988 unpublished report on this study (Matanoski et al. 1988), the Canadian SBR plant population included 4,364 workers, 3,055 of whom were vested (viz. employed 10 or more years or at least 45 years of age during employment). Yet, the largest U.S. plant had only 2,110 workers. Records of production capacity showed that the Canadian plant was much smaller than many of the U.S. plants. For example, the Canadian plant produced about half as much SBR during World War II than the largest U.S. SBR plant and it had roughly half the SBR capacity thereafter (see Himmelstein et al. 1997 for details). An independent enumeration of the Canadian SBR population by Delzell and colleagues (1995) found more than 2,300 workers who either did not work in butadiene-related departments or whose work histories were non-specific with respect to department. The inevitable conclusion is that a large number of workers were mistakenly considered to be SBR workers, when they probably worked elsewhere in the Canadian complex. Since the Canadian plant accounted for more than 40% of the LHCs in the cohort study by Matanoski and colleagues (1990) and in the nested LHC case control analyses by

Santos-Burgoa et al. (1992) and Matanoski et al. (1989, 1993), the probable inclusion of a large number of ineligible workers, incorrectly presumed to be SBR workers, raises questions about the validity of these studies.

This issue aside, the cohort study by Matanoski and colleagues (1990) found mortality from LHCs to be similar to general population rates. This included the LHC subcategories leukemia (22 observed, 22.9 expected, SMR = 1.0, 95% CI 0.6-1.5), lymphosarcoma (7 observed, 11.5 expected, SMR = 0.6, 95% CI 0.2-1.3), and other lymphatic cancers (17 observed, 15.3 expected, SMR = 1.1, 95% CI 0.6-1.8).⁶ Analyses by duration of employment did not find trends for LHCs or other causes of death.

Matanoski and colleagues (1990) also reported analyses for 4 subgroups on the basis of each worker's longest job. The subgroups described were as follows:

- production - jobs involved in the production of SBR;
- maintenance - workers in various trades;
- utilities - workers in plant support activities and not involved in the production of SBR; and

⁶ In light of the questions about the Canadian plant population, it would be informative to look at the results for the U.S. plants in the study. These results have never been presented, though results have been reported for the four (of 7) U.S. plants that had complete records (Matanoski et al. 1988). SMRs were: 0.7 for all LHCs (24 observed, 35 expected, 95% CI 0.4-1.0), 0.7 for leukemia (10 observed, 13.5 expected, 95% CI 0.4-1.4), and 0.2 for lymphosarcoma (2 observed, 7.0 expected, 95% CI 0-1.0).

other - largely administrative and support personnel with no plant duties.

The most important findings from the work area analysis were those for production and maintenance workers. These subgroups have a high proportion of workers with potential for butadiene exposures (*McGraw 1990*).

LHC analyses for production workers showed marked differences by race. White production workers had SMRs of 0.8 for leukemia (4 observed, 4.8 expected, 95% CI 0.2-2.1), 0 for lymphosarcoma (0 observed, 2.4 expected, 95% CI 0-1.5) and 2.3 for other lymphatic cancers (7 observed, 3.1 expected, 95% CI 0.9-4.7). On the other hand, black production workers had elevated mortality from leukemia (3 observed, 0.5 expected, SMR = 6.6, 95% CI 1.4-19.1) and other lymphatic cancers (2 observed, 0.4 expected, SMR = 4.8, 95% CI 0.6-17.6). Four of the five black production worker LHC decedents had very short periods of employment: 1.3, 1.3, 2.0 and 3.8 years, respectively (*Matanoski et al. 1989*).

The results of this work area analysis have been incorrectly characterized as showing a significantly elevated risk for leukemia among production workers (*NTP 1997*). While that characterization is correct for black production workers, it clearly is not true for white production workers (4 observed, 4.8 expected) or for the combined production worker population (7 observed, 5.3 expected, SMR = 1.3, 95% CI 0.5-2.2).⁷ In addition,

⁷ It has been noted that 2,391 workers, or 20% of the cohort, were excluded from the work area analyses because one or more

mechanical workers, a second subgroup with a high proportion of exposed workers, had fewer LHC deaths than expected for both blacks and whites. In contrast to the findings for production workers, there were no LHCs for black maintenance workers versus 2.1 expected (*Matanoski et al. 1988*).

