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Environmental epidemiologic investigation of the styrene-butadiene rubber industry

Mortality patterns with discussion of the hematopoietic and lymphatic malignancies

by Theodore J Meinhardt, MSPH, Richard A Lemen, MSPH, Michael S Crandall, MSPH, Ronald J Young, MS[1]

MEINHARDT TJ, LEMEN RA, CRANDALL MS, YOUNG RJ. Environmental epidemiologic investigation of the styrene-butadiene rubber industry: Mortality patterns with discussion of the hematopoietic and lymphatic malignancies. *Scand j work environ health* 8 (1982) 250–259. A retrospective cohort mortality study and an industrial hygiene assessment were undertaken in two styrene-butadiene rubber producing facilities in eastern Texas. Occupational history records were available from 1943 at plant A and from 1950 at plant B to the study cut-off date of 31 March 1976. With a two-sided test statistic, no statistically significant excesses in total or cause-specific mortality were observed for the overall worker population of either plant. However, the plant A study group demonstrated a nonsignificant statistical excess [standardized mortality ratio (SMR) of 203] for the cause-specific category of leukemia and aleukemia. Additional analyses were performed on a subgroup consisting of all white males with at least six months of employment at plant A between the beginning of 1943 and the end of 1945, a time which coincided with process and operational changes. An SMR of 278, also not statistically significant, was demonstrated for the leukemia and aleukemia cause-specific category. Due to the relative modest study population sizes, the power of this study to detect statistically significant excesses in leukemias or other malignancies of the hematopoietic and lymphatic tissues is not very large unless one is interested in substantial excesses, such as those that would correspond to a fourfold increase in risk.

Key terms: cancer, epidemiology, leukemia, neoplasms, occupational health, synthetic rubber.

Styrene-butadiene rubber (SBR) is the most widely used synthetic rubber in the world. The production of this synthetic was not actively pursued in the United States or elsewhere in the world until the supply of natural rubber had been curtailed by war activities in the Pacific during the late 1930s and early 1940s. In 1941, the Rubber Reserve Company of the US Reconstruction Finance Corporation initiated a program to construct plants which would permit the annual production of 40,642 t (metric) of synthetic rubber. Before the end of the war, this annual capacity had been increased to about one million metric tons. As part of this program, the United States government constructed 15 SBR plants, two butyl rubber plants, 16 butadiene production facilities, and five styrene production facilities. After World War II, these facilities were sold to private corporations (13).

In January 1976, two men who had been employed at adjacent SBR facilities in Port Neches, Texas, died of leukemia. On the basis of preliminary observations (10), the National Institute for Occupational Sa-

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fety and Health decided to conduct detailed environmental and epidemiologic studies at these facilities to test the hypothesis that employment in the SBR production industry was associated, specifically, with an increased risk of leukemia and, more generally, with an increased risk of other malignancies of hematopoietic and lymphatic tissue. In the course of this investigation, mortality information on malignancies of hematopoietic and lymphatic tissue, as well as on other causes of death, was collected. Information on other causes of death was used to explore the possible existence of other previously unrecognized unusual mortality patterns and is presented along with the information on leukemia.

Process description and environmental concentrations

SBR is a copolymer of styrene and butadiene made through an emulsion polymerization process. A typical emulsion system contains water, monomers, initiators, and an emulsifier (soap) (11). A typical recipe, as described by one of the plant managers, is shown in table 1.

The two plants included in this study began operations in 1943. Plant A has been operated continuously by BF Goodrich, which purchased the plant from the United States government in 1955. Personnel employment records and occupational histories were available for all personnel since 1943. According to best estimates, a total of 3,494 persons have worked at this plant. Of this total population, 1,662 were white males who had at least six months of employment. In this latter group of employees, the average length of employment was 9.48 a and the average annual turnover rate was 7.00 %. An estimated 700 people were employed at this plant when the study was initiated.

