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Environmental Epidemiologic Investigations in the Styrene-Butadiene Rubber Production Industry

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A review of the literature and an update that is in progress of a previous retrospective cohort mortality study of the styrene-1,3-butadiene industry are discussed. The follow-up has now been extended from April 1, 1976, through December 31, 1981, for plant B and December 31, 1982, for plant A. The person-years at risk of death have gone from 34,187 to 43,341 in plant A and from 19,742 to 26,314 in plant B. Among the death certificates received to date, observed deaths have increased in both plants, with increases in cancers of the trachea, bronchus and lung and in lymphosarcomas, reticulosarcomas, and cancers of the overall lymphatic and hematopoietic system.

Styrene-butadiene rubber (SBR), a copolymer of styrene and 1,3-butadiene, is the most widely used synthetic rubber in the world. The U.S. government foresaw shortages of natural rubber as a result of the growing demands during World War II and financed construction of fifteen SBR plants, two butyl rubber plants, sixteen 1,3-butadiene production facilities and five styrene plants. Between 1946 and 1955 these plants were sold to various private companies. In 1984, the 1,3-butadiene consumption in the U.S. was estimated to be about 3.24 billion pounds per year with at least 3 billion being used to make synthetic rubber (*1*). In the National Institute for Occupational Safety and Health (NIOSH) Criteria Document on Styrene, it was estimated that the U.S. production of styrene in 1981 was 6.61 billion pounds per year, with approximately 0.44 billion pounds being used to manufacture SBR (*2*). The number of workers employed in rubber and plastic production was estimated to be a little over 9,000 (*1*). The exact number of workers employed in SBR production is unknown. Primarily, styrene is produced by dehydrogenating ethyl benzene, the reaction product of benzene plus ethylene. A small portion is made from ethylbenzene that is recovered directly from refinery streams (*3*).

In January 1976, two men who had been employed at adjacent SBR production facilities in Port Neches, TX, died of leukemia. Simultaneous with these deaths an article was published demonstrating an association between leukemia and employment in a large rubber production facility (*4*). Based on these preliminary observations, a detailed environmental and epidemiological study was conducted at these two SBR facilities to test the hypothesis that employment in the SBR production industry was associated with an increased risk of leukemia and with an increased risk of other malignancies of hematopoietic and lymphatic tissues.

The two plants included in this investigation began operation in 1943. Plant A had employed a total of 3,494 persons, of which 1,662 were white males with at least 6 months of employment. Of the 1,662 white males, the average length of employment was 9.48 years with an average annual turnover rate of 7%. At the time of initiation of the investigation there were 700 persons employed.

Plant B was active from 1943 through 1947, then shut down until 1950 when it was reopened. Personnel records that date from 1950 were available on 2,015 workers. Of these 1,094 were white males having at least 6 months of employment, with an average length of employment of 10.78 years and an average annual turnover rate of 5.10%. An estimated 458 people were employed at the plant at the start of this investigation.

Processes and environmental conditions changed with time in these two plants. Originally, rubber was produced by a hot temperature, batch polymerization process. The batch polymerization process was then converted to a continuous-feed operating system. Finally, a

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cold-temperature, continuous polymerization process was developed to go along with the hot process. Extender oils were added to the process in the early 1950s to ensure that the rubber product was not too hard for future processing. In the first plant, a pilot polyethylene operation was constructed in 1960, and it operated until 1965 when it was discontinued. A general modernization program of the production area was begun in 1967 at both plants.

Styrene and 1,3-butadiene were considered the target chemicals for the investigation; however, benzene exposure was also evaluated because of its known association with leukemia. Air samples were taken in both plants from all areas and were found to be well within the existing Occupational Safety and Health Administration (OSHA) PELs (100 ppm styrene, 1000 ppm butadiene, and 10 ppm benzene). Anecdotal information from discussions with plant A management personnel indicated that benzene was not nor had ever been directly used in the production of SBR; therefore the observed concentrations might be explained by chance, general environmental leaks, and styrene impurities.

The retrospective mortality portion of the investigation began on January 1, 1943, in plant A and January 1, 1950, in plant B and was conducted through March 31, 1976, for each plant. Only white males with 6 months of nonmanagement and nonadministrative employment were included in the analysis. Plant A had a total of 1,356 subjects alive (81.59%), 252 deceased (15.16%), and 54 lost to follow-up (3.25%). Plant B had 980 subjects alive (89.58%), 80 deceased (7.31%), and 34 lost to follow-up. Each death was coded by one nosologist, in accordance with the International Lists of Diseases and Causes of Death in effect at the time of death, and then converted into the seventh revision code for the purposes of comparison. A modified life-table technique *(6,7)* was used to obtain the person-years at risk of dying by 5-year age groups, by 5-year calendar time periods, by duration of work experience (exposure), and by time from initial employment (latency) in the SBR production industry. Person-years at risk of death began accumulating at six months after initial employment. For plant A, the total person-years at risk was 34,186.63; for plant B, it was 19,741.95. The age, race, sex, calendar time, and cause-specific mortality rates of the U.S. population were then applied to the appropriate stratum of person-years at risk to generate the expected number of cause-specific deaths in the study population. This expected number of deaths was then compared to the observed number of deaths in the study population so that any standardized mortality ratio (SMR) (expressed in terms of percentage without % symbol) could be determined. The magnitude of the differences was evaluated by a two-sided test statistic based on the Poisson distribution (with $p < 0.05$).

