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Mortality among workers engaged in the development or manufacture of styrene-based products — an update

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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 Health* 1992; 18:145-54. Mortality was updated another 11 years through 1986 for a previously studied cohort of 2904 male chemical workers who were potentially exposed to styrene and related materials for a year or more between 1937 and 1971. Substantial deficits in mortality from all causes and total cancer were observed in the cohort when it was compared with white males in the United States, and also other chemical workers who were unexposed to styrene-based products. Mortality from leukemia was slightly less than expected during the updated period, in contrast to an excess of lymphatic leukemia observed in the original period. Yet small elevations in risk of other types of lymphatic cancer, particularly multiple myeloma, persisted. The risk of these cancers did not increase with estimated intensity or duration of styrene exposure. The findings are discussed in context with those of studies of similarly exposed workers in related industries.

Key terms: acrylonitrile, benzene, 1,3-butadiene, cancer, multiple myeloma, occupational disease.

In 1980, Ott et al (1) reported the results of a cohort mortality study of 2904 chemical workers engaged in the development or production of styrene-based products. These workers were potentially exposed to a number of agents of current toxicologic interest, including styrene monomer, benzene, acrylonitrile, 1,3-butadiene, ethylbenzene, dyes and pigments, polymer dusts, and extrusion fumes. As a consequence of a mortality surveillance program conducted at The Dow Chemical Company (2), 11 years of additional follow-up are now available for this cohort. The results of their updated mortality experience through 1986 have been analyzed, described, and interpreted in context with the findings from studies of similarly-exposed workers in related but different industries.

Subjects and methods

A detailed description of the methods by which the cohort was recruited and those by which the exposures were classified is provided elsewhere (1). In brief, employees were identified from annual department census lists for each production or research unit beginning in 1937 and continuing through 1970. Copies of work histories were obtained for each of the identified workers, and those men who were employed less

than one year in the work areas of interest were excluded. Twenty-five female employees were also excluded because of their small number.

The original study used a complex exposure classification scheme to handle both the multiple chemical agents in the work environment and the varying levels of exposure that existed between jobs. For consistency, this coding scheme was retained for the updated study. A brief summary of the method is presented below, but once again the reader is referred to the original report (1) for a detailed description.

Manufacturing jobs held between 1937 and 1977 were grouped according to similar exposure profiles to form 57 categories of common exposure experiences. Each of the categories was individually evaluated by an industrial hygienist and was assigned an exposure intensity code with respect to the five chemical agent groupings displayed in table 1. Some of the categories were judged to have involved exposure to more than one of the agent groupings. To improve the clarity of presentation, the convention used by Ott et al to name the agent groups (ie, vapors 1, vapors 2, etc) was abandoned in favor of explicitly presenting the primary agents and exposure levels as outlined in table 1.

Because of their idiosyncratic nature, research jobs were judged as not classifiable with regard to exposure to each of the agent groupings. They were of epidemiologic interest anyway, so they were included in the study, but were analyzed separately.

Coded information on each worker (ie, employee name, employee identification number, social security number, job assignments coded to the 57 common exposure experience categories, and associated dates of assignments) was retrieved from the key-punch cards

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Table 1. Categorization of exposures according to the five primary agent groupings. (TWA = time-weighted average)

Agent grouping ^a	Code ^a	Description of primary agents
Vapors 1	A	Styrene and ethylbenzene
	B	1-4 ppm 8 h TWA ≥ 5 ppm 8 h TWA
Vapors 2	A	Benzene, alkylbenzene compounds
	B	≥ 1 ppm 8 h TWA
Vapors 3	A	Styrene, ethylbenzene and acrylonitrile in approximately equal concentrations
	B	1-4 ppm 8 h TWA ≥ 5 ppm 8 h TWA
Extrusion fumes and polymer dust	A	Styrene, ethylbenzene, oligomers of styrene, mineral oil, polymer dusts
	B	Predominate dust exposure Predominate fume exposure
Colorants	A	A wide variety of dyes and pigments
	B	Indirect exposure Direct exposure

^a As coded by Ott et al (1).

used for the original study. A file of the cohort was then linked to the company's central mortality surveillance data base to identify both the vital status of the workers as of 1 January 1987 and the causes of death of the deceased. This mortality surveillance system has been established and maintained to permit the efficient conduct of health studies of the Dow work force (2).

Table 2 presents the updated employment and vital status of the cohort. During the 11 years of additional follow-up, the total number of deaths among the workers increased from 320 to 687. (One additional death which occurred prior to 1976 and was missed in the original study was identified.) Nine workers (0.4%) could not be traced and were considered lost to the follow-up.

Person-years at risk were accumulated for each eligible worker across five-year age and calendar year intervals beginning with the qualifying date of exposure

(ie, one year after first assignment in a styrene work area for the general analysis or 1 January 1940, whichever was later) and ending with the date last known alive, or 1 January 1987, whichever was earliest. The cohort members contributed nearly 90 000 person-years at risk for an average follow-up of 30.9 years per worker.

Cause-specific mortality among the cohort was compared against that of the white male population of the United States (US) with the use of a modified life-table program developed by Monson (3). The standardized mortality ratio (SMR) was calculated as a ratio of the observed to the expected number of deaths multiplied by 100. The 95% confidence interval (95% CI) was calculated for each SMR estimate.

Analyses were done of mortality across major work areas (ie, styrene monomer and finishing; styrene-butadiene latex; product research and development; polymerization, coloring and extrusion), agent groupings, mutually exclusive groups defined by exposure and socioeconomic status, duration of exposure, and latency. Employees could contribute person-years at risk to several categories of those variables consistent with their time dependency. The trends across SMR estimates specific for different exposure groupings were estimated with the use of Breslow's chi-square test with one-degree of freedom (4).