Plant B was operated by Firestone from 1943 to 1947 and then shut down. Attempts to gain Firestone authorization for access to social security data which would identify early employees have failed. The plant was reactivated in 1950 by the US Rubber Company and operated until 1955. At that time, the plant was purchased by a company jointly owned by US Rubber and Texaco. This jointly owned company operates the facility today. Personnel employment records documenting the employment of 2,015 workers were available from 1950 on. Of this total worker population, 1,094 were white males having at least six months of employment. In this latter group of employees, the average length of employment was 10.78 a, and the average annual turnover rate was 5.10 %. An estimated 485 people were employed at this plant when the study was initiated.

Processes and environmental conditions of an industry change with time. To illustrate the changes in this particular industrial process, some of the important process changes which have occurred at plant A since 1943 are briefly described. Originally, this plant produced rubber by a hot temperature, batch polymerization process. The batch polymerization process was then converted to a continuous feed operating system in 1946. In 1949, a cold temperature, continuous polymerization process was developed to go along with the hot process. Extender oils were added to the chemical process in 1951 to insure that the rubber product was not too hard for future processing. A pilot polyethylene operation was constructed at this plant in 1960, but was discontinued in 1965. A general modernization program of the production area was begun in 1967. Undoubtedly, such changes influence environmental conditions within the plant. Similar process evolution has taken place at plant B.

Styrene and butadiene were considered as the target chemicals for this study because they are the two major components of SBR, and benzene exposure was evalu-

Table 1. Typical recipe for the production of styrene-butadiene rubber.[a]

Ingredients	Parts	Percentage
Butadiene	75.0	26.2
Styrene	25.0	8.8
n-Dodecyl mercaptan	0.5	0.2
Paramenthane hydroperoxide	0.1	0.1
Sodium formaldehyde sulfoxyide	0.1	0.1
Iron ethylenediaminetetra-acetate	0.01	0.01
Soap flakes	5.0	1.8
Water	180	63.0

[a] Source: Correspondence from DT Boumans, Plant Manager, BF Goodrich, 29 December 1976.

ated due to its known leukemogenic activity. Measurements were taken in all areas of both SBR production facilities with an approved method (3).

The results of the environmental samples are presented in table 2. All of the samples were well within existing standards of the Occupational Safety and Health Administration and threshold limit values recommended by the American Conference of Governmental Industrial Hygienists (100 ppm of styrene, 1,000 ppm of butadiene and 10 ppm of benzene for an 8-h time-weighted average). No historical monitoring data were available.

Methods

Vital status determinations were made through 31 March 1976 for all cohort members with the help of several follow-up sources, including the Social Security Administration, the US Post Office, the Texas Bureau of Motor Vehicles, and a commercial case location service. Death certificates were obtained for any study members known to be deceased. The underlying causes of death taken from the certificate were coded by one nosologist in accordance with the revision of the International Lists of Disease and Causes of Death in effect at the time of death and then converted into the 7th revision code for the purposes of comparison.

A modified life-table (4, 5) technique was used to obtain the person-years at risk of dying by 5-a age groups, by 5-a calendar time periods, by duration of work experience (exposure), and by time from initial employment (latency) in the SBR production industry. Only white males with at least six months of nonmanagement and nonadministrative employment were included in these analyses because the other sex-ethnic subgroups were not large enough for meaningful analyses and a shorter employment period would be difficult to correlate with chronic health conditions. Person-years at risk of death began accumulating at six months after initial employment. The age, race, sex, calendar time and cause-specific mortality rates of the US 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 statistically significant differences and the standardized mortality ratio (SMR) could be determined. The magnitude of the differences was evaluated by a two-sided test statistic based on the Poisson distribution (with $p < 0.05$).

Results

The determination of vital status for the workers in plants A and B are shown in tables 3 and 4, respectively. At plant A, 1,356 persons were identified as alive, 252 persons were found to be deceased (with death certificates received for 246 individuals), and for 54 individuals (3.25 %) vital status was undetermined. In the data analyses, the latter 54 were all considered alive, and they thus contributed to the person-years at risk and made the cause-specific death results conservative. A total of 34,187 person-years at risk of dying had accumulated for the entire plant A study

Table 2. Detectable range and mean – Time-weighted-average environmental sampling results.

