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Cancer mortality in a historical cohort study of workers exposed to styrene

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OBJECTIVES — The goal of this study was to determine whether exposure to styrene is associated with an increased risk for neoplasms of the lymphatic and hematopoietic tissues.

METHODS — A historical cohort study was conducted in Denmark, Finland, Italy, Norway, Sweden, and the United Kingdom. It involved 40 688 workers ever employed in the reinforced plastics industry, where high exposure to styrene occurs. Exposure to styrene was reconstructed through job histories and environmental and biological monitoring data. Cause-specific national death rates were used as the reference. Poisson regression was applied for internal comparisons.

RESULTS — Among the exposed workers, no excess was observed for mortality from all neoplasms. Mortality from neoplasms of the lymphatic and hematopoietic tissues increased with time since first exposure and average level of exposure to styrene, but was not consistently associated with duration of exposure or with cumulative exposure.

CONCLUSIONS — These findings leave open the possibility of an excess risk of neoplasms of the lymphatic and hematopoietic tissues among workers exposed to styrene.

KEY TERMS — leukemia, lymphoma, neoplasms.

Styrene is a widely used chemical in the plastics and rubber industry. In the late 1980s, the world annual production was almost 10 million metric tons (1) and it was estimated that about 270 000 workers were exposed to high levels of styrene. In epidemiologic studies, an increase in risk for leukemia or malignant lymphoma has been suggested among workers in the

styrene-butadiene rubber industry (2, 3) and other chemical and plastics industries (4-8), where exposure to styrene is, on the average, fairly low (1). It was not always possible in some of these studies to evaluate adequately concomitant exposure to other chemicals, including agents such as benzene or 1,3-butadiene, which are known or suspected causes of leukemia and lymphoma in humans (9, 10). High airborne levels of styrene occur in the reinforced plastics industry. Concomitant, confounding carcinogenic exposures have been rare or nonexistent in this industry. Of the two larger studies (11, 12), a small increase in the risk of leukemia was observed in one, among workers highly exposed to styrene (12). A third study had only limited power to detect even a high excess risk of leukemia or lymphoma (13). The results of epidemiologic studies have thus not been consistent, and in 1987 a working group convened by the International Agency for Research on Cancer (IARC) concluded that there was inadequate evidence on the carcinogenicity of styrene to humans (9). A potential cancer risk from exposure to styrene is indicated from studies on cytogenetic damage in workers exposed to styrene. Several studies have shown an increase in chromosome aberrations, sister chromatid exchanges, and micronuclei in reinforced plastics workers exposed to styrene; a dose-effect relation between chromosome aberrations, sis-

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ter chromatid exchanges, and exposure to styrene was observed in some studies (14). Styrene-7,8-oxide, the main reactive metabolite of styrene, has been shown to be carcinogenic in experimental studies (9).

In this communication we report the results of a large international historical cohort study of cancer mortality among workers in the reinforced plastics industry in six European countries. The results for one of the cohorts included in the study have been presented earlier, but for a shorter period of follow-up (11), and those of another can be found on pages 272–278 of this issue of the *Scandinavian Journal of Work, Environment & Health*.

Subjects and methods

Subjects

A total of 41 167 potential subjects from eight centers in six countries (Denmark, Finland, Italy, Norway, Sweden, United Kingdom) were enrolled in the study. We excluded 479 workers from the analysis because of unknown date of birth ($N = 249$), unknown date of first employment ($N = 168$), or unknown gender ($N = 62$). The remaining 40 688 workers comprised 34 560 men and 6128 women ever employed in the reinforced plastics industry (table 1). About 60% of the total population ($N = 24 794$) had been employed in the industry for less than two years. The proportion of short-term workers varied among countries from a low of 9% in Finland to a high of 81% in Denmark. Nearly 50% of the cohort was first employed before 25 years of age, and a similar proportion was first employed after 1975.