Mortality among the cohort was also compared with that of all other Michigan-based Dow employees, as adjusted for age, interval since entry into follow-up, and pay status (ie, salary versus hourly). This comparison was achieved through the direct adjustment of mortality rates according to an adaptation of the Mantel-Haenszel method for cohort studies (5). The Michigan-based cohort was chosen for comparison purposes because more than 80% of the styrene-based cohort was also from the Michigan location. It includes a sufficiently large mix of administrative, production, and research staff, a small percentage of whom have had occupational exposures to other potentially haz-

Table 2. Vital and employment status of the cohort by location and type of plant as of 1 January 1987.

Population group	Total	Company records			Left company		
		Working	Retired	Dead	Dead	Alive	Un- known
Company location							
Michigan	2360	375	924	411	150	493	7
Texas	296	27	114	70	25	59	1
Connecticut	161	13	35	8	11	93	1
California	87	17	27	10	2	31	—
Type of plant or activity ^a							
Monomer manufacturing and finishing	448	30	193	114	35	75	1
Polymerization, coloring and extrusion of styrene-based products	1419	246	499	241	85	342	6
Styrene/butadiene latex	420	92	160	57	22	88	1
Product research and development	817	112	343	117	49	195	1
Total eligible	2904	432	1100	499	188	676	9

^a Employees can be counted more than once since some could have worked for one or more years in multiple plants.

ardous materials, including vinyl chloride, asbestos, chloromethyl ethers, and organic dyes (2). These comparison workers were more likely to be socioeconomically similar to the exposed group and to share similar life-style experiences than the US white male comparison group.

Results

Overall, in comparison with the US population, the cohort continued to experience statistically significantly fewer than expected deaths from all causes combined, including nearly every major category (total cancer, arteriosclerotic heart disease, nonmalignant respiratory diseases, diseases of the digestive system, and external causes of death) (table 3). For no cause of death did the cohort display a significantly higher mortality rate. Nonsignificant elevations were observed for stomach cancer (SMR 127, 95% CI 64–228), the category of lymphatic and hematopoietic cancer (SMR 144, 95% CI 95–208), and each of its subcategories, including Hodgkin's disease (SMR 222, 95% CI 71–518), non-Hodgkin's lymphoma (SMR 117, 95% CI 47–240), multiple myeloma (SMR 184, 95% CI 74–380), and leukemia (SMR 118, 95% CI 54–224).

There was a nonstatistically significant increase in mortality from cancers of lymphatic and hematopoietic tissue (SMR 144, 95% CI 95–208). This finding was due to small to modest excesses of mortality from each of the individual causes that comprise the category. Ott et al (1) originally noted seven deaths coded to leukemia and three additional deaths coded to other causes, but for which the death certificate mentioned leukemia as a contributing cause or under other significant conditions. They also discussed one living case of leukemia. During the updated follow-up period, two new deaths occurred from leukemia compared with nearly four expected deaths from this cause. These two included a megakaryocytic leukemia and a subacute granulocytic leukemia. In addition, the one living person identified by Ott et al as having leukemia eventually died in 1984 of a myocardial infarction, 13 years after having been first diagnosed with chronic lymphocytic leukemia.

During the updated period two additional deaths occurred from Hodgkin's disease, four from non-Hodgkin's lymphoma, and four from multiple myeloma. These values compare with 0.6, 3.8, and 1.8 expected deaths from these conditions, respectively. It should be noted that one of the new deaths from multiple myeloma was discussed as an incident case by Ott et al (1).

The same general mortality patterns persisted when the cohort was instead compared with all other Michigan-based Dow employees (table 4). However, the excess multiple myeloma was, in this instance, statistically significant [rate ratio (RR) 2.45, 95% CI

Table 3. Observed (O) and expected (E) deaths by cause, standardized mortality ratio (SMR) and 95% confidence interval (95% CI) — total styrene-based products cohort, 1940–1986.^a

Cause of death ^b	O	E ^c	SMR ^d	95% CI
Infective and parasitic diseases (001–139)	5	12.0	42	13–98
Tuberculosis (010–019)	1	5.7	..	0–97
All malignant neoplasms (140–209)	162	198.8	81	69–95
Buccal cavity and pharynx (140–149)	1	6.0	..	0–92
Digestive organs and peritoneum (150–159)	40	51.6	77	55–105
Esophagus (150)	3	4.8	63	13–185
Stomach (151)	11	8.6	127	64–228
Large intestine (153)	15	17.5	86	48–141
Rectum (154)	2	5.1	..	4–141
Liver and biliary passages (155–156)	3	3.9	76	15–223
Pancreas (157)	5	10.3	49	16–113
Respiratory system (160–163)	58	72.5	80	61–103
Larynx (161)	1	2.9	..	0–195
Lung (162–163)	56	69.0	81	61–105
Bone (170)	1	0.8	..	2–709
Skin (172–173)	4	4.1	99	27–253
Prostate (185)	10	11.7	85	41–157
Testis (186)	1	1.2	..	1–478
Bladder (188)	2	5.0	..	4–144
Kidney (189)	5	5.1	98	32–230
Eye (190)	—	0.2	..	0–2389
Brain and other nervous system tissues (191–192)	6	6.3	95	35–206
Thyroid (193)	—	0.4	..	0–997
Lymphatic and hematopoietic tissue (200–209)	28	19.5	144	95–208
Hodgkin's disease (201)	5	2.3	222	71–518
Non-Hodgkin's lymphoma (202, 203)	7	6.0	117	47–240
Multiple myeloma (203)	7	3.8	184	74–380
Leukemia and aleukemia (204–207)	9	7.6	118	54–224
Other and unspecified sites (171, 175, 194–199)	6	14.5	41	15–90
Diabetes mellitus (250)	11	12.7	87	43–155
Diseases of the circulatory system (390–458)	361	436.4	83	74–92
Arteriosclerotic heart disease (410–413)	251	310.1	81	71–92
Cerebrovascular disease (430–438)	45	49.4	91	66–122
Nonmalignant respiratory diseases (460–519)	30	54.2	55	37–79
Emphysema (492)	9	10.6	85	39–161
Diseases of the digestive system (520–579)	28	44.4	63	42–91
Gastric and duodenal ulcer (531–534)	3	5.2	58	12–169
Cirrhosis of the liver (571)	13	25.2	52	27–88
Diseases of the genitourinary system (580–599)	5	11.7	43	14–100
Symptoms, senility and ill-defined conditions (790–799)	7	10.2	69	27–141
External causes of death (E800–E999)	56	94.8	59	45–77
Accidents (E800–E949)	38	63.9	59	42–82
Motor vehicle accidents (E810–E825)	15	30.3	50	28–82
Suicide (E950–E959)	14	22.3	63	34–105
All causes (001–999)	687	903.3	76	70–82

