AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 45:165–176 (2004)

Mortality Patterns Among Workers Exposed to Styrene in the Reinforced Plastic Boatbuilding Industry: An Update

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Background *Mortality was updated through 1998 for 5,204 workers exposed to styrene between 1959 and 1978 at two reinforced plastic boatbuilding plants. The a priori hypothesis: leukemia and lymphoma excesses would be found.*
Methods *Standardized mortality ratios (SMR) and 95% confidence intervals (CI) used Washington State and U.S. rates.*
Results *Overall, 860 deaths occurred (SMR 1.09, CI 1.02–1.17), with excess mortality for esophageal cancer (n = 12, SMR 2.30, CI 1.19–4.02), prostate cancer (n = 24, SMR 1.71, CI 1.09–2.54), and accidents (n = 99, SMR 1.26, CI 1.02–1.53). Among 2,062 highly exposed workers, urinary tract cancer (n = 6, SMR 3.44, CI 1.26–7.50) and respiratory disease (n = 12, SMR 2.54, CI 1.31–4.44) rates were elevated. Urinary tract cancer SMR increased with duration of employment.*
Conclusions *We found no excess leukemia or lymphoma mortality. Unanticipated excess urinary tract cancer and respiratory disease mortality, possibly associated with styrene exposure, are difficult to interpret and could be chance findings.* Am. J. Ind. Med. 45:165–176, 2004. *Published 2004 Wiley-Liss, Inc.*†

KEY WORDS: styrene; reinforced plastic industry; leukemia; cancer mortality; cohort mortality study; urinary tract cancer

INTRODUCTION

Styrene is an organic solvent, a colorless liquid that evaporates easily and has a sweet smell. It is used to make products such as rubber, plastic, insulation, fiberglass, pipes, automobile parts, food containers, and carpet backing. In 2000, an estimated 21 metric tons of styrene were used worldwide, a 50% increase over 1993 use [Kolstad et al., 1995; Chemical Market Associates, 2001]. Eight companies in the U.S. produced >12 billion pounds in 2000 [Chemical Market Reporter, 2001]. In the early 1980s, an estimated 108,000 workers were potentially exposed to styrene, according to the National Occupational Hazard Survey [NIOSH, 1990], while the Occupational Safety and Health Administration estimated in 1996 that 90,000 workers were potentially exposed [OSHA, 1996]. The current OSHA permissible exposure limit is 100 parts per million (ppm) time-weighted average (TWA) over an 8-hr workday, although in 1996 industries using styrene adopted a voluntary compliance program to reduce exposure to 50 ppm [OSHA, 1996], which is the NIOSH recommended exposure limit [NIOSH, 1983]. The American Conference of Government Industrial Hygienists threshold limit value is 20 ppm [ACGIH, 2002].

A recent re-evaluation of styrene by the International Agency for Research on Cancer (IARC) did not change its previous classification in Group 2B, possibly carcinogenic to

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Received 14 October 2003
DOI 10.1002/ajim.10349. Published online in Wiley InterScience (www.interscience.wiley.com)

humans, with limited evidence of carcinogenicity in experimental animals and inadequate evidence in humans [IARC, 2002]. Concern about the potential carcinogenicity of styrene stems largely from the ability of its metabolite, styrene-7,8-oxide, to bind covalently to DNA and its activity in a variety of genotoxicity test systems [Norppa and Sorsa, 1993]. Styrene-7,8-oxide has been classified by IARC in Group 2A, probably carcinogenic to humans, with sufficient evidence of carcinogenicity in experimental animals and inadequate evidence in humans [IARC, 1994]. Styrene-7,8-oxide has been found in the blood of workers exposed to styrene; one study reported styrene-7,8-oxide concentrations in the range of 0.9 and 4.1 μg/L blood among workers exposed at TWA concentrations between 10 and 73 ppm [Korn et al., 1994]. In vitro, styrene-7,8-oxide induces sister chromatid exchanges as well as increased DNA repair and appears to interfere with normal cell-cycle kinetics [Charkrabarti et al., 1997]. Although an early study of workers employed in the development or production of styrene-based products found a significant increase in lymphatic leukemia [Ott et al., 1980], subsequent studies have shown inconsistent results for lymphatic and hematopoietic cancers [Matanoski et al., 1990; Bond et al., 1992; Kogevinas et al., 1994; Kolstad et al., 1994; Wong et al., 1994; Lynge et al., 1997]. A European multinational study of almost 41,000 workers employed in 660 plants of the reinforced plastics industry found no excess of overall mortality or mortality from malignant neoplasms. Mortality from neoplasms of the lymphatic and hematopoietic tissues increased with time since first exposure and with increasing mean exposure, but not with cumulative exposure [Kogevinas et al., 1994]. Increased mortality among workers with short-term employment in the reinforced plastic industry has been reported, particularly for causes of death associated with mental disorders that might affect employment or with an unhealthy lifestyle. Kolstad and Olsen [1999] found associations between greater numbers of preemployment hospitalizations for lifestyle factors (alcohol, accidents, violence) and shorter durations of employment in the reinforced plastics industry.

This update of the 1985 report [Okun et al., 1985] was done because the carcinogenicity of styrene in humans is unresolved, and because on initial follow-up, both potential latency and statistical power to detect an increase in mortality from lymphatic and hematopoietic neoplasms were limited. The present study updated mortality through December 31, 1998, with an additional 21 years of follow-up.

MATERIALS AND METHODS

Population and Data Collection

In 1978, the National Institute for Occupational Safety and Health (NIOSH) began a cohort study of employees who worked between 1959 and 1978 at two reinforced plastic boatbuilding factories. At these factories boat hulls were constructed by laminating fiberglass sheets together with polyester resins. Company A was located in Kelso, Washington; Company B in Bellingham, more than 400 miles north of Kelso. The cohort includes employees at the two companies who worked at least 1 day at any time between January 1, 1959, and September 30, 1978. Demographic characteristics of workers as well as their departments and dates of employment were abstracted from personnel records. Many of the microfilmed records did not specify job title, so job-title details were not coded in our datafile.

For consistency, the exposure classification developed for the original study was retained. The high-exposure subcohort included individuals who ever worked in the fibrous glass (Company A, mean styrene TWA 42.5 ppm) or lamination (Company B, mean styrene TWA 71.7 ppm) departments while the low-exposure subcohort included workers who never worked in the high-exposure departments (minimal styrene exposure). The classification of jobs at these facilities as high-exposure was supported by air sampling. A detailed description is provided in the previous report [Okun et al., 1985]. At the time of microfilming (October 1978), there were 772 active workers. Company A ceased production in 1993, Company B in 1989. Because company records were incomplete or unavailable after 1993, we were unable to update work histories of employees active at the time of microfilming, or to add employees who began work after 1978 to the cohort.

Vital status had been determined as of 1978 [Okun et al., 1985]. For the present update, the names of cohort members were submitted to the National Death Index [NDI, 2001] for determination of vital status from 1979 through 1994 and death certificates were obtained. Causes of death for deaths from 1995 to 1998 came from an NDI-Plus search. Any worker lost to follow-up as of 1979 was classified as ''vital status unknown'' and considered alive until the date last observed. Death was coded to the revision of the International Classification of Diseases in effect at the time of death. This study was approved by the NIOSH Human Subjects Review Board (HSRB 89-DSHEFS-21).