On balance, then, the results of this cohort study do not

jobs was missing from their work histories (*Acquavella 1990b, Cole et al. 1993*). These exclusions turned out primarily to be active U.S. workers (*Matanoski et al. 1988*) who had extremely low SMRs (*Acquavella 1990b*). For example, the all causes SMR was 0.4 (161 observed, 422.1 expected, 95% CI 0.3-0.5) and the leukemia SMR was 0 (0 observed, 4.5 expected, 95% CI 0-0.8). The effect of excluding these workers, a form of selection bias, was to inflate the SMRs by work area. *Acquavella (1990b)* estimated the production worker leukemia SMR would have been 1.1 (7 observed, 6.3 expected, 95% CI 0.4-2.3) had these workers not been excluded incorrectly from the analysis.

support a relationship between butadiene exposure and leukemia unless an inordinate amount of weight is given to the findings for black production workers and findings for white production workers and black and white maintenance workers are ignored. The results are also not supportive of a relationship between butadiene exposure and NHL.

NTP (1997) has cited a 1993 reanalysis of this study which found elevated LHC mortality, especially for leukemia, among long term workers in three of the SBR plants (Matanoski et al. 1993). These three plants had higher geometric mean exposure monitoring data in the 1970s and 1980s than the other five SBR plants. NTP considers this to be evidence supporting a relationship between butadiene exposure and leukemia.

Acquavella et al. (1994) previously characterized this new analysis as being of uncertain relevance. The reasons for this characterization were two-fold. First, the exposure data cited by Matanoski and colleagues were not collected to estimate exposure similarly across plants. They were collected presumably for reasons specific to the individual plants. Second, historical exposures are obviously more relevant than recent measures for etiologic inferences for leukemia and recent monitoring data, ipso facto, is a questionable basis for comparing historical exposures across plants. Further, it is likely that exposures during the early years of the industry did not differ greatly across plants. Delzell and colleagues did not estimate significant differences in exposure for the three plants in

question based on a thorough industrial hygiene review and exposure modeling effort (Delzell et al. 1995).

LHC nested case control study

In order to further investigate a potential relationship between LHC and butadiene exposure, Matanoski and coworkers (1989 and 1993, Santos-Burgoa et al. 1992,) conducted a case control study "nested" within their SBR workers cohort study. Relative exposure to butadiene and styrene was estimated by a panel of industrial engineers who ranked a condensed list of jobs across the 8 plants on a 1 to 10 scale. Rankings were based on the engineers' memories of how the plants operated over the years. The exposure rankings were linked to individual jobs held by the cases and controls. A cumulative butadiene exposure score was then derived as the sum of the products of the exposure ranks and the length of time in individual jobs.

The OR served as the measure of association between butadiene exposure and the various LHCs.⁸ The ORs for butadiene exposure in excess of the geometric mean butadiene score were 7.6 (95% CI 1.6-35.6) for leukemia, 0.5 (95% CI 0.1-4.2) for lymphosarcoma, 1.5 (95% CI 0.5-4.8) for other lymphatic cancers, and 1.1 (95% CI 0.2-5.2) for Hodgkin's disease.

The elevated OR for leukemia, in contrast to the near null ORs for the other LHCs, suggests a strong relationship with

⁸ The OR is the ratio of exposure odds for cases and controls and serves as an unbiased estimator of the relative risk that would be calculated from a cohort study (Rothman 1986).

butadiene exposure. Sixty percent of the leukemia controls were classified as exposed in this analysis, suggesting, if the controls are representative of the base cohort, that the elevated RR applied to a majority of the study population. Matanoski et al. (1989, Santos-Burgoa et al. 1992) also reported a significant exposure-response trend and concluded that the data supported a relationship between butadiene exposure and leukemia. A reanalysis using a different control group found a similar strong association between the butadiene exposure score and leukemia (Matanoski et al. 1993).

This interpretation of these leukemia results has been questioned (Acquavella 1989, Cole et al. 1993, Acquavella and Cowles 1993) because the base cohort study, from which the case control study derives, did not have an excess of leukemia (22 observed, 22.9 expected). Accordingly, Cole et al. (1993) asserted that the case control findings are statistically incompatible with the findings of the base cohort study. They based this viewpoint on calculations which projected the number of leukemias which should have been seen in the base cohort study if the case control findings were valid.

According to Cole et al.'s calculations, if sixty percent of the cohort had a true relative risk of 7.6, this should be manifest as approximately 104 observed leukemias (viz. $(7.6) \times (60\%) \times (22.9 \text{ expected leukemias for the cohort})$). The remaining unexposed 40% of the cohort would have 9.2 expected leukemias (i.e. $40\% \times 22.9 \text{ expected leukemias for the cohort}$). Thus, there

should have been a total of approximately 113 leukemias for the base SBR workers cohort. However, only 22 leukemias were actually observed. Cole et al. (1993) presented additional analyses to allow for variability in both the exposure prevalence (down to 25%) and the OR (down to 4.0) and concluded that there is no reasonable combination which resolves the incompatibility between the cohort and case control studies.