The reinforced plastics production plants in Italy, Norway, and the United Kingdom (UK-1 cohort) that were included in the study were contacted directly, and the production records of the plants were abstracted together with payroll records of all workers ever employed during periods for which complete ascertainment was possible (table 1). Only records for laminators were obtained from 51 additional smaller plants in the United Kingdom, hereafter distinguished as the UK-2 cohort. The Finnish cohort comprised all workers employed in 157 plants iden-

tified at the time of a cross-sectional survey in 1976. Of the 2085 workers enrolled in the Finnish cohort, complete dates of employment were obtained only for the 598 workers in the three largest plants, and these workers have been included in statistics for duration and cumulative and average exposure. In Denmark, all plants that produced reinforced plastics were initially identified by contacting major dealers of polyester resins, and the proportion of the work force employed in each plant in the production of reinforced plastics was estimated (15). Included in the international study were all workers in 287 plants where the main product during the study period (involving more than 50% of the work force) was reinforced plastics. In Sweden, a cohort of workers from 30 companies producing reinforced plastics was formed in 1976. Workers in these companies had been exposed to styrene since the start of production of reinforced plastics. In 1987, the Swedish investigators tried to locate the companies again. In 16 companies still active in 1987, information was abstracted for all workers employed since the formation of the original cohort and, whenever available, also on the job titles of workers included in the original cohort. No additional information was retrieved for the workers in the 14 companies which had been closed down.

The subjects accumulated 539 479 person-years at risk (214 965 person-years at ≥ 10 years since first exposure) and were followed-up for an average of 13 years. Workers lost to follow-up constituted 1.4% of the total group, and those who had emigrated comprised 1.6% of the total group. In no individual cohort did the total proportion of workers lost to follow-up or having emigrated exceed 8%. The observation period for each subject started on his date of first exposure to styrene (first employment for the unexposed) or on the first date for which complete payroll records were available in the plant (whichever later).

Exposure assessment

A styrene-exposure data base was constructed on the basis of approximately 16 500 personal environmental measurements conducted during the period

Table 1. Description of the international cohort.

Country and research center	Number of plants	Subjects		Person-years	Period of follow-up
		Men	Women		
Denmark	287	13 682	2185	175 640	1970–1990
Finland	157	1 652	433	30 726	1958–1989
Italy, Liguria	3	1 306	132	16 442	1969–1991
Italy, Emilia Romagna	98	4 254	1564	53 268	1956–1989
Norway	26	2 035	—	25 445	1956–1991
Sweden	30	3 231	436	49 278	1955–1987
United Kingdom — 1	8	6 651	1320	161 516	1945–1990
United Kingdom — 2	51	1 749	58	27 164	1961–1988
Total	660	34 560	6128	539 479	

1955—1990 and of around 18 500 measurements of styrene metabolites in urine, conducted in the late 1980s (16, 17). The styrene exposure levels decreased considerably during the study period in all six countries (figure 1). Extensive exposure information for early periods of production (before 1970) were available only for Denmark (18). Recorded average exposure levels were high before 1965 (around 200 ppm) and decreased rapidly after 1970. Exposures in early production periods in the other five countries were estimated by applying two different models. In one (exposure model A), it was assumed that past exposure levels were as high in all countries as those recorded in Denmark. In this model, exposure levels in each country were linearly extrapolated from the level recorded at the earliest period for which valid exposure data were available for the country, towards the 205 ppm which was recorded in Denmark in 1965 and in earlier periods. The levels were kept stable at 205 ppm for all years before 1965. Alternatively, it was assumed (exposure model B) that the styrene levels in each country at the earliest period for which valid exposure data were available for the country adequately reflected levels in all previous periods (horizontal extrapolation).