Analysis

The standardized mortality ratio (SMR) is the ratio of observed to expected deaths. Gender-race-age-calendar period reference rate tables were based on mortality in the Washington State and U.S. populations. Because mortality risk factors and demographics differ from state to state, the use of state rates controls for local conditions that may have no association with occupational exposures. Tables include state and national SMRs; the text presents Washington-based SMRs, except as noted.

Analyzes used the NIOSH personal computer life table analysis system [Waxweiler et al., 1983; Steenland et al.,

1990, 1998; Cassinelli et al., 1997] (http://www.cdc.gov/niosh/ltindex.html). The statistical significance of the SMR was determined by a two-tailed test based upon the Poisson distribution. The 95% confidence interval (CI) was calculated for each SMR estimate. Race- and gender-specific person years at risk were accumulated for each eligible worker across 5-year age and calendar year intervals beginning with the qualified date of first exposure and ending with the date of death, the date last known alive, or December 31, 1998. Latency also began at the date of first exposure and ended with the date of death, the date last known alive, or on December 31, 1998. A multiple-cause-of-death analysis (MCOD) using U.S. rates was done to investigate possible excesses in nonmalignant chronic diseases [Steenland et al., 1992]. Analyses were also conducted using U.S. rate files which have 99 causes of death (instead of 92) because these include rates for different subcategories of lymphatic and hematopoietic cancers and using an exposure file (Department 1 Plant A 42.5 ppm/day; Department 1 Plant B 71.7 ppm/day; all other departments, 5 ppm/day) to estimate cumulative exposure. Cumulative estimated styrene exposure, ranging from 10 to over 100,000 ppm, was grouped in tertiles (5–<500 ppm; ≥500–<5,000 ppm; ≥5,000 ppm) for comparisons.

RESULTS

Cohort Description

The cohort includes 5,204 employees from two plants. Three workers were excluded from the analysis (because of missing information such as date of birth). Table I shows the composition of the cohort by race, gender, and updated vital status. At the end of the observation period (December 31, 1998), 860 (16.5%) were deceased. During the study period, the cohort had a total of 135,707 person years at risk. Only 1,678 of the 5,204 cohort members worked in the plants more than a year (Table II).

Overall Mortality

Observed deaths, corresponding SMRs using Washington State and national rates, and the SMR confidence intervals (CI) are presented in Table III for the total cohort, and high- and low-exposure subcohorts. There was a slight increase in mortality overall (SMR 1.09, CI 1.02–1.17) and in the high-exposure subcohort (SMR 1.26, CI 1.10–1.43). In race- and gender-specific analyses (not shown; available from first author), the overall statistics for white males and females were 788 deaths, SMR 1.11, CI 1.03–1.19 and 46 deaths, SMR 0.98, CI 0.72–1.31, respectively. Only 1 death occurred among the 42 nonwhite female employees; no further analyses were conducted. There were 25 deaths from all causes in nonwhite males (SMR 0.92, CI 0.59–1.36).

Cancer Mortality

Using state comparison rates, excess deaths due to malignant neoplasms were observed overall (n = 233, SMR 1.17, CI 1.02–1.33) and for both the high-exposure (n = 58, SMR 1.26, CI 0.96–1.63) and low-exposure (n = 175, SMR 1.14, CI 0.98–1.32) subcohorts. In the multiple cause analysis for the total cohort, there were 371 deaths with cancer the underlying or a contributing cause (MCOD U.S. SMR 1.15, CI 1.03–1.27), a statistically significant excess.

There was no increase in deaths due to leukemia or lymphoma, as hypothesized a priori, in the cohort or either exposure subcohort. In analyses using a program that has different subcategories for hematopoietic cancers, none of the subcategories (non-Hodgkins lymphoma, Hodgkin's

TABLE I. NIOSH Styrene Cohort: Composition of the Entire Cohort and Subcohorts as of December 31, 1998

Characteristic	Entire cohort (n = 5,204)	High-exposure (n = 2,063)	Low-exposure (n = 3,141)
Excluded from analysis[a]	3	1	2
Race/gender/vital status			
White females (deaths, % dead)[b]	639 (46, 7%)	411 (28, 7%)	228 (18, 8%)
Nonwhite females	42 (1, 2%)	30 (0)	12 (1, 8%)
White males	4,274 (788, 18%)	1,507 (198, 13%)	2,767 (590, 21%)
Nonwhite males	246 (25, 10%)	114 (7, 6%)	132 (18, 14%)
Total analyzed (deaths)	5,201 (860, 16.5%)	2,062 (233, 11%)	3,139 (627, 20%)
Mean age at first employment	28.3	25.3	30.3
Median duration of employment	0.43 year	0.32 year	0.48 year
Mean duration of employment	1.59 ± 3.0 years	1.10 ± 2.1 years	1.80 ± 3.4 years
Person years at risk from styrene	135,588	54,122	81,466

[a]Missing information (such as date of birth) essential for the analysis.
[b]Persons not known to be dead are considered alive, including, 72 persons lost to follow-up before December 31, 1979, when the National Death Index (NDI) was initiated.

TABLE II. Duration of Employment for High- and Low-Exposure Subcohorts

	High-exposure subcohort		Low-exposure subcohort	
	Number of workers	%	Number of workers	%
1 day–<1 month	504	24	516	16
1 month–<6 months	736	36	1,089	35
6 months–<1 year	290	14	438	14
1 year–<3 years	322	16	592	19
≥3 years	211	10	506	16
Total	2,063[a]	100	3,141	100

By definition everyone in the high-exposure subcohort worked at least 1 day in a high-exposure department (fibrous glass or lamination departments), and everyone in the low-exposure subcohort worked at least 1 day in a low-exposure department (all other departments) and never worked in a high-exposure department.
[a]Less than 10% (190/2,063) of the high-exposure subcohort ever worked in a low-exposure department.

disease, leukemia and aleukemia, or myeloma) had a statistically significant excess of deaths (results not shown).

SMRs for several cancer sites not considered a priori to be associated with styrene exposure were significantly elevated (Table III). The esophageal cancer SMR was 2.30 (CI 1.19–4.02). SMRs were increased in the high-exposure subcohort and statistically significantly elevated in the low-exposure subcohort. In the MCOD analysis, there were 13 deaths associated with esophageal cancer (U.S. SMR 2.15, CI 1.14–3.68). The same pattern occurred with prostate cancer (Table III; 27 MCOD deaths, U.S. SMR 1.50, CI 0.99–2.19). In contrast, the SMR for deaths due to cancer of the urinary tract was statistically significantly increased only in the high-exposure subcohort (6 deaths, SMR 3.44, CI 1.26–7.50). Deaths due to cancers of other and unspecified sites were increased in the low-exposure subcohort.