Matanoski and Santos-Burgoa (1994) disagreed with Cole et al.'s (1993) criticism. They argued that the 60% control exposure prevalence from the case control study overestimated exposure prevalence for the base cohort because the matching criteria used in control selection probably produced controls who were not representative of the base SBR population. Cole et al, had addressed this issue, however, by considering a range of exposure prevalences and ORs. Even at exposure prevalences as low as 25%, the case control results equate to 63 leukemias in the cohort study: well in excess of the 22 observed.

It would take an exposure prevalence of approximately 3% to reconcile the findings for the case control and cohort studies. However, if 3% were the true exposure prevalence, 19 of 22 leukemia deaths would have to have occurred in this small part of the SBR cohort (since 88% of the cases were exposed above the geometric mean butadiene score). This would mean that there were only 3 leukemia deaths among the remaining 97% of the study population. The expected number for these workers is approximately 22 leukemia deaths. This would be a very unusual

finding. In fact, the probability of observing 3 deaths when 22 are expected is 0.000002. The 3% exposure prevalence is also refuted by the quantitative exposure estimation done in the study by Delzell and colleagues (1995).

Thus, despite the fact that two separate case control analyses by Matanoski and colleagues (1993, Santos-Burgoa et al. 1982) found ORs of approximately 8.0, these results are nonetheless statistically irreconcilable with the results of the underlying cohort study. This raises concern about systematic error common to both case control analyses. Thus, this study cannot be taken as credible evidence of a relationship between leukemia and butadiene exposure until the discrepancy between the cohort and case control results is resolved.

Delzell et al.

The largest, most comprehensive study of butadiene exposed workers was recently completed by Delzell and colleagues (1995 and 1996, Macaluso et al. 1996). This retrospective follow-up study of SBR workers includes 7 of the 8 plants studied by Matanoski et al. (1990) and the two plants, subsequently combined into one plant, studied by Meinhardt et al. (1982), and extends mortality follow-up through 1991. This study also addresses many of the major limitations cited about the previous SBR studies (Acquavella 1990a, Landrigan 1990) and, importantly, includes a detailed evaluation of LHC mortality patterns in relation to quantitative estimates of exposure to butadiene and styrene.

The study population was restricted to men who had worked at the subject SBR plants for at least 1 year as of January 1, 1992. Based on these criteria, 15,649 SBR workers were included in this study. At the one Canadian facility, which was the only plant with substantial non-butadiene related manufacturing operations, another 2,315 men were enumerated who worked only in non-SBR departments or in unspecified parts of the plant. These men were not included in SMR analyses of SBR workers - a small proportion had potential butadiene and/or styrene exposure and the remainder were included as unexposed workers (to butadiene) in certain within-cohort analyses.

For the total cohort, the SMRs for all causes of death and all cancers were 0.9 (3,976 observed, 4570.1 expected, 95% CI 0.8-0.9) and 0.9 (950 observed, 1021.5 expected, 95% CI 0.9-1.0) respectively. Workers employed 10 or more years and followed for at least 20 years since first employment had similar findings. SMRs for LHCs indicated a slightly elevated rate for leukemia (48 observed, 36.6 expected, SMR = 1.3, 95% CI 1.0-1.7), but not for lymphosarcoma (11 observed, 13.8 expected, SMR = 0.8, 95% CI 0.4-1.4) or other lymphatic cancers (42 observed, 43.3 expected, SMR = 1.0, 95% CI 0.7-1.3). For leukemia, the SMR increased substantially when restricted to hourly workers employed 10 or more years and followed for at least 20 years (28 observed, 12.5 expected, SMR = 2.2, 95% CI 1.5-3.2), but the same pattern was not seen for lymphosarcoma (4 observed, 3.9 expected, SMR = 1.0,

95% CI 0.3-2.6) or other lymphatic cancers (17 observed, 16.0 expected, SMR = 1.1, 95% CI 0.6-1.7).