Contaminant	Number of samples	Concentration		
		Range (ppm)	Mean (ppm)	SD
Plant A				
Styrene	55	0.03– 6.46	0.94	1.23
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
Butadiene	47	0.34–174	13.5	29.9
Benzene	0	–	–	–

group. At plant B 980 persons were identified as alive, 80 persons were found to be deceased (with death certificates received for 78), and vital status was undetermined for 34 individuals (3.11 %). As with their counterparts at plant A, this last group was considered to be alive. A total of 19,742 person-years at risk of dying had accumulated for the entire plant B study group.

Table 5 shows the total mortality pattern for plant A, and it indicates deficits for the categories total mortality, all other cancer, and disease of the respiratory system. Elevated SMRs, though not statistically sig-

Table 3. Vital status of white males with at least six months of employment at plant A between the beginning of January 1943 and the end of March 1976.[a]

Status	Number of study members	Percentage
Alive	1,356	81.59
Deceased	252	15.16
Unknown	54	3.25
Total	1,662	100.00

[a] Person-years at risk from this plant study population: 34,186.63.

Table 4. Vital status of white males with at least six months of employment at plant B between the beginning of January 1950 and the end of March 1976.[a]

Status	Number of study members	Percentage
Alive	980	89.58
Deceased	80	7.31
Unknown	34	3.11
Total	1,094	100.00

[a] Person-years at risk from this plant study population: 19,741.95.

Table 5. Mortality of white males with at least six months of employment at plant A between the beginning of January 1943 and the end of March 1976.[a]

Cause-specific categories	ICD[b] codes	Number of deaths		Standardized mortality ratio
		Observed	Expected	
Tuberculosis	001–019	1	3.66	27
Malignant neoplasms	140–205	45	57.33	78
Digestive organs and peritoneum	150–159	12	16.94	71
Trachea, bronchus, and lung	162–163	16	17.78	90
Male genital organs	177–179	3	3.63	83
Urinary organs	180–181	3	3.11	96
Lymphatic and hematopoietic tissues[c]	200–205	9	5.79	155
Lymphosarcoma and reticulosarcoma[c]	200	3	1.66	181
Hodgkin's disease[c]	201	1	0.87	115
Leukemia and aleukemia	204	5	2.47	203
Other neoplasms of the lymphatic and hematopoietic tissues[c]	202, 203, 205	0	0.79	0
All other cancers		2	10.80	20*
Diseases of the nervous system	330–334, 345	17	20.90	81
Diseases of the circulatory system	400–468	123	139.84	88
Diseases of the respiratory system	470–527	8	16.29	49*
Diseases of the digestive system	540–581	10	12.44	80
Accidents	800–962	19	26.33	72
All other causes		29	38.32	76
Total		252	315.11	80*

[a] At the time that these analyses were done, the life-table analysis program of the National Institute for Occupational Safety and Health assumed mortality rates had remained constant following 1967. Subsequently, the mortality rates for 1968 to 1975 have been incorporated, and the computer program has undergone minor revisions which have resulted in slightly different expected numbers of deaths.

[b] ICD = International Classification of Diseases.

[c] Rates are not available prior to 1950 for three subcategories contributing to malignant neoplasms of the lymphatic and hematopoietic tissues category, the lymphosarcoma and reticulosarcoma category, the Hodgkin's disease category, and the other neoplasms of the lymphatic and hematopoietic tissues category; therefore, they are counted as zero before 1950. No deaths occurred in these categories before 1950.

* $p<0.05$

nificant, were observed for the categories pertaining to malignant neoplasms of the lymphatic and hematopoietic tissues. The deficits in overall and some cause-specific mortality may partially be explained by the widely documented healthy worker effect (6, 7). This effect has been explained by the selection criteria used by most physically demanding industries; these criteria require that new employees have a certain level of good health before being hired.