Death rates for several other malignant neoplasms, including cancer of the pancreas, ovary, and central nervous system, showed slight non-statistically significant increases. Lung cancer mortality was elevated for white females (8 deaths, SMR 1.82, CI 0.78–3.59). Six of the deaths were in the high-exposure subcohort (SMR 2.11, CI 0.77–4.60). Lung cancer mortality was not significantly elevated in the cohort as a whole.

Other Causes of Death

As is typical of a working population, the styrene cohort overall had no statistically significant increased SMRs for diseases other than cancer and decreased SMRs for heart diseases (218 deaths, SMR 0.93, CI 0.81–1.06). The SMR for cirrhosis of the liver was significantly elevated for the low-exposure cohort (27 deaths, SMR 1.90, CI 1.25–2.77).

Among high-exposure workers, deaths from ''pneumoconioses and other respiratory diseases'' were in excess (12 deaths, SMR 2.54, CI 1.31–4.44). These deaths were attributed to ''chronic airways obstruction, not elsewhere classified'' and ''other diseases of lung, not elsewhere classified,'' rather than to pneumoconioses. In the multiple cause of death analysis, the high-exposure subcohort diabetes-related mortality was elevated: 20 deaths, MCOD U.S. SMR 1.73, CI 1.06–2.67.

SMRs for mental, psychoneurotic, and personality disorders were not significantly elevated (Table III). However, in the multiple cause analysis, there was significantly increased mortality from alcoholism (37 deaths, MCOD U.S. SMR 2.76, CI 1.94–3.80) and from ''other mental disorders'' (46 deaths, MCOD U.S. SMR 1.55, CI 1.13–2.07) in the total cohort. Deaths associated with alcoholism were in excess in both the high- and low-exposure subcohorts: 9 deaths, MCOD U.S. SMR 2.16, CI 0.99–4.10 and 28 deaths, MCOD U.S. SMR 3.03, CI 2.01–4.38, respectively. The low-exposure subcohort also had a significant excess of 35 deaths related to ''other mental disorders'' (MCOD U.S. SMR 1.56, CI 1.08–2.17). Multiple sclerosis SMRs were elevated in both subcohorts, but not statistically significant (Table III).

There was a statistically significant increase in deaths due to accidents for the total cohort (99 deaths, SMR 1.26, CI 1.02–1.53) and for the high-exposure subcohort (46 deaths, SMR 1.55, CI 1.14–2.07). No significant excess was found for any particular subcategories of accidents, although SMRs in all subcategories were elevated. In the previous study, it was reported that most of the accidental deaths in the high-exposure subcohort happened long after discontinuing employment [Okun et al., 1985]. This continued to be true. Homicide mortality was in excess for the high-exposure subcohort (9 deaths, SMR 2.12, CI 0.97–4.03).

Latency, Duration of Exposure, and Cumulative Exposure

Over two-thirds of the cancer deaths in the total cohort occurred at least 15 years after first exposure to styrene. However, the all-cancer-deaths SMRs associated with the groups with less than 15 years latency and those with 15 or more years of latency are similar: latency <15 years, n = 63, SMR 1.16, CI 0.89–1.49; latency ≥15 years, n = 170, SMR 1.18, CI 1.01–1.37. Similar results were found for esophageal cancer (latency <15 years, n = 3, SMR 2.61, CI 0.52–8.54; latency ≥15 years, n = 9, SMR 2.23, CI 1.02–4.35) and for prostate cancer (latency <15 years, n = 5, SMR 2.33, CI 0.75–5.78; latency ≥15 years, n = 19, SMR 1.60, CI 0.96–2.52).

Mortality for all cancers was significantly elevated among workers with less than a year of employment: 143 deaths, SMR 1.35, CI 1.14–1.59. There was an inverse relationship between duration of exposure and all cancer SMR (data not

TABLE III. Mortality in the NIOSH Styrene Cohort and Exposure Subcohorts for Selected Causes, Washington (WA) State Rates for 1960–1998 and U.S. Rates for 1959–1998