Leukemia SMRs for hourly workers varied by duration of employment, year of hire, and by time period over the course of the study. Leukemia mortality was not elevated for workers employed less than 10 years (15 observed, 15.8 expected, SMR = 0.9, 95% CI 0.5-1.6), but was elevated for workers employed 10-19 years (11 observed, 6.5 expected, SMR = 1.7, 95% CI 0.8-3.0) and 20 or more years (19 observed, 9.3 expected, SMR = 2.0, 95% CI 1.2-3.2). The majority of the leukemia excess occurred among workers hired in the 1950s (20 observed, 10 expected, SMR = 2.0, 95% CI 1.2-3.1) and the elevated mortality was manifest mostly in the 1985-91 time period (18 observed, 9.6 expected, SMR = 1.9, 95% CI 1.1-3.0). This suggests a long period between first employment in the industry and mortality from leukemia; the excess leukemia emerged with the extended follow-up period of this study. Twenty four of the 48 leukemia deaths occurred subsequent to the previous studies by Meinhardt et al. (1982) and Matanoski et al. (1990) (*E. Delzell, personal communication*).

Analysis of cancer incidence

Although the main thrust of this study (*Delzell et al. 1995 and 1996*) was analysis of mortality patterns, cancer incidence data were evaluated over the period 1965 through 1992 for workers at the lone Canadian facility based on diagnoses and general population rates from the Ontario Cancer Registry. For all cancers, there were 304 incident cases and 290 expected

(standardized incidence ratio (SIR) = 1.0, 95% CI 0.9-1.2).

There were essentially null results for the various lymphopoietic cancers: leukemia (9 observed, 9.1 expected, SIR = 1.0, 95% CI 0.5-1.9, non-Hodgkin's lymphoma 12 observed, 11 expected, SIR = 1.1, 95% CI 0.6-1.9, and multiple myeloma 5 observed, 3.8 expected, SIR = 1.3, 95% CI 0.4-3.1. Thus, the leukemia excess seen in the mortality analyses is not seen in the incidence analysis of SBR workers at this one plant.

Process group analyses

The relationship between mortality rates and exposures to butadiene and styrene was evaluated more specifically by analyses of subgroups in specific departments (called process groups). The authors categorized workers into one of the following five process groups based: rubber production, maintenance, labor, laboratories, and other operations. Mortality analyses were restricted to the six largest plants which had detailed work history information.

Production workers had slight relative deficits of mortality from all causes, all cancers, lymphosarcoma, and other lymphatic cancers. Leukemia mortality was found to be elevated (SMR = 1.7, 95% CI 1.0-2.6) overall and for subgroups of production workers, specifically polymerization (SMR = 2.5, 95% CI 1.4-4.1) and coagulation (SMR = 2.5, 95% CI 1.0-5.1). Laboratory workers showed deficits of mortality from all causes, all cancers, lymphosarcoma, and other lymphatic cancers. Leukemia mortality, however, was markedly elevated for laboratory workers (10

observed, 2.3 expected, SMR = 4.3, 95% CI 2.1-7.9). Maintenance workers showed near null results for all causes, all cancer, leukemia, and a moderate deficit of other lymphatic cancers. They also showed a moderate elevation of mortality from lymphosarcoma (SMR = 1.9, 95% CI 0.8-3.8). Finally, laborers had deficits of mortality from all causes and near null findings for all cancer, lymphosarcoma, and other lymphatic cancers. Leukemia mortality was elevated for these workers, primarily among those classified as maintenance laborers (13 observed, 4.9 expected, SMR = 2.7, 95% CI 1.4-4.5) and not among those classified as production laborers (3 observed, 2.3 expected, SMR = 1.3, 95% CI 0.3-3.8).

Analyses by quantitative estimates of exposure

Delzell and colleagues (1995, 1996, Macaluso et al. 1996) estimated exposure to butadiene and styrene as the sum of background work place exposures and exposures related to specific tasks. The primary exposure metric was the estimated 8 hour TWA exposure. Delzell and colleagues reported an exposure-response trend of increasing leukemia RR with increasing butadiene exposure. Elevated mortality was apparent in the 20-99 ppm-year category (RR = 1.8, 95% CI 0.6-5.4), and in the higher exposure categories of 100-199 ppm-years (RR = 2.1, 95% CI 0.6-5.4), and 200+ ppm-years (RR = 3.6, 95% CI 1.0-13.2)⁹. Styrene (and benzene) exposure did not confound the butadiene-leukemia

⁹ Macaluso et al. (1996) present a slightly different categorization of these data.

association. Leukemia SMRs also increased with increasing styrene exposure. However, this apparent trend appears due to confounding by butadiene as evidenced by the lack of trend in the Poisson regression analysis which controlled for butadiene exposure.