^a Person-years of observation = 89 825.

^b Code of the International Classification of Diseases, eighth revision, in parentheses.

^c Based on United States mortality rates for white males.

^d SMR not calculated when fewer than three deaths were observed.

1.07–5.65), and there was also a significant excess of deaths in the category of symptoms, senility and ill-defined conditions (RR 3.80, 95% CI 1.68–8.56).

Table 4. Summary of mortality among the styrene-based products cohort relative to that among unexposed workers from the Michigan manufacturing location.^a (O = observed number of deaths, E = expected number of deaths, RR = relative risk, 95% CI = 95% confidence interval)

Cause of death ^b	Workers unexposed to styrene-based products		Styrene-based products cohort		
	O	O	E ^c	RR ^d	95% CI
Malignant neoplasms (140—209)	1552	162	184.3	0.87	0.74—1.03
Digestive organs and peritoneum (150—159)	405	40	45.8	0.87	0.63—1.21
Respiratory system (160—163)	519	58	64.5	0.89	0.67—1.17
Genital organs (185, 186)	112	11	10.8	1.00	0.53—1.89
Urinary organs (188, 189)	72	7	8.1	0.86	0.39—1.88
Lymphatic and hematopoietic tissue (200—209)	161	28	20.1	1.39	0.92—2.08
Hodgkin's disease (201)	15	5	2.1	2.43	0.94—6.28
Non-Hodgkin's lymphoma (200, 202)	47	7	6.2	1.09	0.48—2.49
Multiple myeloma (203)	21	7	2.9	2.45	1.07—5.65
Leukemia and aleukemia (204—207)	66	9	7.6	1.18	0.58—2.39
Diabetes mellitus (250)	100	11	10.5	1.07	0.57—1.98
Diseases of the circulatory system (390—458)	3538	361	398.9	0.90	0.81—1.01
Arteriosclerotic heart disease (410—413)	2528	251	289.7	0.86	0.76—0.98
Cerebrovascular disease (430—438)	467	45	47.8	0.95	0.70—1.29
Nonmalignant respiratory system diseases (460—519)	362	30	40.7	0.75	0.52—1.08
Diseases of the digestive system (520—579)	235	28	28.3	0.98	0.65—1.45
Diseases of the genitourinary system (580—599)	67	5	6.7	0.73	0.29—1.85
Symptoms, senility and ill-defined conditions (790—799)	17	7	1.9	3.80	1.68—8.56
External causes of death (E800—E999)	566	56	74.3	0.75	0.56—0.99
All causes (001—999)	6759	687	780.1	0.88	0.81—0.95

^a Person-years: workers unexposed to styrene-based products: 696 765; workers exposed to styrene-based products: 89 825.^b Code of the International Classification of Diseases, eighth revision, in parentheses.^c Expected deaths based on mortality rates of the unexposed workers adjusted for age, interval since entry, and pay status (hourly, salary).^d Mantel-Haenszel risk relative to unexposed workers.

Analysis of mortality across the four major work areas (table 5) showed a nonstatistically significant excess of lymphatic and hematopoietic cancer among employees from the polymerization, coloring and extrusion work area. In particular, multiple myeloma was elevated in this group. By contrast, the excess mortality in the category of symptoms, senility and ill-defined conditions occurred exclusively in the styrene monomer and finishing work area.

The mortality from nearly every cause of death analyzed was less than expected for the employees who worked in product research and development. This was true for both salaried professional and management personnel and hourly technicians and other support staff who worked in this area (not shown). There were, however, nonstatistically significant increases in mortality from Hodgkin's disease and non-Hodgkin's lymphoma, based on two cases of each, among the professionals.

An examination of mortality across the agent groupings taken individually (not shown) revealed deficits of mortality from all causes combined and total cancer within each group. There were statistically significant increases, however, in mortality from lymphatic and hematopoietic cancer among the workers categorized as exposed to styrene and ethylbenzene in the low range of a time-weighted average (TWA) of 1—4 ppm (SMR 236, 95% CI 122—411) and from arterio-

sclerotic heart disease among the workers exposed to a TWA of ≥ 5 ppm of styrene and ethylbenzene (SMR 134, 95% CI 104—171). Further investigation of the heart disease excess showed it to be concentrated primarily among the persons with short (<1 year) to moderate (1—4 years) duration of exposure. Few of the deaths from heart disease occurred while the employees were in exposure areas, the majority occurring only many years after the workers had left work in these areas.