Table 1. Concentrations of styrene, 1,3-butadiene, and benzene in plant A and plant B.

Contaminant	Samples	Concentration		
		Range, ppm	Mean, ppm	SD
Plant A				
Styrene	55	0.03–6.46	0.94	1.23
1,3-Butadiene	41	0.11–4.17	1.24	1.20
Benzene	3	0.08–0.14	0.10	0.035
Plant B				
Styrene	35	0.05– 12.3	1.99	3.00
1,3-Butadiene	47	0.34–174.0	13.50	29.90
Benzene	0	—	—	—

The results of this investigation found a nonsignificant excess of death in the overall category of lymphatic and hematopoietic tissues (ICD codes 200–205) in plant A (9 observed versus 5.79 expected, SMR 155). The majority of this increase was accounted for by an approximate doubling of the number of deaths due to leukemia. (ICD Code 201) (5 observed versus 2.47 expected SMR 203). No appreciable excesses were observed in these categories based on the mortality patterns of plant B employees.

The general mortality pattern for plant A and plant B showed that none of the major categories considered were in excess based on the mortality experience of the worker population from either plant. Many of these categories, including total mortality, appear to have substantial deficits in observed deaths, compared to the expected number of deaths. Such observations have been explained by the selection of healthy individuals when initially employed in this industry and other physically demanding industries *(8,9)*. In other words, this effect results from the differences in the mortality experience of a selected health worker population and in the mortality experience of a general reference group like the U.S. population, which is comprised of people in a spectrum of health statuses.

When the records of the individuals identified with leukemia (for those who qualified and did not qualify for inclusion in the study analysis) at plant A were reviewed, it was observed that most of these employees had started work before the end of December 1945. The date corresponds to the time when the batch process was converted to a continuous feed operation and the wartime production conditions were discontinued. Because of these process changes, it was decided to evaluate the mortalities of plant A white male employees who had previously worked at least six months between the beginning of January 1943, and the end of December 1945. This subgroup consisted of 600 workers with an average length of employment of 11.89 years and an average annual turnover rate of 7.0%. The vital status for this subcohort was: 365 subjects alive, 201 deceased, and 34 (5.6%), for which the vital status was unknown. The experience of this subcohort resulted in the accumulation of 17,086 person-years at risk of death.

The results showed deficits of mortality for the categories of total mortality, all other cancers, and accidents. Excesses in cause-specific mortality were observed in the overall category of malignant neoplasms of the lymphatic and hematopoietic tissues and its subcategory, leukemia and aleukemia with associated

SMRs of 212 and 278, respectively. The SMRs for the subcategories of lymphatic and hematopoietic tissue malignancies in this restricted subgroup are greater, because this subgroup contained not only all qualifying leukemia deaths, but also all of the remaining lymphatic and hematopoietic tissue deaths that qualified for inclusion in the analysis. Since the evaluation of this subcohort's mortality experience was *a posteriori*, the use of statistical tests may not appropriately assess chance occurrence. However, if a one-sided test statistic was used to evaluate the excesses observed in the subcategories of the lymphatic and hematopoietic tissue malignancies, then the excess in the leukemia and aleukemia category was significant with $p < 0.05$.

The findings of this study provided limited support for the suggestion that the production or manufacture of SBR might be associated with an excess of lymphatic and hematopoietic neoplasms, and continued follow-up of these cohorts seemed warranted. In summary, no statistically significant excesses in cause-specific mortality were found in the overall populations at plant A, plant B, or the restricted plant A, based on an evaluation using a two-sided statistical test. There was a nonstatistically significant excess for neoplasms of the lymphatic and hematopoietic tissues found in the overall plant A population and the restricted plant A population.

Since the completion of the Meinhardt et al. report (*5*), two animal inhalation bioassays have found 1,3-butadiene to be carcinogenic in rats (*10*) and in mice (*11*). Additionally, the findings of McMichael et al. (*4*) prompted a more detailed case-referent study of these cancer deaths by Spirtas et al. (*12*); this evaluation revealed an estimated relative risk of 2.4 for fatal lymphatic and hematopoietic malignancies associated with employment in the SBR production plant.