Delzell et al.'s (1995, 1996) study provides the first internally consistent evidence of a relationship between butadiene exposure and leukemia. The study design and implementation, particularly the effort to estimate workers' exposures, address many criticisms of previous epidemiologic studies of butadiene exposed workers (Acquavella 1990a, Landrigan 1990). The leukemia excess resulted primarily from increased mortality over the last ten years of the study period, a presumptive manifestation of a long induction-latent period between initial employment and disease development. Employees affected were primarily laboratory workers and maintenance laborers, and perhaps, to a lesser extent, certain production workers. The exposure-response relationship was of moderate strength, inconsistent in magnitude with the findings for the previous SBR workers case control study; though precise judgments about the consistency of these two studies should require analyses of Delzell et al.'s cohort data over the 1943-82 case control study period.

Several important issues remain unresolved. Exposure levels appear to have been underestimated (Macaluso et al. 1997), the importance of peak versus chronic exposures could not be resolved, and the lack of a leukemia excess in the butadiene

monomer studies is consistent with the possible contribution of styrene or confounding by other SBR co-exposures¹⁰ in the etiology of leukemia among SBR workers. It also remains unclear which leukemia cell types are related to occupational exposures, due to the limitations of diagnostic information on death certificates. Further industry sponsored research is ongoing to clarify these issues.

With the exception of leukemia, this study showed SBR worker mortality rates to be similar to or less than general population rates over a 48 year study period. In particular, mortality from LHCs other than leukemia were not in excess in this cohort and were not related meaningfully to estimates of exposure to butadiene and styrene (Delzell et al. 1995). Thus, the SBR studies do not support a relationship between butadiene exposure and NHL, Hodgkin's disease, and multiple myeloma. NTP's (1997) characterization of consistent excess mortality from LHCs associated with butadiene exposure conflicts with the findings from this most comprehensive study of butadiene exposed workers.

¹⁰ Due to a correspondence between the temporal pattern of leukemias as reported by Delzell and colleagues (1995) and certain SBR process changes, Irons has hypothesized an etiologic role for certain short-stopping agents (Irons R. *Toxicology Forum* 1997, see also comments to NTP from the Chemical Manufacturers Association).

Butadiene monomer worker studies

Divine et al.

The largest study of butadiene monomer workers was first reported by Downs et al. (1987) and updated three times subsequently by Divine and colleagues (*Divine 1990, Divine et al. 1993, Divine and Hartman 1996*). The plant, which was located in the immediate vicinity of the plants studied by Meinhardt and colleagues (1982), started as a cooperative effort of 5 oil companies during World War II. The most recent mortality analysis for this cohort included 2,795 male workers employed at least 6 months between 1942-1994. SMRs for all causes, all cancer, and lung cancer indicated worker mortality that was approximately 10% less than U.S. general population rates.

Leukemia findings for these monomer workers are obviously of paramount interest in light of the leukemia findings for SBR workers (*Delzell et al. 1995 and 1996*). Leukemia mortality was, in fact, comparable to U.S. rates (13 observed, 11.5 expected, SMR = 1.1, 95% CI 0.6-1.9). On the other hand, mortality from lymphosarcoma was elevated (9 observed, 4.7 expected, SMR = 1.9, 95% CI 0.9-3.6). Mortality from other LHCs was also elevated compared to U.S. rates (15 observed, 9.9 expected, SMR = 1.5, 95% CI 0.9-2.5). Of the 15 observed deaths, there were 8 NHLs, 6 multiple myelomas, and 1 polycythemia vera. It would be useful to

combine findings for lymphosarcoma and other NHLs so as to enable an overall assessment of NHL mortality.¹¹

Divine and Hartman (1996) evaluated worker mortality by duration of employment and did not find an appreciable increase in mortality with duration worked for any cause of death. Analysis of lymphosarcoma and leukemia showed a pattern of moderately elevated rates for workers employed less than five years (lymphosarcoma: 6 observed, 2.3 expected, SMR = 2.6, 95% CI 1.0-5.7; leukemia: 8 observed, 5.4 expected, SMR = 1.5, 95% CI 0.6-2.9), but not for workers employed five or more years (lymphosarcoma: 3 observed, 2.4 expected, SMR = 1.3, 95% CI 0.3-3.7; leukemia: 5 observed, 6.1 expected, SMR = 0.8, 95% CI 0.3-1.9).¹²

Lymphosarcoma mortality was elevated for workers hired during World War II (7 observed, 2.9 expected, SMR = 2.4, 95% CI 1.0-5.0), but not for those hired thereafter (2 observed, 1.7 expected). Leukemia mortality, on the other hand, was similar to expected for workers hired during World War II (7 observed, 7.0 expected) and subsequently (6 observed, 4.5 expected).