Table 6 presents a summary of mortality from lymphatic and hematopoietic cancer by duration of exposure to each of the agent groupings. (Only those groupings with at least two lymphatic and hematopoietic cancer deaths are shown.) None of the excess mortality in this category of death appeared to be concentrated in the longer-term exposure category. Instead, the excess appeared to be confined to workers who were exposed for less than five years. In addition, there was no apparent relation to intensity of styrene exposure, since the risk among workers in the high exposure group (ie, ≥ 5 ppm) was unremarkable. There was no pattern evident when lymphatic and hematopoietic cancer mortality was examined by year of first exposure. Analyses allowing for a 15-year minimum latency period revealed a statistically significant mortality risk (24 observed, SMR 160, 95% CI 102—238). However, there was no significant trend of increasing

Table 5. Observed (O) and expected^a (E) deaths and the standardized mortality ratio (SMR) by major work area — styrene-based products cohort, 1940–1986.^b

Cause of death ^c	Work Area ^d											
	Styrene monomer and finishing			Styrene-butadiene latex production			Product research and development			Polymerization, coloring, extrusion		
	O	E	SMR ^e	O	E	SMR ^e	O	E	SMR ^e	O	E	SMR ^e
Malignant neoplasms (140–209)	39	41.7	94	13	22.0	59	44	65.0	68 ^f	82	92.7	88
Buccal cavity and pharynx (140–149)	..	1.3	..	—	0.7	..	—	2.0	..	1	2.8	—
Digestive organs and peritoneum (150–159)	14	11.2	125	5	5.5	92	10	16.6	60	15	23.9	63
Respiratory system (160–163)	14	15.1	93	5	8.3	60	12	24.2	50 ^f	33	33.6	98
Genital organs (185, 186)	1	3.0	..	1	1.2	..	4	4.1	98	5	6.0	83
Urinary organs (188, 189)	1	2.2	..	—	1.1	..	3	3.2	94	4	4.7	85
Lymphatic and hematopoietic tissue (200–209)	5	3.9	128	1	2.2	..	6	6.3	95	16	9.3	172
Hodgkin's disease (201)	2	0.4	..	—	0.3	..	2	0.7	..	1	1.1	..
Non-Hodgkin's lymphoma (200, 202)	1	1.2	..	—	0.7	..	2	2.0	..	4	2.9	138
Multiple myeloma (203)	1	0.9	..	—	0.4	..	1	1.3	..	5	1.7	294
Leukemia and aleukemia (204–207)	1	1.5	..	1	0.9	..	1	2.4	..	6	3.6	165
Diabetes mellitus (250)	3	2.7	112	..	1.3	..	3	4.0	75	7	6.0	117
Diseases of the circulatory system (390–458)	87	95.7	91	42	44.0	95	88	137.5	64 ^f	187	204.6	91
Arteriosclerotic heart disease (410–413)	53	67.4	79	30	32.2	93	59	98.7	60 ^f	140	145.0	97
Cerebrovascular disease (430–438)	16	11.3	141	2	4.4	..	9	14.8	61	19	23.5	81
Nonmalignant respiratory system diseases (460–519)	6	12.1	50	3	5.3	56	8	17.4	46 ^f	16	24.9	64
Diseases of digestive system (520–579)	5	8.8	57	3	5.1	59	7	14.3	49	18	21.2	85
Diseases of genitourinary system (580–599)	2	2.6	..	1	1.0	..	2	3.6	..	2	5.4	..
Symptoms, senility and ill-defined conditions (790–799)	6	2.0	299 ^f	1	1.2	..	—	3.3	..	..	4.9	.. ^f
External causes of death (E800–E999)	7	14.9	47 ^f	13	12.0	108	17	29.3	58 ^f	26	48.0	54 ^f
All causes (001–999)	162	188.5	86	82	96.3	85	178	287.4	62 ^f	350	426.4	82 ^f

^a Expected deaths based on United States mortality rates for white males.^b Person-years: styrene monitoring and finishing: 13 421; styrene-butadiene latex production: 11 754; product and research development: 27 972; polymerization, coloring and extrusion: 46 046.^c Code of the International Classification of Diseases, eighth revision, in parentheses.^d Employees may be counted more than once in the table since some could have worked for one or more years in multiple plants.^e SMR not calculated when fewer than three deaths were observed.^f Statistically significant at $\alpha = 0.05$, two tailed.**Table 6.** Observed (O) and expected^a (E) mortality from lymphatic and hematopoietic cancer by agent grouping and duration of exposure — styrene-based product cohort, 1940–1986.

Agent grouping ^b	Duration of exposure ^c								Chi-square test for trend (p-value)
	<1 year		1—4 years		≥5 years		Total		
	O	E	O	E	O	E	O	E	
Styrene and ethylbenzene 1—4 ppm	4	1.4	7 ^d	2.2	1	1.5	12 ^d	5.1	0.19
Styrene and ethylbenzene ≥5 ppm	—	1.2	4	1.1	—	0.7	4	3.0	0.80
Benzene and alkylbenzenes ≥1 ppm	—	0.8	3	1.6	2	2.3	5	4.8	0.88
Predominate dust exposure	2	0.8	1	1.6	2	1.2	5	3.6	0.80
Predominate fume exposure	5 ^d	1.5	3	1.7	2	2.0	10	5.1	0.13
Colorants									
Indirect exposure	3 ^d	0.6	2	0.7	—	0.8	5	2.1	0.05
Direct exposure	2	1.9	4	2.1	1	0.9	7	4.9	0.87

^a Expected deaths based on United States mortality rates for white males.^b Employees may be counted more than once in the table since some could have been exposed to several agent groupings as a consequence of job mobility.^c Exposure duration calculated through 1 January 1976.^d Statistically significant at $\alpha = 0.05$, two-tailed.

risk across three categories (ie, <15, 15–34, and ≥35 years) of time since first exposure ($P=0.36$).