When the records of the individuals identified with leukemia in plant A were reviewed (presented in table 6), it was observed that most of these employees had started work before the end of December 1945. This date corresponds to the time when the batch process was converted to a continuous feed operation and the war time production conditions were discontinued. Because of these process changes, it was decided to evaluate the mortality experience of white male employees with at least six months of employment in plant A between the beginning of January 1943 and the end of December 1945. This subgroup of the plant A population consisted of 600 workers. For this group of employees, the average length of employment

Table 6. Description of cases involving leukemia among plant A and plant B workers.

Age (a)	Beginning date of employment	Approximate length of employment (months)	Date of death	Time from initial employment to death (a)	Cause of death or disease condition	Reason not qualified
Plant A qualifying cases						
55	1944	18	14 November 1947	3	1a Circulatory failure 1b Due to general arterial venous thrombosis 1c Chronic myeloid leukemia	
77	1943	208	29 September 1972	29	1a Leukemia 1b Acute lymphoblastic leukemia 1c Osteomyelitis transverse myelitis, paraplegia	
32	1943	7	12 May 1946	3	1a Myelogenous leukemia Other Psychosis with syphilitic meningo encephalitis	
46	1943	128.5	12 January 1967	23	1a Intracerebral hemorrhage 1b Thrombocytopenia 1c Acute leukemia myeloblastic	
64	1943	336	6 December 1971	28	1a Chronic granulocytic leukemia	
Plant A nonqualifying cases						
54	1944	1	18 May 1972	28	1a Respiratory arrest 1b Acute leukemia and pseudomonas	Worked <6 months
69	1943	4	13 January 1964	20	1a Medullary failure 1b Cardiac arrest 1c Renal and hepatic failure 2a Myelogenous leukemia	Worked <6 months; leukemia not cause[b]
42	1951	319	14 February 1978	27	1a Acute myelogenous leukemia 1b Sepsis	Died after cut-off date
58	1951	295	5 January 1976	25	1a Gastrointestinal hemorrhage 1b Thrombocytopenia 1c Acute myelocytic leukemia	Nonwhite
66	1942	270	Alive		Chronic lymphatic leukemia[a]	Alive
51	1956	242	Alive		Chronic lymphocytic leukemia and subsequent small cell of the lung	Alive; nonwhite
Plant B qualifying case						
41	1950	10	11 February 1955	4	1a Monocytic leukemia	
Plant B nonqualifying cases						
46	1955	245.5	29 January 1976	20	1a Lobar pneumonia 1b Chronic myelogenous leukemia	Leukemia not cause[b]
47	1955	254	Alive		Lymphatic leukemia	Alive
63	1950	242	31 October 1971	20	1a Malignant lymphoma, well-differentiated Lymphocytic type with lymphocytic leukemia	Leukemia not cause[b]

[a] Concensus diagnosis of company medical staff.
[b] Leukemia was not coded as underlying cause of death by the nosologist.

was 11.89 a and the average annual turnover rate was 6.84 %. Table 7 presents the vital status: 365 were identified as alive, 201 were found to be deceased, and for 34 (5.67 %) the vital status was unknown. The experience of this subgroup resulted in the accumulation of 17,086 person-years at risk of death.

Table 8 contains the observed and expected numbers of deaths and the SMRs for the cause-specific death categories for this subgroup. Deficits of mortality were observed for the categories total mortality, all other cancers, and accidents. The same difficulties with classification prior to 1950, as was previously discussed, affect the same cause-specific categories in table 8. Excesses in cause-specifc mortality were observed in the overall category malignant neoplasms of the lymphatic and hematopoietic tissues and its subcategory leukemia and aleukemia with associated SMRs of 212 and 278, respectively.

Table 9 shows the total mortality pattern for plant B, and it indicates deficits for

Table 7. Vital status of the restricted white males with a least six months of employment at plant A between the beginning of January 1943 and the end of December 1945.[a]

Status	Number of study members	Percentage
Alive	365	60.83
Deceased	201	33.50
Unknown	34	5.67
Total	600	100.00

[a] Person-years at risk from this study population: – 17,085.53.

