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Critical Assessment of Epidemiologic Studies on the Human Carcinogenicity of 1,3-Butadiene

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1,3-Butadiene, a major ingredient of synthetic rubber, has been shown to be carcinogenic in two animal species. To assess the possible human carcinogenicity of 1,3-butadiene, a critical review was undertaken of the epidemiologic literature.

An early retrospective study of 8017 males employed in tire manufacturing found excess mortality for lymphatic and hematopoietic neoplasms in production workers (standardized mortality ratio, SMR = 560); these workers were exposed to 1,3-butadiene as well as to styrene and possibly to benzene. A recently updated epidemiologic study of 2568 workers at a butadiene manufacturing plant in Texas reported low mortality overall (SMR = 84) but found excess deaths for lymphosarcoma and reticulum cell sarcoma (SMR = 229). A retrospective study of workers employed at two synthetic rubber plants in Texas found excess mortality for lymphatic and hematopoietic malignancies in the older of these facilities; the excesses for lymphosarcoma (SMR = 224) and leukemia (SMR = 278) were most significant in wartime workers. A large, recently updated retrospective study of 12,113 workers employed in eight synthetic rubber manufacturing plants in the United States and Canada found excess mortality for lymphatic and hematopoietic cancer in production workers; the SMR for other lymphatic cancers in white production workers was 230, and the SMR for all lymphatic malignancies in black production workers was 507.

These updated epidemiologic results strongly suggest an etiologic association between occupational exposure to 1,3-butadiene and human cancer. It is reasonable, therefore, to conclude that there now exists at least limited evidence for the human carcinogenicity of 1,3-butadiene.

Introduction

1,3-Butadiene is a major component of synthetic rubber manufacture. Annual production in the United States is a 2.7 billion pounds (*1*). 1,3-Butadiene is among the top 20 organic chemicals in annual volume.

1,3-Butadiene has been found to produce cancer at multiple anatomic sites in two species of experimental animals—rats and mice (*2,3*). In both species, cancer occurs at exposure levels equal to or below the current federal standard of 1000 parts per million (ppm). In $B6C3F_1$ mice increased incidences were noted of malignant lymphoma and cardiac hemangiosarcoma; excesses were seen also of alveolar-bronchiolar neoplasms, tumors of the forestomach, carcinomas of the mammary gland, neoplasms of the ovary, and hepatocellular neoplasms (*2*). In Sprague-Dawley rats, increases were seen in pancreatic adenoma, uterine sarcoma, Zymbal gland carcinoma, mammary tumors, thyroid tumors and testicular cancers (*3*). Nonneoplastic toxic effects in mice included anemia (at exposure level of 62.5 ppm), testicular atrophy (at 200 and 625 ppm), and ovarian atrophy (at 20 ppm) (*4*). 1,3-Butadiene has been found to exhibit genetic toxicity and cytotoxicity in mouse bone marrow; cytogenetic changes included increased frequencies of chromosomal aberrations (at 625 ppm), of micronucleus formation (at 625 ppm), and of sister chromatid exchange at (6.25 ppm) (*5*).

Four epidemiologic studies have been undertaken to evaluate the possible human health effects of occupational exposure of 1,3-butadiene. Three of these analyses were updated substantially in preparation for the 1988 International Symposium on the Toxicology, Carcinogenesis, and Human Health Aspects of 1,3-Butadiene held at the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. This review will examine critically the current epidemiologic evidence on the human carcinogenicity of 1,3-butadiene.

North Carolina Study

An early retrospective epidemiologic study conducted by the Occupational Health Studies Group at the University of North Carolina examined the cause-specific

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mortality of 8017 male workers employed at two tire manufacturing plants in Ohio (*6,7*).

Overall excess mortality was observed for cancer of the stomach and for malignancies of the hematopoietic and lymphatic system. The data were examined separately for workers in different job categories. In the synthetic plant—a work area which involved production of elastomers, including styrene-butadiene rubber (SBR)—relative risks of 5.6 for lymphatic and hematopoietic malignancies and of 3.7 for lymphatic leukemia were reported among workers employed for more than five years; workers in that area may also have had exposures to organic solvents, including benzene. The North Carolina study was not updated for this NIEHS symposium.