The subjects were allocated to one of 13 mutually exclusive groups on the basis of exposure and socioeconomic considerations (table 7). This grouping showed the elevated lymphatic and hematopoietic cancer mortality to be mostly confined to persons who were professionals (7 observed, SMR 177, 95% CI 71–365), and to production workers who were exposed to extrusion fumes and directly or indirectly to colorants (9 observed, SMR 263, 95% CI 120–500).

Discussion

In 1980, Ott et al (1) reported the mortality experience of this cohort of workers through 1975. At that time, the group displayed fewer than expected deaths from all causes combined and from malignant neoplasms. An excess of lymphatic leukemia incidence and mortality was observed among a subgroup of employees who had exposure to polymer extrusion fumes, solvents, and colorants. However, no relationship was found with duration or estimated intensity of exposure to these agents. The authors were unable to establish an etiology for the leukemias.

The current study updated the mortality among this cohort of workers another 11 years through 1986. During this updated period, the total number of deaths increased by more than twofold. Even so, mortality

from all causes and total cancer remained below the expected levels, based on death rates of either the US male population or a comparable group of workers without exposure to styrene-based products. There were some statistically significant excesses in specific categories of death among particular subgroups of workers, and these deserve further discussion.

Mortality from symptoms, senility and ill-defined conditions was significantly elevated in the total cohort in comparison with that of the unexposed workers, and it was particularly increased among employees assigned to styrene monomer and finishing operations. Six of the seven deaths in this category occurred among employees from the Texas facility. The state of Texas is known to have an abnormally high death rate from symptoms, senility and ill-defined conditions, and this regional phenomenon appears to be the most likely explanation for the finding in this cohort (6).

A statistically significant excess of mortality from arteriosclerotic heart disease was observed among the employees who were categorized as having a potential for styrene and ethylbenzene exposures of ≥5 ppm. There was no evidence of a trend with duration of exposure, nor did the excess occur among workers while they were employed in jobs with potential exposure at these levels. Lacking a biological model or any support for this finding from other studies, it might reasonably be ascribed to chance. This is especially true given the multiple comparisons that were done.

Given the a priori focus on mortality from lymphatic and hematopoietic cancer, a more-detailed discussion of the findings in this area is warranted. Mortality from each form of lymphatic and hemopoietic cancer was slightly elevated in the total cohort. Yet the excesses were not concentrated among the workers categorized as having the most intense exposures to styrene, nor were they concentrated among workers with longer term exposure in any of the areas. Instead the excesses were confined to men who had worked for relatively brief periods of time (ie, <5 years) in polymerization, extrusion, and colorant operations. In particular, employees who had exposure to extrusion fumes and colorants showed the highest risks, especially from leukemia and multiple myeloma. This finding is in accord with the findings originally reported by Ott et al (1). Once again, the relatively small number of deaths and the multiple exposures of the workers make it impossible to isolate a particular agent as a likely cause of the excess, if indeed, any of these cases are related to the work environment.

The results of cohort studies conducted in related, but different, industries are important to consider. Table 8 summarizes seven published mortality studies (7–13) of workers who were potentially exposed to styrene-based products in the three general industry classifications of styrene-butadiene rubber, styrene monomer and polymerization, and reinforced plastics. It is critical to differentiate the exposure circumstances

Table 7. Observed (O) and expected^a (E) deaths from lymphatic and hematopoietic cancer, the standardized mortality ratio (SMR), and 95% confidence intervals (95% CI) by mutually exclusive exposure and socioeconomic groupings.

Grouping	O	E ^b	SMR ^c	95% CI
Professionals	7	3.6	177	71–365
Research only, nonprofessionals	1	3.0	..	0–187
None of the agents present	—	0.5	..	0–784
Styrene/ethylbenzene only	2	1.1	..	21–661
Benzene/alkylbenzenes	3	2.5	119	21–347
Mixed exposures to styrene, ethylbenzene, benzene, alkylbenzenes, acrylonitrile	2	0.6	..	36–1141
Polymer dusts only	1	0.4	..	3–1295
Colorants and polymer dusts	1	1.5	..	1–367
Extrusion fumes, no colorants	—	0.2	..	0–1951
Extrusion fumes; indirect colorants; styrene, ethylbenzene or acrylonitrile	5	1.5	334	108–780
Extrusion fumes; direct colorants; styrene, ethylbenzene or acrylonitrile	4	2.3	177	48–453
Benzene plus fumes, dusts or colorants	—	1.1	..	0–326
Polymer dusts plus styrene/ethylbenzene	2	0.2	..	94–3028

^a Expected deaths based on United States mortality rates for white males.

^b Person-years were not accumulated for an employee until he satisfied the criteria of the grouping to which he was ultimately assigned. Thus the person-years and expected numbers of deaths obtained by summing across all mutually exclusive groupings were slightly less than when summed independent of groupings.

^c SMR not calculated when fewer than three deaths were observed.

in each of these industries before considering their individual or collective results.