Table 8. Mortality of the subgroup of white males with at least six months of employment at plant A between the beginning of January 1943 and the end of December 1945.[a]

Cause-specific categories	ICD[b] codes	Number of deaths		Standardized mortality ratio
		Observed	Expected	
Tuberculosis	001–019	1	3.13	32
Malignant neoplasms	140–205	39	45.14	86
Digestive organs and peritoneum	150–159	10	13.96	72
Trachea, bronchus and lung	162–163	13	13.87	94
Male genital organs	177–179	3	3.14	97
Urinary organs	180–181	3	2.58	116
Lymphatic and hematopoietic tissues[c]	200–205	9	4.25	212**
Lymphosarcoma and reticulosarcoma[c]	200	3	1.34	224
Hodgkin's disease[c]	201	1	0.47	213
Leukemia and aleukemia	204	5	1.80	278**
Other neoplasms of the lymphatic and hematopoietic tissues[c]	202, 203, 205	0	0.64	0
All other cancers		1	7.34	14*
Diseases of the nervous system	330–334, 345	15	17.85	84
Diseases of the circulatory system	400–468	102	113.69	90
Diseases of the respiratory system	470–527	8	13.43	60
Diseases of the digestive system	540–581	7	8.88	79
Accidents	800–962	7	14.05	50**
All other causes		22	25.92	85
Total		201	242.09	83*

[a] At the time that these analyses were done, the life-table analysis program of the National Institute for Occupational Safety and Health was assuming mortality rates had remained constant following 1967. Subsequently, the mortality rates for 1968 to 1975 have been incorporated and yield slightly different expected numbers of deaths. For this subgroup of plant A the expected number of leukemia and aleukemia deaths (ICD 204), determined with the updated rates, is 1.83, yielding a standardized mortality ratio of 2.73. This ratio would have a $0.05 < p < 0.1$ with a two-sided test statistic and a $p < 0.05$ with a one-sided test statistic.

[b] ICD = International Classification of Diseases.

[c] Rates are not available prior to 1950 for three subcategories contributing to malignant neoplasms of the lymphatic and hematopoietic tissues category, the lymphosarcoma and reticulosarcoma category, Hodgkin's disease category, and the other neoplasms of the lymphatic and hematopoietic tissues category; therefore, they are counted as zero before 1950. No deaths occurred in these categories before 1950.

* $p < 0.05$, ** $0.05 < p < 0.1$.

Table 9. Mortality of white males with at least six months of employment at plant B between the beginning of January 1950 and the end of March 1976.[a]

Cause-specific categories	ICD[b] codes	Number of deaths		Standardized mortality ratio
		Observed	Expected	
Tuberculosis	001–019	0	0.77	0
Malignant neoplasms	140–205	11	20.78	53*
Digestive organs and peritoneum	150–159	1	5.42	18**
Trachea, bronchus and lung	162–163	5	6.83	76
Male genital organs	177–179	2	0.93	215
Urinary organs	180–181	0	0.99	0
Lymphatic and hematopoietic tissues	200–205	2	2.55	78
Lymphosarcoma and reticulosarcoma	200	1	0.76	132
Hodgkin's disease	201	0	0.51	0
Leukemia and aleukemia	204	1	0.99	101
Other neoplasms of the lymphatic and hematopoietic tissues	202, 203, 205	0	0.29	0
All other cancers		1	4.06	25
Diseases of the nervous system	330–334, 345	3	5.69	53
Diseases of the circulatory system	400–468	39	46.32	84
Diseases of the respiratory system	470–527	5	5.13	97
Diseases of the digestive system		2	5.43	37
Accidents	800–962	11	14.07	78
All other causes		9	16.80	54*
Total		80	114.99	66*

[a] At the time that these analyses were done, the life-table analysis program of the National Institute for Occupational Safety and Health assumed mortality rates had remained constant following 1967. Subsequently, the mortality rates for 1968 to 1975 have been incorporated, and the computer program has undergone minor revisions which have resulted in slightly different expected numbers of deaths.
[b] ICD = International Classification of Diseases.
* $p < 0.05$, ** $0.05 < p < 0.1$.

total mortality, overall malignant neoplasms, malignant neoplasms of the digestive organs and peritoneum, and all other causes. These deficits may also be explained in part by the healthy worker effect. None of the elevated SMRs were statistically significant or appeared to represent a trend in mortality.