Texaco Study

This retrospective study of the mortality of a cohort of 2586 workers employed for at least 6 months between 1943 and 1979 at a 1,3-butadiene manufacturing facility in Texas was analyzed previously for mortality through 1979 (*8*). Quantitative data on past exposures were not available. However, a qualitative exposure scale was constructed, based on department codes. Four groups were defined: low exposure (Group I); routine exposure (Group II), which included process workers; nonroutine exposure (Group III), which included maintenance workers; and unknown exposures (Group IV).

The previous analysis found lower-than-expected mortality for most causes of death with an overall standardized mortality ratio (SMR) in comparison to national rates of 80. However, a statistically significant excess of deaths was observed for lymphosarcoma and reticulum cell sarcoma (SMR 235; 95% CI = 101 to 463).

Mortality was examined relative to the duration of employment. For all lymphatic and hematopoietic neoplasms, the SMR was higher in workers with less than 5 years of employment (SMR = 167) than for those with more than 5 years (SMR = 127). No comment is provided as to whether the short-term workers might have been wartime workers (in wartime, exposure was likely to have been heavier than in subsequent periods); also no information is provided on the types of work in which the short-term employees were engaged.

Mortality of this cohort was analyzed for each of the four exposure groups. Elevated mortality for all lymphatic and hematopoietic neoplasms (SMR = 187) was seen in Group II (routine exposure); this excess was explained principally by excess mortality for Hodgkin's disease (SMR = 197) and for other lymphomas (SMR = 282). In Group III (nonroutine exposure), mortality for all hematopoietic neoplasms was again elevated (SMR = 167), with excess mortality for Hodgkin's disease (SMR = 130), leukemia (SMR = 201) and non-Hodgkin's lymphoma (SMR = 150).

Finally, mortality in this cohort was compared between blacks and whites. Blacks composed 6.8% of the cohort (175 of 2586 persons). SMRs for blacks were higher than those for whites for several causes of death, including arteriosclerotic heart disease and cancer of the lymphatic and hematopoietic system.

At the NIEHS symposium, the mortality experience of the Texaco cohort was updated through 1985 (*9*). The authors found the SMR for all causes to be 84 and the SMR for all cancers to be 80. One additional death from lymphosarcoma had occurred since the previous analysis, giving a statistically significant excess mortality ratio of 229, a finding consistent with the previously noted excess mortality for lymphosarcoma. On updated analysis by exposure group, the strongest excesses for lymphatic and hematopoietic malignancy were again seen in Groups II (process workers) and III (maintenance workers); in process workers, the SMR for lymphosarcoma was 561. As seen previously, excess mortality was concentrated in workers employed for less than ten years and in workers employed during the war; in wartime workers the SMR for lymphosarcoma was 269.

In interpreting the Texaco studies, the most striking finding is the consistently elevated mortality for lymphosarcoma. This finding is consistent with the animal data (*2,4*). It is noteworthy that excess risk was concentrated in production and maintenance workers (exposure Groups II and III); both of those observations are consistent with the notion that the incidence of lymphatic malignancy is highest in groups with heaviest occupational exposure to 1,3-butadiene. The authors note that most cases of malignancy were concentrated in workers employed for less than 10 years. That comment must be understood in the context that most of those brief exposures appear to have occurred during the wartime years when exposures were undoubtedly higher than in subsequent periods. Thus, the finding of a high incidence of malignancy in short-term employees cannot be used to discount the notion of dose-response; instead that finding must be interpreted with the realization that duration of employment is only a crude surrogate for total cumulative exposure (*10*).