Two studies have been done of workers in the styrene-butadiene rubber industry (7, 8). The ratio of 1,3-butadiene to styrene used to manufacture styrene-butadiene rubber was approximately three parts butadiene to one part styrene. No industrial hygiene monitoring data are available prior to the 1970s to estimate historical exposures to butadiene, styrene, or other chemicals (14). Surveys done since the middle 1970s have shown considerable variability in exposures across jobs within the industry. Typically, styrene and butadiene exposures have been measured below 5 ppm as an 8-h TWA, and benzene exposures have been below 1 ppm. Yet exposures were likely to have been higher in the past, especially during World War II when the industry was getting started and the demand for large production volumes was great.

Likewise, historical exposures in the styrene monomer and polymerization industry are largely unknown, but are likely to have been similar to those that existed

in the styrene-butadiene rubber industry, except that exposures to butadiene monomer would have been minimal. Multiple concomitant exposures were common to both industries. The list of materials includes benzene and alkylbenzene compounds, styrene, formaldehyde, antioxidants, extender oils, acrylonitrile, organic dyes, and pigments.

By contrast, exposures to styrene in the reinforced plastics industry have been much higher, ranging upwards to several hundred parts per million as recently as the 1970s (Ahlmark A: "Styrene Research Epidemiological Report"; prepared for the Swedish Plastics Federation, 1 October 1978). A much narrower spectrum of confounding agents was encountered, but did include glass fibers, acetone, methyl ethyl ketone, organic peroxides, and asbestos. For the aforementioned reasons, studies of workers in the reinforced plastics industry may be more suitable for addressing the potential hazards of styrene than studies in either the styrene-butadiene rubber or styrene monomer and polymerization industries.

Table 8. Summary of studies of workers potentially exposed to styrene.

Study	Industry type	Cause									
		Leukemia		Hodgkin's disease		Non-Hodgkin's lymphoma		All lymphomas		All lymphatic and hematopoietic cancer ^a	
		O	E	O	E	O	E	O	E	O	E
Matanoski et al (7)	Styrene-butadiene rubber										
White workers		18	20.9	8	6.1	6	10.7	14	16.8	48	52.2
Black workers		4	1.8	—	0.6	1	0.8	1	1.4	7	4.8
Total		22	22.7	8	6.7	7	11.5	15	18.2	55	57.0
Meinhardt et al (8)	Styrene-butadiene rubber										
Plant A		5	2.5	1	0.9	3	1.7	4	2.6	9	5.8
Plant B		1	1.0	—	0.5	1	0.7	1	1.2	2	2.5
Total		6	3.5	1	1.4	4	2.4	5	3.8	11	8.3
Hodgson & Jones (9)	Styrene monomer and polymer operations										
Total		—	0.3	..	..	..	..	3	0.6	3	0.9
Nicholson et al (10)	Styrene monomer and polymer operations										
Total		1	0.8	..	..	..	..	1	1.3	2	2.0
Coggon et al (11)	Reinforced plastics industry										
Total		3	6.0	1	2.4	1	4.2	2	6.6	6	14.9
Okun et al (12)	Reinforced plastics industry										
Total		—	1.7	..	..	..	..	—	2.1	0	4.2
Wong (13)	Reinforced plastics industry										
Males		4	3.9	3	2.0	—	2.2	3	4.2	8	10.2
Females		1	0.9	—	0.4	—	0.4	—	0.8	1	2.1
Total		5	4.8	3	2.4	—	2.6	3	5.0	9	12.3

^a Includes multiple myelomas; however observed and expected deaths from multiple myeloma were not explicitly presented in any of the studies.

Almost without exception, each of the seven studies listed in table 8 reported mortality from all causes and total cancer among the cohorts to be at or below expected levels. Small numbers of observed and expected deaths from lymphatic and hematopoietic cancer plagues the interpretation of this outcome in six of the studies. An exception was the study by Matanoski et al (7), which combined data on 12 160 workers from eight styrene-butadiene rubber plants. That study reported no increase in lymphatic and hematopoietic cancer mortality overall in the cohort. When the 9769 workers with complete work histories were assigned to one of four work areas based on the job they had held the longest, there was a statistically significant excess for black (6 observed, SMR 507, 95% CI 187–1107), but not white (13 observed, SMR 110, 95% CI 58–187), workers assigned to production. An examination of the subcategories showed statistically significant excess leukemia among black production workers (3 observed, SMR 656, 95% CI 135–1906) and excess other lymphatic cancer among all production workers (9 observed, SMR 260, 95% CI 119–494). The nine deaths from other lymphatic cancer included four cases of non-Hodgkin's lymphoma and five of multiple myeloma.

No trend in mortality risk was apparent by duration of work or elapsed time since first employment in the styrene-butadiene rubber industry. The authors recommended that an assessment of estimated levels of exposure to butadiene and styrene be done for each job and used in a case-referent study (7). They then reported the preliminary results of such a study in which they found the risk of leukemia to be associated with exposure specifically to butadiene (odds ratio 9.4, 95% CI 2.1–22.9), whereas there was no statistically significant increased risk associated with exposure to styrene (7). No other details of the case-referent study were reported, although Acquavella (15) has indicated that there was no validation of the death certificate diagnoses, and the exposure classification did not make use of available industrial hygiene monitoring data, nor did it consider differences in exposure potential across the eight plants. Additional research is being done on this cohort to address these criticisms (15).