Divine and Hartman (1996) conducted further analyses based on groupings of occupations judged to have similar exposure

¹¹ Lymphosarcoma, a type of NHL, went out of favor as a diagnostic entity in the early 1980s. As diagnosed currently, it would be included in the other LHC category.

¹² There is some overlap in this study and the study in the nearby SBR plants: 1 leukemia decedent and 1 lymphoma decedent were common to the Divine et al. (1993) and Meinhardt et al. (1982) studies.

potential. Work histories were reviewed for each employee and each job-unit assignment was categorized into one of three exposure groups:

background - workers with no plant duties,

low - workers with very limited time in the plant,

varied - workers with daily exposure potential and

maintenance workers who worked frequently in the plant.

Focusing on workers with frequent exposure potential, mortality from all cancers was slightly less than expected based on U.S. rates (178 observed, 191.6 expected, SMR = 0.9, 95% CI 0.8-1.1). LHC findings were variable for longer and shorter-term workers in this exposure category. The leukemia SMR was 1.1 (3 observed, 2.6 expected) for workers employed 10 or more years and 1.8 (8 observed, 4.5 expected) for those employed less than 10 years. The lymphosarcoma SMR was 1.0 (1 observed, 1.0 expected) for those with 10 or more years exposure and 3.3 (6 observed, 1.8 expected) for employees with shorter employment durations. The opposite pattern was seen for other lymphatic cancers. The SMR was higher for those employed 10 or more years (SMR = 2.0, 5 observed, 2.5 expected) than for those employed for shorter periods (SMR = 1.3, 5 observed, 3.9 expected). The 10 other lymphatic cancers were split equally between NHL and multiple myeloma (*B. Divine, personal communication*). There were 3 multiple myeloma and 2 NHLs in the other LHC subgroup with 10 or more years exposure.

Divine and Hartman (1996) also conducted a proportional hazards analysis to examine the relationship between semi-quantitative estimates of butadiene exposure and various LHCs. To estimate butadiene exposure, each worker was assigned a yearly exposure score based on the product of job title rankings (6 categories) and period of employment rankings (5 categories based on anecdotal information about the plant's history). Scores were accumulated over each worker's career at the plant. The results showed no association between butadiene exposure and leukemia (RR = 0.99), lymphosarcoma (RR = 1.00), NHL (RR = 1.01), and multiple myeloma (RR = 1.01). Hire age was a significant predictor for all LHCs except multiple myeloma.

Divine and Hartman (1996) concluded that their leukemia and NHL findings were not suggestive of a causal relationship for butadiene exposure. Their rationale was based on two findings:

- 1 the absence of elevated mortality among long term workers with frequent exposure potential;
- 2 the lack of an association between estimated butadiene exposure and any LHC in their proportional hazards analysis.

NTP (1997) has interpreted this study as showing a moderate association between butadiene and certain LHCs. In light of the arguments by Divine and Hartman, this interpretation must be based primarily on results for short term workers. It seems illogical to consider elevated mortality among short term workers to be related to butadiene exposure in the absence of similar or

more pronounced findings for workers with additional exposure opportunity. The only exception would be if short term workers were known to have had higher exposures than longer term workers, but there is no evidence to support such a conjecture in this instance.

It bears noting, however, in any review of the literature that the lack of a leukemia excess for these monomer workers and the lack of a relationship between leukemia and estimated butadiene exposure are inconsistent with the results reported by Delzell and colleagues (1995 and 1996).

Ward et al.

Ward et al. (1995) studied 364 men who worked at any time on one of three butadiene monomer units operated by Union Carbide Corporation. The butadiene units were part of larger petrochemical facilities. Two hundred and seventy seven of these men worked on one unit that operated only during World War II (1943-1946).

The cohort had 48 cancer deaths and 45.5 expected based on U.S. rates (SMR = 1.1, 95% CI 0.8-1.4). Findings for LHCs were: leukemia, 2 observed and 1.6 expected (SMR = 1.2, 95% CI 0.2-4.4); lymphosarcoma, 4 observed and 0.7 expected (SMR = 5.8, 95% CI 1.6-14.8); and other lymphatic cancer, 1 observed and 1.3 expected (SMR = 0.8, 95% CI 0-4.2).