NIOSH Study

Following the occurrence in January 1976 of two deaths from leukemia in workers employed at adjacent styrene-butadiene (SBR) production facilities in Port Neches, TX, the National Institute for Occupational Safety and Health (NIOSH) undertook, a retrospective mortality study of the total population of 2,756 white males employed in these plants (*11*). Cohort members were all workers employed in these plants for at least 6 months between 1943 and 1976. The plants used as a raw material the 1,3-butadiene produced by the adjacent Texaco facility, the subject of the previous study (*8,9*).

Overall mortality (SMR = 80) and mortality from all malignancies (SMR = 78) were depressed in the older of these plants (Plant A). The total number of deaths in this plant was 252, with 45 deaths from malignant neoplasms. Elevated, although not statistically significant, mortality was observed for lymphatic and hematopoietic neoplasms (SMR = 155). This excess was explained

principally by excesses for lymphosarcoma and reticulum cell sarcoma (SMR = 181) and for leukemia (SMR = 203).

Mortality was examined separately for the subgoup of the Plant A population employed during the wartime years (January 1943 through December 1945). In these wartime workers, an excess was seen for mortality from lymphatic and hematopoietic malignancies (SMR = 212); statistically significant increases in mortality were seen for lymphosarcoma and reticulum cell sarcoma (SMR = 224) and for leukemia (SMR = 278).

At Plant B where data were available only for workers employed from 1950 to 1976 and where only 201 deaths had occurred, overall mortality was low (SMR = 66). No excess mortality was seen either for all cancers combined (SMR = 53) or for lymphatic and hematopoietic neoplasms (SMR = 78).

The NIOSH study was updated for the NIEHS symposium (*12*). Mortality of the cohort was followed through 1981 for Plant B and through 1982 for Plant A. Overall mortality remained low. Mortality in Plant A from all lymphatic and hematopoietic neoplasms was found in this reanalysis to again be elevated. As in the previous analysis, the major increase in cancer mortality was found to have occurred in the wartime subcohort in Plant A.

No excess mortality was seen in Plant B in the updated analysis.

Considerable similarities exist between the overall findings of the NIOSH and the Texaco studies, and 116 (4.5%) of the workers in the Texaco cohort were also members of the NIOSH cohort. Both studies found excess mortality for malignancies of the lymphatic and hematopoietic system. These findings are consistent with the animal studies (*2,4*). Both studies found also that excess mortality from lymphatic malignancies was concentrated in workers employed during the wartime years, which were presumably a period of particularly intense exposure to 1,3-butadiene.

Matanoski Study

The largest epidemiologic study of workers exposed to 1,3-butadiene is that reported by Matanoski et al. (*13*). In their initial analysis completed in 1982, mortality was analyzed for 13,920 workers employed for more than 1 year in eight styrene-1,3-butadiene rubber production plants in the United States and Canada. In that analysis 10,899 (78.3%) members of the cohort were known to be alive, 2,097 (15.5%) were known to be deceased, and vital status was not known for 924 (6.6%). A total of 1,041 (7.5%) members of the cohort were black; 12,567 (90.2%) were white.

Overall mortality was low in the initial analysis (SMR = 81). Mortality for all cancers was also low (SMR = 84). For all lymphatic and hematopoietic cancers, the SMR was 85 (Table 1). A racial difference was noted, however, for lymphatic and hematopoietic cancers; an SMR of 141 was noted in blacks as compared to 80 in whites. Overall, in the initial analysis, no statistically significant excesses in mortality from cancer at any site were noted in either the white or the black populations in this large cohort.

No quantitative information on past exposures was available in that initial analysis by Matanoski et al. (*14*). However in an effort to assess variations in mortality in relation to qualitative variations in exposure, job categories in this cohort were classified into four groups: production, maintenance, utilities, and other. In the utilities workers, an SMR of 198 was noted for leukemia (based on two deaths). Slight excesses were seen for Hodgkin's disease in all four categories (SMRs from 129 to 345, based on a total of 8 deaths).