Meinhardt et al (8) conducted a cohort study at two styrene-butadiene rubber plants not studied by Matanoski and her co-workers. Attention was originally directed at these two plants because of a 1976 report of two deaths from leukemia among the workers. Subsequent study of the 2756 white males with six or more months of employment at either of the two plants found a nonsignificant excess of lymphatic and hematopoietic cancer mortality among the workers from plant A (9 observed, SMR 155, 95% CI 71–295), but not among the workers from plant B (2 observed, SMR 80, 95% CI 10–289). The majority of the excess mortality at plant A was attributable to an excess of leukemia (5 observed, SMR 203, 95% CI 66–474).

The authors noted that all five men with leukemia at plant A had worked in the period 1943–1945 for at least six months, prior to an operational change from batch to continuous polymerization. They then reanalyzed the data, restricting the cohort to those members meeting that condition. Not surprisingly, the SMR values for total lymphatic and hematopoietic cancer and leukemia were much increased in this subcohort. Lemen et al (16) recently reported that an update to the study by Meinhardt et al is underway.

Initial speculation had focused on styrene as a possible etiologic agent for the increased lymphatic and hematopoietic cancer mortality in the styrene-butadiene rubber industry. In recent years, toxicologic evidence has focused attention on the potential carcinogenic effect of 1,3-butadiene (17, 18) rather than on that of styrene (19). A critical evaluation of the two studies conducted in the styrene-butadiene rubber industry (7, 8) and additional studies of 1,3-butadiene monomer production workers (20, 21) led one reviewer (14) to conclude that there was no convincing evidence linking adverse mortality effects to 1,3-butadiene exposure. This reviewer noted the poor quality of exposure data available and the absence of any relationship between duration of employment or latency and lymphatic and hematopoietic cancer mortality risk. By contrast, a second reviewer (22) examined the same three studies and concluded that they strongly suggested an etiologic association between occupational exposure to 1,3-butadiene and human cancer, specifically lymphatic and hematopoietic cancer. The second reviewer noted that the excess mortality in the three studies tended to be greatest among production and maintenance workers and was absent for office staff. According to this reviewer, the finding of excess mortality among workers exposed during World War II in two of the cohorts (8, 20, 21) was further evidence of a dose-response relationship. He also discounted the apparent inconsistency of subtypes of lymphatic and hematopoietic cancer reported in the different studies, citing evidence that indicates they may all derive from a common multipotential progenitor cell (23). Both reviewers (14, 22) recommended that further efforts be made to quantify the butadiene exposures in the three cohorts, to permit firmer conclusions.

A subset of employees in the current study, particularly the group engaged in styrene-butadiene latex production, experienced 1,3-butadiene monomer exposures similar to those of workers in the styrene-butadiene rubber industry. A possible difference is that the latex product was maintained as an emulsion throughout the operation of the plants. Mortality from lymphatic and hematopoietic cancer was not excessive among the styrene-butadiene latex production workers in the current study (1 observed, SMR 45, 95% CI 1–253). However, this subcohort of workers was small, and only a moderately increased risk could have been detected.

Interpretation of the two studies of workers in general styrene monomer production and polymerization operations (9, 10) is similarly hampered by the small number of observed and expected deaths. Hodgson & Jones (9) reported statistically significant excess lymphatic and hematopoietic cancer mortality among workers producing styrene monomer and polymers (3 observed, SMR 536, 95% CI 110–1565). All three of the deaths were from non-Hodgkin's lymphoma, although one was listed as Hodgkin's disease on the death certificate. Lymphatic leukemia was also reported for one man who was alive. Further analysis found no relationship between risk and length of service in styrene-exposed jobs. The authors noted that one man had worked in styrene-butadiene rubber production, another had had exposure to benzene, a third had had exposure to dyestuffs, antioxidants, and polyolefins, and the fourth had potential exposure to ethylene oxide.

Nicholson et al (10) reported one death each from malignant lymphoma and leukemia (2 observed, SMR 98, 95% CI 12–354) in a cohort of 550 unionized workers with at least five years of employment at a styrene monomer and polymerization facility. They concluded that the information was not definitive, except to indicate that any environmental risk of styrene exposure could not be extraordinary.

In the current study, the subcohort of employees engaged in the production of styrene monomer and polymers experienced exposures most similar to those of the workers in the two studies in the styrene monomer and polymerization industry. Small, nonstatistically significant excesses of mortality from lymphatic and hematopoietic cancer were observed among the employees assigned to styrene monomer and finishing production, or to polymerization, coloring, and extrusion operations. In the former group, the excess was confined to Hodgkin's disease (2 observed, SMR 526, 95% CI 59–1899), whereas in the latter the excess was particularly evident for multiple myeloma (5 observed, SMR 294, 95% CI 95–686) and leukemia (6 observed, SMR 165, 95% CI 60–359). In contrast to the study by Hodgson & Jones (9), non-Hodgkin's lymphoma mortality was not especially elevated in either group.

Other studies of styrene-exposed workers (11–13) have examined mortality in the reinforced plastics industry. None reported lymphatic and hematopoietic cancer or its specific variants to be elevated either overall or in subcohorts defined by duration of exposure, estimated intensity of exposure, or latency. In fact, each found a deficit of mortality, that reported by Coggon et al (10) reaching statistical significance (6 observed, SMR 40, 95% CI 15–88). Thus, among workers from the industry with the highest documented exposures to styrene, there is no evidence of an increased risk of mortality from lymphatic and hematopoietic cancer. This observation is qualified by the fact that the reinforced plastics industry is relatively young, and consequently the length of follow-up of the workers

is modest (ie, <25 years). Continued monitoring of these three cohorts could provide more useful information.

