



STATEMENT

Synopsis of Research Report 132

HEALTH
EFFECTS
INSTITUTE

Mortality Among Workers Exposed to Butadiene

BACKGROUND

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

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

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

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

The study aimed to (1) determine if employment in the SBR industry, assessed by factors such as

duration of employment or type of job, is associated with mortality from specific causes; and (2) evaluate if exposure to BD, or styrene, or dimethyldithiocarbamate (DMDTC; the agents of interest) is related to death from leukemia, other LHCs, or other selected cancers.

APPROACH

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

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

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

The models for BD exposure estimated several parameters. The estimates for each parameter contained considerable uncertainty about the true numeric values. A mean exposure estimate was calculated for each work area/job group. Cumulative exposure was computed for each worker by multiplying the estimated exposure in each of his work area/job groups by the number of days he worked in each, and by summing the resulting quantities over all of his jobs for his duration of employment.

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Neither the parameters used in this model nor the estimates that resulted from it were validated with actual measurements of workplace concentrations.

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

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

RESULTS AND INTERPRETATION

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

Internal analyses revealed associations between mortality rates from leukemia and cumulative exposures to BD, styrene, and DMDTC. When analyses of the effects of one agent did not take into account exposure to the other agents, results suggested that each compound independently affected rates of death from leukemia. Furthermore, the relative rates generally increased as cumulative exposure increased: mortality rates from leukemia in the highest exposure categories increased by 170% to 270% compared with rates

for the no-exposure category. When analyses did take into account exposure to the other agents, only BD and DMDTC retained their association with increased leukemia mortality.

CONCLUSIONS

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

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

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