NTP (1997) has made special note of the lymphosarcoma findings for workers with more than 2 years employment and 30 years latency (3 observed, 0.15 expected, SMR = 19.8, 95% CI 4.1-

57.8). These findings were characterized as representative of a strong association with exposure duration and latency. It is easy to see how such a conclusion could be made in isolation, but not in the context of the other available studies. After all, approximately 75% of the workers in this study worked on a unit that operated only during World War II. There were no long term workers in this study compared to the other studies of SBR or monomer workers. If 2 years employment and 30 years latency were, in truth, causally related to a 20-fold excess of lymphosarcoma, then such a finding should have been readily apparent among longer employed workers in the studies by Divine and colleagues (1990, 1993, 1996) and Delzell and colleagues (1995 and 1996). One would also have expected a dose response in those studies. It seems more likely that the magnitude of this subgroup finding is a function of a serendipitous categorization that happens to maximize the ratio of observed to expected deaths for lymphosarcoma. I can find no precedent in the other butadiene studies for categorizing workers with 2 years employment and 30 years latency. Put in proper context, this very small study adds little to our knowledge of butadiene epidemiology.

Cowles et al.

Cowles et al. (1994) evaluated mortality results for 614 BDM workers employed during the period 1948-1989 at a multi-purpose petrochemical complex. The BDM subcohort was defined to include workers with 5 years employment in butadiene related manufacturing or workers who had spent at least half of their

total employment in butadiene manufacturing. The all cancer SMR based on local county rates was 0.3 based on 4 observed deaths. There were no LHC deaths versus 1.2 expected.

Other small studies of butadiene exposed workers

For completion, I mention two other recent small studies of butadiene exposed workers. Bond et al. (1992), in a study of 2,904 male chemical workers involved in the manufacture of styrene based products, reported SMRs for a subgroup of 420 workers who manufactured SB latex. These workers had mortality rates 40% lower than the general population rates for all cancer (13 observed, 22.0 expected). There was 1 LHC versus 2.2 expected. The one LHC was a leukemia versus 0.9 expected.

Downs et al. (1993) reported an abstract on 1,037 ABS plastics workers employed during the period 1950-84. SMRs were 0.7 for all cancers (19 observed, 27.5 expected) and 0.7 for LHCs (2 observed, 2.8 expected).

Conclusion

NTP has characterized the butadiene epidemiologic literature as showing a consistent excess of LHCs associated with butadiene exposure. In fact, the epidemiologic literature for butadiene shows variable results for LHCs. The evidence for leukemia is not consistent across studies, though one large study (Delzell et al. 1995 and 1996, Macaluso et al. 1996) provides credible, internally consistent evidence of a relationship with butadiene exposure. The evidence for lymphosarcoma/NHL is not consistent with a causal relationship with butadiene exposure. While two

studies show elevated mortality among short term butadiene monomer workers (*Divine and Hartman 1996, Ward et al. 1995*), the larger study did not find excess mortality for long term exposed workers and there was no exposure response relationship. In addition, none of the SBR workers studies to date provide evidence to suggest a relationship between butadiene and lymphosarcoma/NHL. Accordingly, the butadiene epidemiologic literature should not be characterized as showing a consistent relationship between butadiene exposure and the various LHCs.

References

Acquavella JF. The paradox of butadiene epidemiology. *Experimental Pathology* 1989; 37:114-118.

Acquavella JF. Future directions in epidemiologic studies of butadiene exposed workers. *Environ Health Perspect* 1990a;86:129-134.

Acquavella JF. Direct testimony before the Occupational Safety and Health Administration. November 1990b.

Acquavella JF, Cowles SR. Butadiene exposure and leukemia. *Amer J Epidemiology* (letter to the editor) 1993;138:765-766.

Acquavella JF, Delzell E, Cole P. Butadiene and lymphatic and hematopoietic cancers: The authors reply. *Epidemiology* 1994;5:262-3.

Acquavella JF. Butadiene Epidemiology: A summary of results and outstanding issues. *Toxicology* 1996;113:148-156.

Bond GG, Bodner KM, Olsen GW, Cook RR. Mortality among workers engaged in the development or manufacture of styrene-based products - an update. *Scand J Work Environ Hlth* 1992; 18; 145-154.

Cole P. Direct testimony before the Occupational Safety and Health Administration. October 1990.

Cole P, Delzell E, Acquavella J. Exposure to Butadiene and Lymphatic and Hematopoietic Cancer. *Epidemiology* 1993; 4:96-103.

Cowles SR, Tsai SP, Snyder PJ, Ross CE. Mortality, morbidity, and haematologic results from a cohort of long term workers involved in 1,3-butadiene monomer production. *Occup Environ Med* 1994;51:323-329.