With respect to the current study, the subcohort with styrene exposures which most closely parallel those in the reinforced plastics industry, the styrene-ethylbenzene ≥ 5 ppm TWA group, experienced four deaths from lymphatic and hematopoietic cancer compared with about three expected. It is difficult to draw conclusions based on such small numbers, but it would appear that there is no major risk associated with the potential for higher level styrene exposure in this cohort.

In summary, this update of mortality among employees who have manufactured styrene-based products continued to show the workers to have experienced lower than expected death rates from all causes and total cancer. This is in accord with other studies of workers with similar exposures in related, but different industries. An excess of mortality from lymphatic and hematopoietic cancer was observed for a subgroup of employees who held jobs which involved potential exposure to extrusion fumes, solvents, and colorants. Interpretation of this excess was complicated by the relatively small number of cases, their multiple chemical exposures, and possible confounding by life-style factors.

An excess of lymphatic and hematopoietic cancer mortality was not seen for the workers who produced styrene-butadiene latex, in contrast to recent reports of excess mortality among similarly exposed workers in the styrene-butadiene rubber industry. Nor was a statistically significant excess of mortality observed among the employees considered to have the highest potential exposures to styrene. This observation is consistent with findings from studies of workers in the reinforced plastics industry, which have failed to show excess lymphatic and hematopoietic cancer mortality associated with high-level exposure to styrene.

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References

1. Ott MG, Kolesar RC, Scharnweber HC, Schneider EJ, Venable JR. A mortality survey of employees engaged in the development or manufacture of styrene-based products. *J Occup Med* 1980;22:445–60.
2. Bond GG, McLaren EA, Cartmill JB, Wymer KT, Sobel W, Lipps TE, et al. Cause-specific mortality among male chemical workers. *Am J Ind Med* 1987;12:353–83.
3. Monson RR. Analysis of relative survival and proportional mortality. *Comput Biomed Res* 1974;7:325–32.
4. Breslow NE, Lubin JH, Marek P, Langholtz B. Mul-

- tiplicative models and the analysis of cohort data. *J Am Stat Assoc* 1983;78:1—12.
5. Hakulinen T. A Mantel-Haenszel statistic for testing the association between polychotomous exposure and a rare outcome. *Am J Epidemiol* 1981;113:192—6.
 6. Bond GG, Shellenberger RJ, Fishbeck WA, Cartmill JB, Lasich BJ, Wymer KT, et al. Mortality among a large cohort of chemical manufacturing employees. *J Natl Cancer Inst* 1985;75:859—69.
 7. Matanoski GM, Santos-Burgoa C, Schwartz L. Mortality of a cohort in the styrene-butadiene polymer manufacturing industry (1943—1982). *Environ Health Perspect* 1990;86:107—17.
 8. 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* 1982;8:250—9.
 9. Hodgson JT, Jones RD. Mortality of styrene production, polymerization and processing workers at a site in northwest England. *Scand J Work Environ Health* 1985;11:347—52.
 10. Nicholson WJ, Selikoff IJ, Seidman H. Mortality experience of styrene-polystyrene polymerization workers: initial findings. *Scand J Work Environ Health* 1978;4 Suppl 2:247—52.
 11. Coggon D, Osmand C, Pannett B, Simmonds S, Winter PD, Acheson ED. Mortality of workers exposed to styrene in the manufacture of glass-reinforced plastics. *Scand J Work Environ Health* 1987;13:94—9.
 12. Okun AH, Beaumont JJ, Meinhardt TJ, Crandall MS. Mortality patterns among styrene-exposed boatbuilders. *Am J Ind Med* 1985;8:193—205.
 13. Wong O. A cohort mortality study and a case-control study of workers potentially exposed to styrene in the reinforced plastics and composites industry. *Br J Ind Med* 1990;47:753—62.
 14. Ott MG. Assessment of 1,3-butadiene epidemiology studies. *Environ Health Perspect* 1990;86:135—41.
 15. Acquavella JF. Future directions in epidemiologic studies of 1,3-butadiene-exposed workers. *Environ Health Perspect* 1990;86:129—34.
 16. Lemen RA, Meinhardt TJ, Crandall MS, Fajen JM, Brown DP. Environmental epidemiologic investigations in the styrene-butadiene rubber industry. *Environ Health Perspect* 1990;86:103—6.
 17. Owen PE, Glaister JR. Inhalation toxicity and carcinogenicity of 1,3-butadiene in Sprague-Dawley rats. *Environ Health Perspect* 1990;86:19—25.
 18. Melnick RL, Huff JE, Roycroft JH, Chou BJ, Miller RA. Inhalation toxicology and carcinogenicity of 1,3-butadiene in B6C3F1 mice following 65 weeks of exposure. *Environ Health Perspect* 1990;86:27—36.
 19. Bond JA. Review of the toxicology of styrene. *CRC Crit Rev Toxicol* 1989;19:227—49.
 20. Downs TD, Crane MM, Kim KW. Mortality among workers at a butadiene facility. *Am J Ind Med* 1987;12:311—29.
 21. Divine BJ. An update on mortality among workers at a 1,3-butadiene facility — preliminary results. *Environ Health Perspect* 1990;86:119—28.
 22. Landrigan PJ. Critical assessment of epidemiologic studies on the human carcinogenicity of 1,3-butadiene. *Environ Health Perspect* 1990;86:143—8.
 23. Keinänen M, Griffin JD, Bloomfield CD, Machnicki J, de la Chapelle A. Clonal chromosomal abnormalities showing multiple-cell-lineage involvement in acute myeloid leukemia. *N Engl J Med* 1988;318:1153—8.

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