Leukemia cases

A number of leukemia cases were identified in former plant A or plant B employees who did not qualify for consideration in the analyses for any of several reasons, including employment of less than six months, employee nonwhite, the death having occurred after the end of the study follow-up, and leukemia listing as secondary cause of death. Table 6 presents personal and general employment data for both the qualifying and the nonqualifying cases from plants A and B.

Discussion

At the same time the National Institute for Occupational Safety and Health became aware of the leukemias at the SBR facilities in Port Neches, Texas, an article by McMichael et al (8) reported the mortality experience of 6,678 male rubber workers observed between 1964 and 1973. The study examined total mortality and various cause-specific categories in the overall rubber worker population and specific worker subgroups. McMichael et al examined age-standardized risk ratios for cause-specific deaths in specific worker subgroups. The risk ratio for lymphatic and hematopoietic malignancies was 6.2 in the synthetic plant. The synthetic plant would be similar to the two Port Neches facilities as far as the styrene-butadiene production operations are concerned. However, this plant also produced other types of rubber periodically. Later, other researchers in the Occupational Health Study Group of the

University of North Carolina (where the research effort of the McMichael et al study was based) expressed reservations about the publicity and the significance of the relative risks since they were based on small numbers (12).

The findings by McMichael et al prompted a more-detailed case-referent study of these cancer deaths by Spirtas et al; the study is described in an unpublished University of North Carolina report entitled "Toxicologic Industrial Hygiene and Epidemiologic Considerations in the Possible Association Between SBR Manufacturing and Neoplasm of Lymphatic and Hematopoietic Tissue." This study revealed an estimated relative risk of dying due to lymphatic and hematopoietic malignancies of 2.4 associated with employment in the synthetic plant.

Andjelkovich et al (1), also from the University of North Carolina's Occupational Health Studies Group, reported the mortality experience of a population from another rubber manufacturing plant observed between 1964 and 1973. The population studied was defined as "any persons who, as of January 1, 1964, were 40 or more years of age and an active or living retired hourly worker from the plant [p 387]." The SMR for neoplasms of the lymphatic and hematopoietic tissues for white male cohort members in the 65- to 84-year-old age group and the 40- to 85-year-old age group demonstrated a statistically significant excess in the monocytic leukemia and the other neoplasms of the lymphatic and hematopoietic tissues subcategories.

In a second paper, Andjelkovich et al (2) reported SMRs for persons employed in specific work areas at the same rubber manufacturing plant studied earlier; they used the entire cohort's mortality experience as a reference for comparison. A statistically significant excess of deaths for malignant neoplasms of lymphatic and hematopoietic tissues was reported for persons whose most representative work area was general services, which would not necessarily involve contact with SBR production.

In an earlier paper by Monson et al (9), mortality experience of all members of the same local union who worked for one company in Akron, Ohio, was presented. The study included 13,571 men who had worked during or after 1935 for at least 5 a. Excesses of deaths due to leukemia were observed for those men working in the tire and the processing divisions. The results of the Monson et al study reinforce the possibility of an association between exposure to SBR production and the development of lymphatic and hematopoietic malignancies.