Delzell E, Sathiakumar N, Macaluso M, Hovinga M, Larson R, Barbone F, Beall C, Cole P. A Follow-up Study of Synthetic Rubber Workers. Final report prepared under contract to International Institute of Synthetic Rubber Producers. October 1995

Delzell E, Sathiakumar N, Hovinga M, Macaluso M, Julian J, Larson R, Cole P, Muir D. A Follow-up Study of Synthetic Rubber Workers. *Toxicology* 1996;113:182-189.

Divine BJ. An update on mortality among workers at a 1,3-butadiene facility - preliminary results. *Environ Hlth Perspect* 1990;86:119-128.

Divine BJ, Wendt JK, Hartman CM. Cancer mortality among workers at a butadiene production facility. IARC Sci Publ 1993; No. 127: 345-362.

Divine BJ, Hartman CM. Mortality update of butadiene production workers. Toxicology 1996;113:169-181.

Downs TD, Crane MM, Kim KW. Mortality among workers at a butadiene facility. Amer J Ind Med 1987;12: 311-329.

Downs T, Pier S, Crane M, Yim K, Kim K. Cause-specific mortality in a cohort of 1000 ABS workers. Abstract presented at the Symposium - Butadiene and Styrene: Assessment of Health Hazards. Espoo, Finland, 1993.

Himmelstein MW, Acquavella JF, Recio L, Medinski MA, Bond JA. Toxicology and epidemiology of 1,3-butadiene. Crit Rev Toxicol 1997;27:1-108.

Landrigan PJ. Critical assessment of epidemiologic studies on the human carcinogenicity of 1,3-butadiene. Environ Health Perspect 1990;86:143-148.

Landrigan PJ. Critical assessment of epidemiologic studies on the human carcinogenicity of 1,3-butadiene and styrene. IARC Sci Publ 1993; No. 127: 375-388.

Macaluso M, Larson R, Delzell E, Sathiakumar N, Hovinga M, Julian J, Muir D, Cole P. Leukemia and cumulative exposure to butadiene, styrene, and benzene among workers in the synthetic rubber industry. Toxicology 1996;113:190-202.

Macaluso M, Delzell E, Sanders M, Larson R. Historical estimation of exposures to butadiene and styrene among synthetic rubber workers. Final report prepared under contract to the International Institute of Synthetic Rubber Producers. August 1997.

Matanoski GM, Schwartz L. Mortality of workers in styrene-butadiene polymer production. J Occup Med 1987;29:675-680.

Matanoski GM, Santos-Burgoa C, Schwartz L. Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry 1943-1982. Final report prepared under contract to International Institute of Synthetic Rubber Producers. April 1988.

Matanoski GM, Santos-Burgoa C, Zeger SL, et al. Epidemiologic data related to health effects of 1,3-butadiene. In: Mohr U., ed., Assessment of Inhalation Hazards: Integration and

Extrapolation Using Diverse Data. ISLI Monographs, Springer-Verlag, New York, 1989:201-214.

Matanoski GM; Santos-Burgoa C, Swartz L. Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry. Environ Health Perspect 1990;86:107-117.

Matanoski G, Francis M, Correa-Villasenor A, Elliott E. Santos-Burgoa C, Schwartz L. Cancer Epidemiology among styrene-butadiene rubber workers. IARC Sci Publ 1993; No. 127: 363-374.

Matanoski G, Santos-Burgoa C. Butadiene and lymphatic and hematopoietic cancer. Epidemiology (letter to the editor) 1994;5:261-2.

McGraw J. Supplemental Written Testimony to the Occupational Safety and Health Administration - Part B. Time Weighted Average Exposure Data. Part C. "Short-term" Exposure Data. November 1990.

Meinhardt TJ, Lemen RA, Crandall MS, Young RJ. Environmental epidemiologic investigations of the styrene-butadiene rubber industry. Scand J Work Environ Health 8: 250-259, 1982.

NTP draft on 1,3-butadiene, 1996.

Occupational Safety and Health Administration. Occupational Exposure to 1,3 butadiene: Proposed rule. 55 Federal Register, page 32747, August 10, 1990.

Rothman KJ. Modern Epidemiology. Little, Brown and Company, Boston, 1986.

Santos-Burgoa C, Matanoski GM, Zeger S, Schwartz L. Lympho-hematopoietic cancer in styrene-butadiene polymerization workers. Amer J Epidemiol 1992;136:843-54.

Ward EM, Fajen JM, Ruder A, Rinsky RA, Halperin WE, Fessler-Flesch CA. Mortality study of workers in 1,3-butadiene production units identified from a chemical workers cohort. Environ Health Perspect 1995;103, 598-603.