		Total cohort			High-exposure			Low-exposure		
Causes of death	**ICD codes (9th revision)**	**n**	**WA SMR (95% CI)**	**U.S. SMR (95% CI)**	**n**	**WA SMR (95% CI)**	**U.S. SMR (95% CI)**	**n**	**WA SMR (95% CI)**	**U.S. SMR (95% CI)**
All cancer	140–208	233	1.17* (1.02–1.33)	1.08 (0.95–1.23)	58	1.26 (0.96–1.63)	1.15 (0.88–1.49)	175	1.14 (0.98–1.32)	1.06 (0.91–1.23)
Buccal & pharyngeal	140–149	4	0.94 (0.26–2.40)	0.77 (0.21–1.96)	1	1.06 (0.03–5.88)	0.83 (0.02–4.59)	3	0.90 (0.19–2.64)	0.75 (0.15–2.19)
Digestive system	150–159	53	1.17 (0.88–1.53)	1.06 (0.79–1.38)	13	1.34 (0.71–2.28)	1.20 (0.64–2.06)	40	1.12 (0.80–1.53)	1.02 (0.73–1.39)
Esophagus	150	12	2.30* (1.19–4.02)	2.19* (1.13–3.83)	2	1.85 (0.22–6.67)	1.65 (0.20–5.94)	10	2.42* (1.16–4.44)	2.34* (1.12–4.31)
Stomach	151	7	1.16 (0.47–2.39)	1.06 (0.42–2.18)	2	1.55 (0.19–5.61)	1.43 (0.17–5.15)	5	1.06 (0.34–2.47)	0.96 (0.31–2.25)
Intestine (except rectum)	152–153	14	0.91 (0.49–1.52)	0.77 (0.42–1.28)	5	1.55 (0.50–3.63)	1.29 (0.42–3.02)	9	0.74 (0.34–1.40)	0.62 (0.28–1.18)
Liver & biliary	155, 156	4	0.89 (0.24–2.46)	0.80 (0.22–2.22)	0			4	1.18 (0.32–3.26)	1.04 (0.28–2.88)
Pancreas	157	14	1.43 (0.78–2.41)	1.38 (0.76–2.32)	4	1.88 (0.51–4.81)	1.81 (0.49–4.64)	10	1.31 (0.63–2.41)	1.26 (0.61–2.33)
Respiratory system	160–165	79	1.14 (0.90–1.42)	1.04 (0.82–1.29)	19	1.30 (0.79–2.04)	1.17 (0.71–1.83)	60	1.09 (0.83–1.41)	1.00 (0.76–1.29)
Trachea, bronchus, lung	161	76	1.14 (0.90–1.43)	1.04 (0.82–1.31)	18	1.29 (0.76–2.04)	1.16 (0.69–1.84)	58	1.10 (0.84–1.43)	1.01 (0.77–1.31)
Breast	175–175	3	0.64 (0.13–1.86)	0.60 (0.12–1.76)	2	0.69 (0.08–2.49)	0.65 (0.08–2.34)	1	0.55 (0.01–3.08)	0.52 (0.01–2.91)
Female genital organs	179–184	3	1.26 (0.26–3.69)	1.24 (0.25–3.61)	2	1.35 (0.16–4.89)	1.33 (0.16–4.79)	1	1.11 (0.03–6.18)	1.09 (0.03–6.05)
Ovary, Fallopian tube, broad ligament	183	3	2.20 (0.45–6.42)	2.39 (0.49–7.00)	2	2.32 (0.28–8.38)	2.54 (0.31–9.16)	1	1.98 (0.05–11.0)	2.15 (0.05–11.9)
Male genital organs	185–187	25	1.64* (1.06–2.42)	1.71* (1.10–2.52)	4	2.12 (0.58–5.41)	2.21 (0.60–5.65)	21	1.58 (0.97–2.41)	1.64* (1.01–2.50)
Prostate	185	24	1.71* (1.09–2.54)	1.77* (1.13–2.63)	3	2.06 (0.43–6.04)	2.10 (0.43–6.14)	21	1.67* (1.03–2.55)	1.73* (1.07–2.64)
Urinary organs	188–189	13	1.43 (0.76–2.44)	1.31 (0.70–2.24)	6	3.44* (1.26–7.50)	3.10* (1.13–6.75)	7	0.95 (0.38–1.96)	0.88 (0.35–1.81)
Kidney	189.0–189.2	7	1.43 (0.57–2.95)	1.29 (0.52–2.65)	4	3.60 (0.98–9.20)	3.18 (0.87–8.12)	3	0.80 (0.16–2.33)	0.72 (0.15–2.10)
Bladder & other urinary	188, 189.3–189.9	6	1.42 (0.52–3.09)	1.34 (0.49–2.92)	2	3.17 (0.38–11.5)	2.96 (0.36–10.7)	4	1.11 (0.30–2.84)	1.05 (0.29–2.69)
Other & unspecified sites	170–173, 190–199	37	1.36 (0.96–1.88)	1.22 (0.86–1.68)	7	0.96 (0.38–1.97)	0.87 (0.35–1.79)	30	1.51* (1.02–2.16)	1.35 (0.91–1.93)
Brain & nervous system	191–192	13	1.62 (0.86–2.76)	1.80 (0.96–3.08)	3	1.28 (0.26–3.75)	1.41 (0.29–4.11)	10	1.75 (0.84–3.22)	1.96 (0.94–3.61)
Other & unspecified sites	194–199	19	1.68* (1.01–2.62)	1.30 (0.78–2.03)	3	1.14 (0.23–3.32)	0.87 (0.18–2.54)	16	1.84* (1.05–2.99)	1.43 (0.82–2.32)
Lymphatic & hematopoietic	200–208	16	0.74 (0.42–1.20)	0.73 (0.42–1.19)	4	0.72 (0.20–1.84)	0.71 (0.19–1.81)	12	0.74 (0.38–1.30)	0.74 (0.38–1.29)
Lymphosarcoma & reticulosarcoma		1	0.39 (0.01–2.19)	0.51 (0.01–2.86)	0			1	0.53 (0.01–2.93)	0.68 (0.02–3.77)
Hodgkin's disease		1	0.61 (0.02–3.40)	0.57 (0.01–3.15)	1	1.78 (0.05–9.89)	1.66 (0.04–9.24)	0		
Leukemia & aleukemia		5	0.60 (0.19–1.40)	0.59 (0.19–1.38)	1	0.47 (0.01–2.63)	0.46 (0.01–2.58)	4	0.64 (0.18–1.65)	0.64 (0.17–1.63)
Other lymphatic & hematopoietic neoplasms		9	0.98 (0.45–1.85)	0.92 (0.42–1.75)	2	0.89 (0.11–3.23)	0.82 (0.10–2.96)	7	1.00 (0.40–2.07)	0.96 (0.38–1.97)
Benign neoplasms	210–239	0			0			0		
Tuberculosis	010–018	2	3.32 (0.40–12.0)	1.68 (0.20–6.05)	2	15.79* (1.91–57.0)	6.89 (0.83–24.9)	0		
Diabetes mellitus	250	22	1.49 (0.93–2.25)	1.42 (0.89–2.14)	8	2.11 (0.91–4.16)	2.07 (0.89–4.08)	14	1.27 (0.70–2.14)	1.20 (0.66–2.01)
Blood & blood-forming diseases	281–289	1	0.43 (0.01–2.38)	0.36 (0.01–1.97)	0			1	0.55 (0.01–3.08)	0.47 (0.01–2.59)
Alcoholism & mental disorders	290–319	12	1.26 (0.65–2.20)	1.19 (0.62–2.09)	1	0.45 (0.01–2.52)	0.34 (0.01–1.88)	11	1.50 (0.75–2.69)	1.55 (0.77–2.77)
Nervous system diseases	320–337, 340–389	13	0.90 (0.48–1.54)	1.04 (0.55–1.77)	1	0.30 (0.01–1.67)	0.33 (0.01–1.81)	12	1.08 (0.56–1.88)	1.27 (0.65–2.21)

(*Continued*)

TABLE III. (*Continued*)