Matanoski reanalyzed the mortality of this cohort in preparation for the NIEHS symposium (*14*) and restructured the cohort. The most significant change was the removal of Canadian workers who had not qualified for pension benefits. This change reduced the size of the population to 12,113. Follow-up was completed through 1982. A total of 2,441 deaths were identified. The proportion of the cohort lost to follow-up was reduced to 416 (3.4%), a substantial improvement over the previous effort.

Overall analysis of mortality indicated an SMR for whites of 79 and for blacks of 95. Mortality from all malignant neoplasms was 78.

For lymphatic and hematopoietic malignancies, no overall increases were observed in whites (SMR = 92). In blacks, based on small numbers, overall increased mortality was seen for lymphopoietic malignancies (SMR = 146), and specific increases were noted for lymphosarcoma (SMR = 132), leukemia (SMR = 218), and other lymphatic neoplasms (SMR = 116).

When the cohort was subdivided by exposure groups, excess mortality for lymphatic and hematopoietic neo-

Table 1. Mortality from hematopoietic malignancies in published studies on workers occupationally exposed to 1,3-butadiene in the United States.[a]

	Matanoski et al. (*14*)				Divine (*9*)	
Type of malignancy	All whites	All blacks	*White production* workers	*Black production* workers	Total cohort	*Process workers* (Group II)
All hematologic	92	146	110	507	130	177
Lymphosarcoma	56	132	0	532	229	561
Hodgkin's disease	131	0	131	0	141	179
Leukemia	86	218	84	656	102	56
Other lymphatic	110	116	230	482	97	80

[a]Mortality is expressed as standardized mortality ratio (SMR).

plasms was observed in production workers of both races. In white production workers, the SMR for all lymphatic and hematopoietic malignancies was 110; that excess was explained principally by excess mortality for other lymphatic neoplasms (SMR = 230). For black production workers, based on small numbers, the SMR for all lymphatic and hematopoietic neoplasms was 507. That overall increase reflected an SMR of 532 for lymphosarcoma, of 656 for leukemia and of 482 for other lymphatic malignancies. A pattern of excess mortality for lymphatic and hematopoietic neoplasms was seen also in the small group of utility workers; included in that group were workers in the tank farm. No increases in lymphatic or hematopoietic malignancy were seen in maintenance or other workers.

On the basis of these findings, Matanoski et al. (*14*) concluded in their updated analysis that there is "excess risk of death from hematologic neoplasms especially leukemia and other lymphomas in production workers" occupationally exposed to 1,3-butadiene (*14*). They suggest that this finding warrants further examination of the exposures associated with work in this industry.

In interpreting the results of the Matanoski studies, the most significant methodologic differences between the first and second analyses are *a*) the extension of the follow-up, *b*) the improved tracing of the cohort, and *c*) the deletion of Canadian workers with relatively short-term exposure. With those changes, an excess in mortality from lymphatic and hematopoietic malignancy, which had not been evident initially, became visible. Information on mortality in specific plants was not provided.

Discussion

The epidemiologic data on 1,3-butadiene presented at the NIEHS symposium are most exciting, and they embody major advances in the understanding of the health effects of this important compound. On the basis of these new data, a significantly enhanced assessment is possible on the risk of 1,3-butadiene to man.

Critical review of the new epidemiologic data indicates that a picture, which was only faintly visible 5 years ago, is now coming more sharply into focus. All of the newer studies have consistently shown excess mortality for lymphatic and hematopoietic cancer. Lymphatic neoplasms were noted also in mice exposed to 1,3-butadiene (*2*).

Qualitative evidence that carcinogenicity in persons exposed to 1,3-butadiene is dose-related is provided by the observation that excess mortality is greatest in production workers and maintenance workers, but is not seen in office staff (*8,9,14*). Typically, in industrial populations production workers and maintenance workers are the groups most heavily exposed to potentially toxic substances. Further evidence for a positive dose-response relationship is provided by the observation that the greatest excess mortality is seen among workers exposed to 1,3-butadiene during the war years; presumably that was a period when exposures were especially intense, both because of wartime production pressures and possible upsets during process start-up periods.