The following five mutually exclusive groups of workers were distinguished on the basis of exposure measurements and individual job titles: (i) laminators ($N = 10\,629$), including workers involved in hand or spray lamination, who constituted the most heavily exposed group; (ii) workers with unspecified tasks ($N = 19\,408$), a mixed group of workers including predominantly those involved in lamination in small plants where job titles could not be retrieved or in plants where they had rotating tasks; they had, on the average, lower exposures than laminators although some workers in this group may have had very high exposures; (iii) workers in other exposed jobs, ($N = 5406$), including those not involved in lamination but regularly exposed to styrene, such as maintenance workers, painters, forklift truck drivers, and laminators in nonmanual semiautomatic processes (a low exposure group); (iv) workers not exposed to styrene ($N = 4044$), who were manual and clerical workers in the industry and were not regularly exposed to styrene; and (v) workers with unknown job titles ($N = 1201$). Workers were classified according to the longest-held exposed job. Laminators, workers with unspecified tasks, and those with other exposed jobs were aggregated for some of the analyses (indicated in the text as "exposed workers"). In Sweden, all of the workers in the 14 companies closed before 1987 and some of the workers in the remaining 16 companies were classified as having unspecified tasks. All of the subjects in the Danish and Finnish cohorts were classified as having unspecified tasks.

Duration of exposure was calculated using data from individual payroll records in combination with plant records showing the dates of production of re-

Figure 1. Recorded levels of exposure to styrene among laminators in the reinforced plastics industry. (UK = United Kingdom)

inforced plastics in the plant. In Denmark, subjects were identified by means of a unique personal identification number in records of the Supplementary Pension Fund, and duration of exposure was estimated using the payment records of the Pension Fund (15). Use of the Pension Fund records provided more accurate and, in general, shorter estimates of duration of exposure than those obtained from plant records used in previous reports (19, 20). Use of the Pension Fund records especially affected estimates of duration of exposure for short-term, high-mobility workers, who constituted a large fraction of the Danish cohort.

Cumulative exposure (ppm-years) and average exposure (ppm, calculated as cumulative exposure divided by total exposure time) were estimated for each subject on the basis of individual job records and country-, period-, and job-specific exposure estimates with the use of both exposure models. Cumulative exposure was calculated both for the total exposure period and with the application of a five-year lag (ie, ignoring any exposure which occurred five years prior to death, loss, or end of follow-up).

Statistical analysis

The person-years method was used to derive standardized mortality ratios (SMR) with 95% confidence intervals (95% CI) on the basis of a Poisson distribution (21). An excess or deficit in a standardized mortality ratio was regarded as statistically significant at $P < 0.05$ (two-tail) when the 95% confidence interval did not include 100. Test for trend in the standardized mortality ratios were conducted using the method described by Breslow & Day (22). An international mortality data bank including number of deaths and population statistics was provided by the World Health Organization (23). The data bank was used to compute national mortality reference rates by gender, age (in five-year age groups), and calendar period [in five-year periods, except when periods coincided with a revision of the International Classification of Diseases (ICD)]. National mortality

ty rates were used without adjustment for possible variations in mortality by socioeconomic status or region of residence. Wide social or regional variations in mortality from specific neoplasms, such as lung cancer, have been recorded in some European countries, but there is little evidence of such systematic variation for leukemias and lymphomas. Underlying causes of death were coded nationally. A conversion table prepared at IARC allowed the results to be pooled over different revisions of the ICD.

Internal comparisons were limited to exposed subjects and focused, a priori, on neoplasms of the lymphatic and hematopoietic tissues. Poisson regression models were fitted to country-, age-, gender-, time- and exposure-specific rates (22) with the use of the statistical package GLIM (24). Rate ratios (RR) and 95% confidence intervals were estimated. No external mortality rates were used for the regression models. Mortality from major neoplasms, for which the risk increased with time since first exposure in this study, and from cancers of the lung and kidney, for which an increased risk has been suggested in other studies (12, Wong personal communication), was also examined with the Poisson regression. All regression models included age (five levels: <35, 35–44, 45–54, 55–64, ≥65 years), calendar period (four levels, 1974 and earlier, 1975–1979, 1980–1984, 1985 and later), country, gender, and time since first exposure (three levels: <10, 10–19, ≥20 years). Cumulative and average exposures were categorized into four or five levels (see tables 4 and 5). The cut-off points were chosen according to models for neoplasms of the lymphatic and hematopoietic tissues so that each level included an approximately equal number of cases and also so that none of the levels were restricted to a very narrow range of exposure. Tests for linear trend were performed by introducing an exposure term into the model as a continuous variable and by comparing the deviance of the model with and without the variable (22).