		Total cohort			High-exposure			Low-exposure		
Causes of death	**ICD codes (9th revision)**	**n**	**WA SMR (95% CI)**	**U.S. SMR (95% CI)**	**n**	**WA SMR (95% CI)**	**U.S. SMR (95% CI)**	**n**	**WA SMR (95% CI)**	**U.S. SMR (95% CI)**
Multiple sclerosis	340	4	2.54 (0.69–6.50)	3.63 (0.99–9.29)	1	1.78 (0.04–9.87)	2.58 (0.07–14.3)	3	2.97 (0.61–8.69)	4.20 (0.87–12.3)
Diseases of the heart	390–398, 402–404, 410–414, 420–429	218	0.93 (0.81–1.06)	0.78** (0.68–0.89)	48	1.15 (0.85–1.52)	0.92 (0.68–1.22)	170	0.88 (0.76–1.03)	0.75** (0.64–0.87)
Ischemic heart disease	410–414	176	1.03 (0.88–1.19)	0.83* (0.71–0.96)	37	1.27 (0.90–1.75)	0.98 (0.69–1.36)	139	0.98 (0.82–1.15)	0.80** (0.67–0.94)
Other diseases of the heart	420–423, 425–428, 429.2–429.9	30	0.59** (0.40–0.85)	0.57** (0.38–0.81)	7	0.67 (0.27–1.39)	0.62 (0.25–1.27)	23	0.57** (0.36–0.86)	0.56** (0.35–0.83)
Other diseases of the circulatory system	401, 403, 405, 415–417, 430–438, 440–459	64	1.13 (0.87–1.44)	1.06 (0.81–1.35)	13	1.34 (0.71–2.30)	1.15 (0.61–1.97)	51	1.08 (0.81–1.42)	1.03 (0.77–1.36)
Respiratory system diseases	460–466, 470–478, 480–487, 490–519	63	1.14 (0.88–1.46)	1.10 (0.84–1.40)	19	2.07** (1.24–3.23)	1.92* (1.15–3.00)	44	0.95 (0.69–1.28)	0.93 (0.67–1.24)
Pneumoconioses, other resp. diseases[a]	470–478, 494–519	39	1.36 (0.97–1.86)	1.39 (0.99–1.90)	12	2.54** (1.31–4.44)	2.56** (1.32–4.47)	27	1.13 (0.74–1.64)	1.16 (0.76–1.69)
Digestive system diseases	520–537, 540–543, 550–553, 555–558, 560, 562–579	44	1.27 (0.93–1.71)	1.06 (0.77–1.43)	9	1.03 (0.47–1.96)	0.82 (0.37–1.56)	35	1.36 (0.94–1.88)	1.15 (0.80–1.60)
Cirrhosis of liver	571	33	1.67** (1.15–2.34)	1.39 (0.96–1.96)	6	1.07 (0.39–2.34)	0.87 (0.32–1.89)	27	1.90** (1.25–2.77)	1.61* (1.06–2.34)
Genitourinary system diseases	580–608, 610, 611, 614–629	5	0.77 (0.25–1.80)	0.51 (0.16–1.19)	1	0.82 (0.02–4.55)	0.52 (0.01–2.89)	4	0.76 (0.21–1.95)	0.51 (0.14–1.30)
Skin & subcutaneous tissue diseases	680–686, 690–709	1	2.18 (0.06–12.1)	1.45 (0.04–8.06)	0			1	2.80 (0.07–15.6)	1.84 (0.05–10.2)
Musculoskeletal diseases	710–739	3	1.79 (0.37–5.24)	1.56 (0.32–4.57)	2	4.28 (0.52–15.4)	3.59 (0.43–13.0)	1	0.83 (0.02–4.60)	0.74 (0.02–4.08)
Symptoms & ill-defined conditions	780–796, 798, 799	3	0.95 (0.20–2.79)	0.28* (0.06–0.82)	1	1.05 (0.03–5.83)	0.31 (0.01–1.73)	2	0.91 (0.11–3.29)	0.27* (0.03–0.96)
Accidents	E800–848, E850–888, E890–949	99	1.26* (1.02–1.53)	1.28* (1.04–1.57)	46	1.55** (1.14–2.07)	1.59** (1.16–2.12)	53	1.08 (0.81–1.41)	1.10 (0.83–1.44)
Transportation accidents		60	1.30 (0.99–1.68)	1.28 (0.98–1.65)	26	1.43 (0.93–2.09)	1.40 (0.91–2.05)	34	1.22 (0.85–1.71)	1.20 (0.83–1.68)
Accidental poisoning		7	1.12 (0.45–2.31)	1.13 (0.45–2.33)	4	1.52 (0.42–3.90)	1.56 (0.42–3.98)	3	0.83 (0.17–2.42)	0.83 (0.17–2.42)
Accidental falls		9	1.38 (0.63–2.63)	1.60 (0.73–3.03)	4	2.31 (0.63–5.90)	2.68 (0.73–6.85)	5	1.05 (0.34–2.45)	1.21 (0.39–2.82)
Other accidents		22	1.21 (0.76–1.84)	1.22 (0.76–1.85)	11	1.72 (0.86–3.08)	1.72 (0.86–3.09)	11	0.94 (0.47–1.68)	0.95 (0.47–1.69)
Medical complications		1	1.03 (0.03–5.72)	0.85 (0.02–4.74)	1	3.96 (0.10–22.0)	3.38 (0.09–18.8)	0		
Suicide	E963, E970–979	33	1.00 (0.69–1.40)	1.07 (0.74–1.51)	9	0.76 (0.35–1.44)	0.81 (0.37–1.54)	24	1.14 (0.73–1.69)	1.22 (0.78–1.82)
Homicide	E964, E980–985	17	1.66 (0.96–2.65)	0.98 (0.57–1.58)	9	2.12* (0.97–4.03)	1.25 (0.57–2.37)	8	1.33 (0.57–2.62)	0.79 (0.34–1.57)
Other causes/CODs not obtained	Residual codes	27	0.89 (0.58–1.29)	0.75 (0.49–1.09)	6	0.55 (0.20–1.19)	0.46 (0.17–1.00)	21	1.08 (0.67–1.65)	0.91 (0.56–1.39)
All causes		860	1.09* (1.02–1.17)	0.97 (0.91–1.04)	233	1.26** (1.10–1.43)	1.10 (0.96–1.25)	627	1.04 (0.96–1.13)	0.93 (0.86–1.01)

[a]In analyses using 99 causes of deaths, all deaths in this category were from "other respiratory diseases, not asbestosis, silicosis, or other pneumoconioses."

*$P < 0.05$.

**$P < 0.01$.

shown). Workers with more than a year of employment had a deficit for all cancer deaths (90 deaths, SMR 0.97, CI 0.78–1.20). Our study found excess overall mortality among those employed less than 1 year. These short-term workers (excluding short-term workers still employed at the time records were microfilmed) experienced an SMR of 1.24 (CI 1.14–1.35, 539 deaths), compared with long-term workers who experienced an SMR of 0.91 (CI 0.81–1.01, 319 deaths). Significantly elevated SMRs for these short-term workers were found for esophageal, prostate, and brain cancer, pneumoconioses and other respiratory diseases, and accidents (results not shown).

Table IV presents mortality analyses for the 1,678 workers (580 high-exposure, 1,098 low-exposure) employed for more than 1 year. None of the SMRs is in excess. However, differences between high- and low-exposure workers can be seen for esophageal, intestinal, and urinary tract cancer, heart disease, and respiratory disease (higher SMRs for the high-exposure group), and for cirrhosis and liver cancer (higher SMRs for the low-exposure group).

Looking at duration of high-exposure employment in the total cohort in Table V, we can see that SMRs for urinary tract (including kidney and bladder) and prostate cancer, ''other respiratory diseases,'' and accidents are higher among those who worked in the high-exposure departments. For urinary tract cancer, there was a trend toward increasing SMR with increasing duration of employment in high-exposure departments; the exposure–response relationships for prostate cancer and for ''other respiratory diseases'' were heterogenous but there was no clear trend. No exposure–response relationship was seen in analyses of leukemia mortality.

Overall death rates were negatively associated with tertiles of estimated cumulative styrene exposure. The lowest exposure tertile (5–500 ppm) had the highest rate (256 deaths, SMR 1.28, CI 1.13–1.45); the next tertile (500–5,000 ppm) had an intermediate rate (322 deaths, SMR 1.13, CI 1.01–1.26); and the highest exposure tertile (5,000+ ppm) had the lowest rate (280 deaths, SMR 0.93, CI 0.82–1.05). Overall cancer death and esophageal cancer death rates were also negatively associated with estimated styrene exposure (results not shown). There was no dose–response relationship for prostate cancer deaths or for pneumoconioses and other respiratory diseases (results not shown). However, there was a positive trend for urinary tract cancer: two deaths, SMR 0.85, CI 0.10–3.70, in the lowest exposure tertile, four deaths, SMR 1.26, CI 0.34–3.49 in the middle tertile, and seven deaths, SMR 1.96, CI 0.79–4.21 in the highest exposure tertile.