Criticism has been leveled against the apparent consistency of these epidemiologic findings on the ground that different subtypes of lymphatic and hematopoietic neoplasms were seen in the different studies (*8,9,15,16*). However, it is important to realize that the diagnostic categories in this area are imprecise and overlapping (*17*). Transitions of lymphomas and multiple myelomas into leukemias are seen frequently in clinical practice, and a leukemic phase is seen commonly in cases of non-Hodgkin's lymphoma. In addition, some patients with lymphoma or multiple myeloma may subsequently develop leukemia as a result of their treatments with radiation or cytotoxic drugs (*18*). These natural and iatrogenic transitions from lymphoma to leukemia are complicated further by historical changes in nomenclature. Indeed, certain lymphomas and certain leukemias such as chronic lymphatic leukemia are now considered by Berard et al. (*19*) "simply to represent different clinical expressions of the same neoplastic process." Further, recent immunologic (*20*) and cytogenetic (*21*) studies have shown that there are stem cells which appear to have the capacity to develop variously into T-cell lymphocytes, plasma cells, granulocytic cells, erythrocytes or monocytes. Accordingly, transformation events that occur in these cells at an early multipotent level can be manifest as malignancy involving any of the daughter cell lines. For all of these reasons, undue insistence on the argument that different lymphatic malignancies represent etiologically distinct entities appears to be misplaced.

Conclusion

On the basis of the updated epidemiologic evidence presented at the NIEHS symposium, it is reasonable to conclude that there now exists at least limited evidence for the carcinogenicity of 1,3-butadiene to man. Previously, the human evidence was considered to be insufficient to permit a determination of possible carcinogenicity (*22*). This updated conclusion, taken together with the previous determination by the International Agency for Research on Cancer (IARC) that there exists sufficient evidence for the carcinogenicity of 1,3-butadiene to animals, signifies that it will be prudent henceforth to treat 1,3-butadiene as though it were a human carcinogen (*23*). Indeed, in 1984, the National Institute for Occupational Safety and Health (NIOSH) recommended that 1,3-butadiene be regarded as a potential occupational carcinogen (*23*).

The major shortcoming in the current understanding of the carcinogenicity of 1,3-butadiene is a lack of quantitative data on exposure. None of the epidemiologic studies currently available has developed sufficient information on exposure to permit description of a quantitative dose-response relationship or to serve as a basis

for quantitative estimation of risk. For the future, quantitative epidemiologic studies will therefore be required. These studies will need to link mortality outcomes with data on cumulative exposures to 1,3-butadiene. Probably the most efficient approach to achieving this goal will be to create job-exposure matrices in already-established cohorts and then to undertake nested case-control studies (*24*). Also, additional toxicologic studies will be required to better delineate the mechanisms of carcinogenicity of 1,3-butadiene (*2,16*).

Finally, it is most important from the perspective of public health and preventive medicine to urge that reduction of the occupational exposure standard for 1,3-butadiene not be delayed while additional research continues. The available toxicologic studies have shown clearly that malignancies are caused by exposures to 1,3-butadiene at levels equal to and below the current federal occupational exposure standard of 1000 ppm (*2–4*). NIOSH has urged already that the current standard be re-examined and has noted that while "the excess risk of cancer to workers exposed to specific airborne concentrations of 1,3-butadiene has not yet been determined, . . . the probability of developing cancer could be decreased by reducing exposure" (*23*).

I caution strongly against further delaying the regulatory process while we await further epidemiologic and toxicologic data on 1,3-butadiene (*25*). Sophisticated research into alternate metabolic pathways (*26*) and into the possible role of viruses (*27*) in the carcinogenicity of 1,3-butadiene is important. Such research should not, however, be used as a basis for delaying reduction in exposure standards either in this country or abroad. Sufficient evidence exists today to justify stringent reduction in exposure standards for 1,3-butadiene on the grounds of prudent prevention.

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