Monson and Nakano (*13*), examined the mortality rates of all members of the same local union working for one rubber company in Akron, Ohio. The study included 13,571 men who had worked during or after 1935 for at least 5 years. Excesses of leukemia deaths were observed for those men working in the tire and the processing divisions with SMRs of 150 and 240, respectively. The processing department included synthetic rubber production. These results reinforce the possibility of an association between exposure to SBR production and the development of lymphatic and hematopoietic malignancies.

Matanoski et al. (*14*) found no significant excesses in cause-specific mortality in a study consisting of small numbers of workers in the cohorts from 8 facilities, which had relatively short latency periods among workers thought to be exposed to SBR. The study had limited ability to detect any significant excesses. In addition, the environmental data were insufficient to characterize and quantify chemical exposures by the workers.

Downs et al. (*15*) reported on the mortality among a cohort of 2,586 male workers who were employed at least 6 months between 1943 and 1979 in a 1,3-butadiene manufacturing plant supplying 1,3-butadiene to the two SBR plants studied by Meinhardt et al.(*5*). These authors compared the mortality patterns of the worker cohort with both national U.S. mortality and with local mortality patterns. As in the Meinhardt et al. report (*5*), the overall total mortality was less than expected, with an SMR of 80 ($p < 0.05$) for the comparison with the U.S. mortality. For the all-cancer category the SMR was 84. and corresponding comparisons with the local mortality rates resulted in SMRs of 96 for total mortality and 76 ($p < 0.05$) for all cancer. The only significant excess of death observed for those in the routinely exposed group was for lymphosarcoma and reticulum cell sarcoma with an SMR of 235 (8 observed versus 3.4 expected, $p < 0.05$) when compared with the national U.S. rates. Strokes were significantly increased in the nonroutinely exposed group when compared with the local mortality rates only. The authors emphasized the shortcomings of the study to be *(a)* unreliable race designations, *(b)* lack of work histories and industrial hygiene data, *(c)* an employment period of less than 5 years for almost half of the total cohort, *(d)* the possibility that the cohort was incomplete, and a comparatively small sample size. On the positive side, the authors point out that the study involved one of the largest cohorts studied to date. They also affirmed that the power of the study was adequate to detect a doubling of risks for many causes of death and was sufficient to detect a tripling of risk for most causes. In conclusion, the authors evaluated the role of 1,3-butadiene in the excess deaths noted and felt that further follow-up and additional studies need careful attention.

The findings from each of the previously outlined studies show similar observations of deaths. However, they do not provide sufficient insight into the risks posed to workers in the SBR production industry.

Currently the follow-up to the Meinhardt et al. study (*5*) has been increased through December 31, 1982, for plant A and December 31, 1981, for plant B. Crude calculations suggest that the person-years at risks of death have increased in plant A from 34,187 to 43,341 and in plant B from 19,742 to 26,314. In the subcohort, the increase in person-years at risk of death has increased from 17,086 to 19,582. In addition, there are now 390 observed deaths in plant A, compared to 252 in the first analysis, and 148 in plant B, compared to 80 at the time of first analysis. For the subcohort of plant A, there are now 294 observed deaths, compared to 201 at the time of the last analysis. The mortality from malignant neoplasms in plant A is now 77, compared to 45 in the first analysis. In the subcohort of plant A, the mortality from malignant neoplasms increased from 39 to 61. For plant B the mortality for malignant neoplasms has increased from 11 to 29.

In plant A, mortality from trachea, bronchus, and lung (ICD Codes 162-163) has increased from 16 deaths to 34. The only other increases in SMRs were for lymphosarcoma and reticulosarcoma (ICD Code 200) from 3 deaths in the first analysis to 5 deaths currently. One death has now been observed for other neoplasms of the

lymphatic and hematopoietic tissues (ICD Codes 202, 203 and 205).

In the subcohort from plant A, maligant neoplasms of the trachea, bronchus, and lung (ICD Codes 162-163) have increased from 13 deaths to 24. The two additional deaths from lymphosarcoma and reticulosarcoma in the overall plant A cohort occurred in the subcohort. The one new death from other neoplasms of the lymphatic and hematopoietic tissues also occurred in this subcohort. In the plant B cohort, malignant neoplasms of the trachea, bronchus, and lung increased from 5 to 14. The only other new death occurred in the category leukemia and aleukemia (ICD Code 204), increasing the observation from 1 to 2 deaths.

The continued analysis of the mortality occurring to SBR production workers may never provide definitive answers about the health effects associated with either styrene or 1,3-butadiene because of the diffuse and poorly defined nature of exposure in this industry. At the present time, it is not clear from this study whether a real leukemogenic risk is associated with SBR production or whether the reported excesses in lymphatic and hematopoietic malignancies are artifacts in the populations studied. However, since there are continuing reports of additional cancers occurring to individuals exposed to this industrial process and since the evaluation of a mixed chemical exposure environment with very low levels of exposure may provide evidence of health risks not detected in single-agent evaluations, the continued evaluation of workers in this industry seems warranted.

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