DISCUSSION

Studies of styrene-exposed worker cohorts, conducted in both Europe and the United States, have been reviewed recently [Cohen et al., 2002; IARC, 2002]. Statistically significant excess overall mortality generally has been found only among short-term workers, employed less than 1 year [Wong et al., 1994; Kolstad et al., 1995; Boffetta et al., 1998]. This mortality excess does not appear to be related to styrene exposure. Our study also found excess overall mortality among short-term workers.

This study found no evidence for an excess risk of lymphatic and hematopoietic cancer associated with exposure to styrene in the reinforced plastic boatbuilding facilities studied. Results of previous studies of lymphatic and hematopoietic cancer in styrene-exposed workers [reviewed in Cohen et al., 2002 and IARC, 2002] have varied widely, including a statistically significant deficit of deaths [Coggon et al., 1987] and an association of increased mortality with longer latency and higher average level of exposure [Kogevinas et al., 1994].

Significant elevated mortality from cancer of the urinary tract (kidney and bladder) was found among workers in the high-exposure subcohort; these causes of death were not elevated among workers in the low-exposure subcohort (Table III). Among the styrene cohort studies only Wong et al. [1994] reported elevated kidney cancer mortality (15 deaths, SMR 1.75, CI 0.98–2.89). One recent study of renal cell carcinoma found an association with styrene-butadiene exposure [Parent et al., 2000] but another [Mandel et al., 1995] did not mention styrene exposure as associated with increased risk of disease. In rats, styrene has been found to accumulate in fat, pancreas, liver, and kidneys [Sumner and Fennell, 1994].

Prostate cancer was elevated in both exposure subcohorts, but the excess was statistically significant only in the low-exposure subcohort (Table III). A geographic gradient in prostate cancer mortality has been reported in some migrant studies [Nomura and Kolonel, 1991; Schwartz, 1992], but presumably an effect of latitude on prostate cancer mortality in our cohort would no longer be significant when local rates were used. Prior studies in the reinforced plastics industry (including some in northern Europe at latitudes higher than Washington State), have not reported elevations in prostate cancer mortality. The discrepancy between our results and those of other cohort studies could be due to differences in styrene exposure among the cohorts or to differences in lifestyle factors, known to be associated with prostate cancer risk [Nomura and Kolonel, 1991], or in access to medical care [Merrill, 2001].

The excesses for these nonhematopoietic cancers were not anticipated and are difficult to interpret, especially for causes of death without similar excesses in other styrene cohorts.

Significantly elevated mortality from ''pneumoconioses and other respiratory diseases'' was found among workers in the high-exposure subcohort; this cause of death was not elevated among workers in the low-exposure subcohort

TABLE IV. Mortality for Selected Causes Among NIOSH Styrene Cohort and Exposure Subcohorts Workers Employed Over 1 Year Washington (WA) State Rates for 1960–1998 and U.S. Rates for 1959–1998

		Total cohort			High-exposure			Low-exposure		
Causes of death	**ICD codes (9th revision)**	**n**	**WA SMR (95% CI)**	**U.S. SMR (95% CI)**	**n**	**WA SMR (95% CI)**	**U.S. SMR (95% CI)**	**n**	**WA SMR (95% CI)**	**U.S. SMR (95% CI)**
All cancer	140–208	90	0.97 (0.78–1.20)	0.91 (0.73–1.12)	20	1.15 (0.70–1.77)	1.08 (0.66–1.66)	70	0.93 (0.73–1.18)	0.87 (0.68–1.10)
Buccal & pharyngeal	140–149	1	0.53 (0.01–2.94)	0.44 (0.01–2.47)	0			1	0.64 (0.02–3.55)	0.54 (0.01–3.00)
Digestive system	150–159	20	0.95 (0.58–1.46)	0.86 (0.53–1.33)	4	1.12 (0.31–2.87)	1.03 (0.28–2.63)	16	0.91 (0.52–1.48)	0.83 (0.47–1.35)
Esophagus	150	3	1.27 (0.26–3.72)	1.26 (0.26–3.69)	1	2.71 (0.07–15.0)	2.60 (0.07–14.4)	2	1.01 (0.12–3.64)	1.00 (0.12–3.62)
Stomach	151	2	0.73 (0.09–2.62)	0.66 (0.08–2.39)	0			2	0.86 (0.10–3.12)	0.79 (0.10–2.85)
Intestine (except rectum)	152–153	3	0.41 (0.08–1.19)	0.34 (0.07–1.01)	2	1.63 (0.20–5.88)	1.37 (0.17–4.96)	1	0.16* (0.00–0.90)	0.14* (0.00–0.77)
Liver & biliary	155, 156	3	1.50 (0.30–4.91)	1.32 (0.27–4.33)	0			3	1.63 (0.37–6.04)	1.61 (0.32–5.27)
Pancreas	157	7	1.54 (0.62–3.17)	1.49 (0.60–3.08)	1	1.23 (0.03–6.85)	1.23 (0.03–6.82)	6	1.60 (0.59–3.49)	1.55 (0.57–3.38)
Respiratory system	160–165	32	0.98 (0.67–1.38)	0.91 (0.63–1.29)	7	1.24 (0.50–2.56)	1.17 (0.47–2.41)	25	0.93 (0.60–1.37)	0.86 (0.56–1.27)
Trachea, bronchus, lung	161	31	0.99 (0.67–1.41)	0.93 (0.63–1.31)	6	1.11 (0.40–2.41)	1.05 (0.38–2.28)	25	0.97 (0.62–1.43)	0.90 (0.58–1.33)
Breast	175	2	0.82 (0.10–2.98)	0.78 (0.09–2.80)	1	0.64 (0.02–3.58)	0.61 (0.02–3.37)	1	1.15 (0.03–6.36)	1.08 (0.03–5.99)
Female genital organs	179–184	2	1.61 (0.20–5.81)	1.58 (0.19–5.69)	1	1.26 (0.03–7.00)	1.24 (0.03–6.88)	1	2.23 (0.06–12.4)	2.17 (0.05–12.0)
Ovary, Fallopian tube, broad ligament	183	2	2.79 (0.34–10.1)	3.02 (0.37–10.9)	1	2.13 (0.05–11.8)	2.32 (0.06–12.9)	1	4.02 (0.10–22.3)	4.31 (0.11–24.0)
Male genital organs	185–187	11	1.35 (0.68–2.42)	1.41 (0.70–2.53)	1	1.44 (0.04–7.98)	1.51 (0.04–8.39)	10	1.35 (0.64–2.48)	1.40 (0.67–2.58)
Prostate	185	11	1.41 (0.70–2.53)	1.47 (0.73–2.64)	1	1.66 (0.04–9.22)	1.74 (0.04–9.64)	10	1.39 (0.67–2.56)	1.45 (0.69–2.67)
Urinary organs	188–189	5	1.15 (0.37–2.69)	1.07 (0.34–2.49)	3	4.71 (0.97–13.8)	4.32 (0.89–12.6)	2	0.54 (0.07–1.95)	0.50 (0.06–1.81)
Kidney	189.0–189.2	3	1.38 (0.28–4.04)	1.25 (0.26–3.67)	2	5.11 (0.62–18.4)	4.64 (0.56–16.8)	1	0.56 (0.01–3.12)	0.51 (0.01–2.83)
Bladder & other urinary	188, 189.3–189.9	2	0.92 (0.11–3.32)	0.87 (0.11–3.14)	1	4.08 (0.10–22.7)	3.80 (0.10–21.1)	1	0.52 (0.01–2.88)	0.49 (0.01–2.73)
Other & unspecified sites	170–173, 190–199	12	1.05 (0.54–1.84)	0.94 (0.49–1.64)	2	0.82 (0.10–2.97)	0.75 (0.09–2.70)	10	1.11 (0.53–2.05)	0.99 (0.47–1.82)
Brain & nervous system	191–192	2	0.63 (0.08–2.27)	0.71 (0.09–2.55)	0			2	0.82 (0.10–3.00)	0.93 (0.11–3.34)
Other & unspec. sites	194–199	8	1.53 (0.66–3.02)	1.21 (0.52–2.38)	2	2.06 (0.25–7.44)	1.62 (0.20–5.85)	6	1.41 (0.52–3.08)	1.11 (0.41–2.42)
Lymphatic & hematopoietic	200–208	5	0.54 (0.17–1.26)	0.53 (0.17–1.25)	1	0.56 (0.01–3.09)	0.54 (0.01–3.01)	4	0.53 (0.15–1.37)	0.53 (0.15–1.36)
Tuberculosis	010–018	1	3.68 (0.09–20.4)	2.00 (0.05–11.1)	1	24.3 (0.62–135)	11.9 (0.30–65.9)	0		
Diabetes mellitus	250	8	1.23 (0.53–2.43)	1.15 (0.50–2.27)	1	0.78 (0.02–4.35)	0.75 (0.02–4.19)	7	1.35 (0.54–2.77)	1.25 (0.50–2.57)
Blood & blood-forming diseases	281–289	1	0.92 (0.02–5.11)	0.78 (0.02–4.33)	0			1	1.10 (0.03–6.09)	0.94 (0.02–5.22)
Alcoholism & mental disorders	290–319	2	0.46 (0.06–1.68)	0.51 (0.06–1.85)	0			2	0.55 (0.07–1.98)	0.64 (0.08–2.30)
Nervous system diseases	320–337, 340–389	8	1.18 (0.51–2.32)	1.42 (0.61–2.79)	0			8	1.41 (0.61–2.78)	1.72 (0.74–3.39)
Multiple sclerosis	340	2	3.32 (0.40–12.0)	4.77 (0.58–17.2)	0			2	4.93 (0.60–17.8)	7.00 (0.85–25.3)