Both plants in the current study experienced statistically significant deficits in the total mortality category. Excesses of mortality in plant A, though not statistically significant, were observed in the categories of overall malignant neoplasms of the hematopoietic and lymphatic tissues and its subcategories lymphosarcoma and reticulosarcoma, Hodgkin's disease, and leukemia and aleukemia, the largest number of deaths occurring in the last mentioned. The mortality experience of white males with six months of employment in plant A between the beginning of January 1943 and the end of December 1945, a period prior to a major process change, revealed increases in the mortality excesses of the same three categories. The p-values associated with the excesses in the overall category malignant neoplasms of the lymphatic and hematopoietic tissues and the subcategory leukemia and aleukemia, though greater than the arbitrarily chosen significance level of 0.05, were less than 0.1. Such excesses, though derived from relatively small numbers of observed deaths, are approaching statistical significance. These findings are consistent with those of McMichael et al (8) and the unpublished report by Spirtas et al. In addition, the independent investigations of rubber manufacturing facilities by Andjelkovich et al (1, 2) and Monson et al (9) reinforce the possibility of an association between working with SBR and the development of lymphatic and hematopoietic malignancies.

Analyses using detailed work history assignments of the study group members could not be conducted at the time of this report. Such analyses are planned and will help clarify whether the observed excess in malignancies of the hematopoietic and lymphatic tissues might be based on a risk experienced by specific subgroups of the overall cohort. Length of employment and time since initial employment were considered but did not demonstrate any discernible pattern in these three popula-

tions. In an attempt to avoid the oversimplification of these issues, we have deferred their discussion until the detailed work history assignment can be incorporated into the analyses. Of particular interest would be the association between mortality experience and specific work assignments of employees who had worked at least six months before the end of December 1945. The available information indicates that the excesses in mortality of neoplasms of the lymphatic and hematopoietic tissues were greater for this group, though not statistically significant.

In closing we would like to make two observations about the results of this study. One concerns the ability of an investigation to detect a significant difference between observed and expected cause-specific mortality which is the statistical power of the study. The statistical power is derived from the expected rate of the cause-specific mortality and the person-years at risk. In this study, three modest study cohorts (which had accumulated 34,187; 19,742 and 17,086 person-years at risk) were considered, and the cause-specific mortality of interest was that of leukemia (which has an annual mortality rate for white males of approximately 8.81/100,000 in the United States). These data result in low power, ie, limited ability to detect significant differences, unless one is interested in large relative risk associated with exposure. In the table of appendix 1, the power percentages indicate that it is unlikely that a doubling of the expected occurrence of leukemia would be identified as significant, but likely that four times the expected occurrence would be identified.

The second observation has to do with the use of a two-sided test statistic, which is conservative in its ability to detect significant differences, if there is no reason to believe the environment would be protective against cause-specific mortality (acknowledging the operation of the employment selection bias known as the healthy worker effect). Historically, it was the custom at the National Institute for Occupational Safety and Health to use the conservative two-sided test statistic. Prior to and at the time this report was prepared and originally presented, two of the authors (TJM and RAL) were debating the relative merits of one-sided versus two-sided test statistics. Although we subsequently agreed that the one-sided test statistic was more appropriate for tests of a specific hypothesis about a potential excess risk of cause-specific mortality, we have left the two-sided test statistic in this paper since the results had already been presented in that way. The reader may want to consider these two observations in evaluating the results, especially in those related to malignancies of the hematopoietic and lymphatic tissues. If a one-sided test statistic had been used, the mortality for the leukemia and aleukemia subcategory would have been statistically significant at the 0.05 level for the subgroup of plant A.

Conclusions

No statistically significant excess in cause-specific mortality was detected in any of the three study groups (overall plant A, plant B, or restricted plant A). Excess mortality, though not statistically significant for specific categories of neoplasms of the lymphatic and hematopoietic tissues, was observed for both overall plant A and the restricted plant A study groups. These findings continue to suggest, as have four previous reports, that the production or manufacturing of SBR may be associated with an excess of lymphatic and hematopoietic neoplasms.

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Appendix 1

Determination of power percentages

Power = $Z_{1-\beta} = Z\alpha - 2(R-1)(E)$ based on the Poisson distribution and a two-sided test statistic

R = minimum relative risk to be detected

E = the expected number of leukemia deaths, calculated from the expected rates and person-years at risk

Power in percent

Cohort	Relative risks 2X	Relative risks 4X
Overall plant A	26 %	88 %
Overall plant B	13 %	51 %
Subgroup of plant A	20 %	77 %

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