Diseases of the heart	390–398, 402–404, 410–414, 420–429	88	0.77* (0.62–0.95)	0.66** (0.53–0.81)	21	1.39 (0.86–2.13)	1.14 (0.71–1.74)	67	0.68** (0.53–0.86)	0.58** (0.45–0.74)
Ischemic heart disease	410–414	71	0.85 (0.66–1.07)	0.69** (0.54–0.87)	15	1.39 (0.78–2.30)	1.10 (0.62–1.82)	56	0.77* (0.58–0.99)	0.63** (0.47–0.81)
Other diseases of the heart	420–423, 425–428, 429.2–429.9	12	0.50* (0.26–0.88)	0.49* (0.25–0.86)	4	1.15 (0.31–2.94)	1.08 (0.29–2.76)	8	0.39** (0.17–0.77)	0.38** (0.17–0.76)
Other diseases of the circulatory system	401, 403, 405, 415–417, 430–438, 440–459	30	1.03 (0.69–1.47)	1.00 (0.67–1.42)	5	1.35 (0.44–3.15)	1.22 (0.39–2.85)	25	0.98 (0.64–1.45)	0.96 (0.62–1.42)
Respiratory system diseases	460–466, 470–478, 480–487, 490–519	27	0.94 (0.62–1.36)	0.92 (0.61–1.34)	7	1.92 (0.77–3.95)	1.87 (0.75–3.85)	20	0.80 (0.49–1.23)	0.78 (0.48–1.21)
Pneumoconioses & other resp. diseases[a]	470–478, 494–519	17	1.13 (0.66–1.81)	1.17 (0.68–1.88)	4	2.03 (0.55–5.19)	2.13 (0.58–5.45)	13	1.00 (0.53–1.70)	1.03 (0.55–1.76)
Digestive system diseases	520–537, 540–543, 550–553, 555–558, 560, 562–579	14	0.94 (0.52–1.58)	0.82 (0.45–1.38)	0			14	1.17 (0.64–1.96)	1.03 (0.56–1.72)
Cirrhosis of liver	571	13	1.66 (0.88–2.83)	1.43 (0.76–2.45)	0			13	2.14* (1.14–3.66)	1.86 (0.99–3.18)
Genitourinary system diseases	580–608, 610, 611, 614–629	1	0.31 (0.01–1.71)	0.21 (0.01–1.14)	0			1	0.36 (0.01–1.97)	0.24 (0.01–1.32)
Skin & subcutaneous tissue diseases	680–686, 690–709	1	4.64 (0.12–25.8)	2.93 (0.07–16.3)	0			1	5.52 (0.14–30.7)	3.43 (0.09–19.0)
Musculoskeletal diseases	710–739	2	2.61 (0.32–9.42)	2.31 (0.28–8.35)	1	5.67 (0.14–31.5)	4.78 (0.12–26.6)	1	1.69 (0.04–9.41)	1.52 (0.04–8.47)
Symptoms & ill-defined conditions	780–796, 798, 799	1	0.82 (0.02–4.54)	0.24 (0.01–1.35)	0			1	1.05 (0.03–5.85)	0.31 (0.01–1.72)
Accidents	E800–848, E850–888, E890–949	27	1.13 (0.74–1.64)	1.15 (0.76–1.68)	10	1.44 (0.69–2.65)	1.48 (0.71–2.71)	17	1.00 (0.58–1.61)	1.02 (0.60–1.64)
Suicide	E963, E970–979	11	1.04 (0.52–1.85)	1.12 (0.56–2.00)	1	0.33 (0.01–1.85)	0.36 (0.01–1.98)	10	1.31 (0.63–2.41)	1.42 (0.68–2.61)
Other causes/CODs not obtained	Residual codes	7	0.69 (0.27–1.41)	0.58 (0.23–1.20)	0			7	0.94 (0.38–1.95)	0.80 (0.32–1.64)
All causes		319	0.91 (0.81–1.01)	0.82** (0.73–0.92)	67	1.10 (0.85–1.40)	0.98 (0.76–1.25)	252	0.87* (0.76–0.98)	0.79** (0.69–0.89)

[a]In analyses using 99 causes of deaths, all deaths in this category were from "other respiratory diseases, not asbestosis, silicosis, or other pneumoconioses."

*$P < 0.05$.

**$P < 0.01$.

TABLE V. NIOSH Styrene Cohort: Mortality From Selected Causes of Death According to Duration of Employment in High-Exposure Department (Washington State Rates)

	Duration of employment		
	None (low-exposure subcohort)	<1 year	>1 year
Causes of death	**n. deaths, SMR (CI)**	**n. deaths, SMR (CI)**	**n. deaths, SMR (CI)**
All causes	627, 0.93 (0.86–1.01)	170, 1.15 (0.98–1.34)	63, 0.98 (0.75–1.26)
All cancer	175, 1.06 (0.91–1.23)	41, 1.26 (0.90–1.71)	17, 0.96 (0.56–1.55)
Esophagus	10, 2.34* (1.12–4.31)	1, 1.18 (0.02–9.61)	1, 2.74 (0.04–22.3)
Lung	58, 1.01 (0.77–1.31)	14, 1.40 (0.77–2.39)	4, 0.73 (0.20–2.03)
Prostate[a]	21, 1.73* (1.07–2.64)	2, 2.31 (0.26–10.0)	1, 1.78 (0.02–14.5)
Kidney[a]	3, 0.72 (0.15–2.10)	2, 2.35 (0.26–10.2)	2, 4.91 (0.55–21.3)
Bladder	4, 1.05 (0.29–2.69)	1, 2.38 (0.03–19.4)	1, 3.94 (0.05–32.2)
Brain & nervous system	10, 1.96 (0.94–3.61)	3, 2.00 (0.40–6.54)	
Lymphatic and hematopoietic	12, 0.74 (0.38–1.29)	3, 0.76 (0.15–2.50)	1, 0.58 (0.01–4.70)
Pneumoconioses & other respiratory diseases[a]	27, 1.16 (0.76–1.69)	8, 2.78* (1.20–5.66)	4, 2.21 (0.59–6.12)
Cirrhosis of liver	27, 1.61* (1.06–2.34)	6, 1.21 (0.44–2.75)	
Accidents[a]	53, 1.10 (0.83–1.44)	36, 1.58* (1.11–2.20)	10, 1.61 (0.77–3.04)

[a]Breslow and Day heterogenity test for SMRs, χ^2 test $P < 0.05$.
*$P < 0.05$.

(Table III). Styrene exposure has been associated with a significant increase in reported lower respiratory symptoms during active employment [Lorimer et al., 1978]. Wong and Trent [1999] also found an increase in mortality from ''other respiratory diseases,'' but only in short-term or low-exposure workers. A study of mortality from nonmalignant respiratory disease in the European styrene cohort [Welp et al., 1996b] found mortality from pneumonia associated with intensity of styrene exposure, but concluded that the association was not strong enough to exclude it being due to chance. Case-control studies of nonmalignant respiratory disease mortality nested within styrene cohorts and/or cross-sectional studies to better define the respiratory effects, obtaining information on smoking history and other employment, should be designed to address this issue. Our cohort may not be suitable for such studies because many of our work-history records do not indicate specific job title, and styrene and other exposures varied widely within the high-exposure departments (at Company A, the 8-hr TWA range varied from 7.3 to 84.7 ppm. At Company B, the 8-hr TWA range varied from 14.5 to 183 ppm). In addition, we have no information on employment prior to or after their work in these plants, and over half of the cohort was employed for less than a year in these plants.

The effect of concomitant exposure to fiberglass, classified by IARC in Group 2B [IARC, 1988] should be taken into account, although two recent publications [Berrigan, 2002; Chiazze et al., 2002] found no association with respiratory cancer or disease.

Increased mortality among short-term workers in this industry has been reported in several studies, particularly for causes of death associated with disorders that might affect employment or with an unhealthy lifestyle. Kolstad and Olsen [1999] found associations between greater numbers of pre-employment hospitalizations related to alcohol use, accidents, and the effects of violence, and shorter durations of employment. We have no lifestyle or hospitalization information on workers in our cohort, but multiple cause analysis in our study did show that members of this cohort experienced excess mortality from mental disorders and alcoholism. In addition, deaths from esophageal cancer were in significant excess and deaths from cirrhosis were elevated among short-term workers in our cohort. All 17 homicide deaths occurred to short-term workers.

The elevation in mortality from multiple sclerosis is intriguing because of the established neurotoxicity of styrene [Kolstad et al., 1995]. However, the epidemiological evidence from our study is weak, because the excess in mortality from multiple sclerosis is based on small numbers, is concentrated in the low-exposure subcohort, and declines when state referent rates are used (the distribution of multiple sclerosis is related to geographic latitude [Schwartz, 1992]). Kolstad et al. [1995] did find an increased mortality rate ratio for degenerative disorders of the nervous system (multiple sclerosis, Parkinsonism, and motor neuron disease) of 1.8 (CI 0.9–3.8) in a Danish styrene cohort. In the multinational European styrene cohort, Welp et al. [1996a] found higher mortality from degenerative disorders of the nervous system

among workers with a long duration of exposure or high cumulative exposure, but the increase was not consistent. None of the deaths was due to multiple sclerosis.

The differences in SMRs in analyses using Washington State and United States rates underline the importance of comparing worker cohorts where possible to local populations. In addition to the gradient of disease with latitude seen for multiple sclerosis [Schwartz, 1992] and prostate cancer [Nomura and Kolonel, 1991; Schwartz, 1992], regional differences can affect other causes of death [Mansfield et al., 1999; Cubbin et al., 2000].

As for most cohort studies, ours is limited to data from personnel records at these facilities and some industrial hygiene data. We have no information on lifestyle choices, such as smoking or drinking, that affect mortality. Additionally, alcohol use during styrene exposure affects the metabolism of styrene, and could therefore impact any styrene health effects [Cerny et al., 1990]. However, deaths due to alcohol-related causes are concentrated among short-term and low-exposure workers.

We have no information on previous or subsequent employment in this cohort. This limitation is significant for the 3,526 cohort members who worked less than 1 year in the plants. Our cumulative styrene exposure estimates are not job-specific, because job titles were missing for many workers, and do not include any exposure between 1978, when personnel records were microfilmed, and 1989 (Plant B) or 1993 (Plant A), when the plants closed. We have no exposure data on levels of fiberglass, solvents, wood dust, or wood finishing agents, all known to have been present in the plants. The lack of job information after 1978 means that for both cumulative exposure and duration of exposure our exposure estimates are underestimates, and would bias results toward the null.

In conclusion, we found no evidence for an excess in mortality from leukemia and lymphoma. Exposure to styrene may be associated with an increased risk of urinary tract cancer and respiratory disease mortality. The evidence for an association of prostate cancer with styrene exposure is not as strong, but this cohort is definitely experiencing excess prostate cancer mortality. Among those who worked more than 1 year in a high-exposure department (Table V) there was statistically significant elevated mortality for deaths from pneumoconiosis and other respiratory diseases and accidents. None of these findings were considered likely a priori; they are difficult to interpret and could be due to chance.

ACKNOWLEDGMENTS

Authors thank Dr. Teresa Schnorr and Dr. Kyle Steenland, and reviewers, for their valuable comments. Also thank Lian Luo, Chris Gersic, and Lihing Chang in data preparation. Thanks to Lucy Schoolfield for help with literature searches.

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