Results

Mortality from all causes in the total cohort was lower than expected from national rates (2714 observed deaths, SMR 92, 95% CI 88–95), due mainly to low mortality from malignant neoplasms (686 deaths, SMR 87, 95% CI 81–94), circulatory diseases (1114 deaths, SMR 92, 95% CI 87–97), and respiratory diseases (169 deaths, SMR 79, 95% CI 67–92). Accidents, poisoning, and violence constituted the only major disease category for which the standardized mortality ratio exceeded 100 (402 deaths, SMR 110, 95% CI 99–121). For the men, mortality from all causes (SMR 94, 2513 deaths), all neoplasms (SMR 88, 609 deaths), and other major causes was higher than for the women (all causes: SMR 74, 201 deaths; all neoplasms: SMR 79, 77 deaths,).

Table 2 gives the standardized mortality ratios, 95% confidence intervals, and observed numbers of deaths from major nonneoplastic causes and from malignant neoplasms by site and exposure group for both genders combined. Mortality from all causes was the highest among the workers with "unspecified tasks." Mortality from all neoplasms was slightly higher for the laminators and workers with unspecified tasks than for the other two groups. Excess mortality from accidents, poisoning, and violence was seen among workers with unspecified tasks. Statistically significant deficits were seen for circulatory diseases among those unexposed and for respiratory diseases among the laminators and workers in other exposed jobs (table 2).

Neoplasms of the lymphatic and hematopoietic tissues

Mortality from neoplasms of the lymphatic and hematopoietic tissues was slightly higher among the workers with unspecified tasks (SMR 119) than among the laminators (SMR 81), workers in other exposed jobs (SMR 65), and the unexposed workers (SMR 91) (table 2). For the exposed workers, most cases were registered for the men (SMR 102, 49 deaths), and only one death occurred among the women (SMR 25). Table 3 gives the SMR values and observed numbers of deaths for the exposed subjects from all neoplasms, as well as from neoplasms of the lymphatic and hematopoietic tissues by time since first exposure and by duration of exposure. Mortality from neoplasms of the lymphatic and hematopoietic tissues increased with time since first exposure, to a standardized mortality ratio of 132 (95% CI 64–244) for those with ≥20 years since first exposure (chi-square for linear trend 3.91, $P < 0.05$). This pattern was observed for non-Hodgkin's lymphoma, Hodgkin's disease, and the leukemias. No similar increase was seen with time since first employment for the unexposed (SMR at ≥20 years since first employment 44, 95% CI 6–176, 2 deaths). The pattern of risk with length of exposure was inconsistent. Workers who had been exposed for less than two years tended to have slightly higher mortality rates for neoplasms of the lymphatic and hematopoietic tissues than longer term workers. The standardized mortality ratios for neoplasms of the lymphatic and hematopoietic tissues were 102 (29 deaths) for workers with <2 years of exposure, 89 (8 deaths) for 2–4 years of exposure, 84 (6 deaths) for 5–9 years, 116 (4 deaths) for 10–14 years of exposure, and 102 (2 deaths) for ≥15 years of exposure. Among workers with more than two years of exposure, a statistically nonsignificant twofold increased risk for non-Hodgkin's lymphoma, Hodgkin's disease, and leukemia (7 deaths, SMR 225, 95% CI 91–464) was observed for ≥20 years since first exposure (table 3).

Table 2. Mortality by detailed cause and job-category for the men and women combined.^a (SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

Cause of death ^b	Laminators			Unspecified task			Other exposed jobs			Unexposed			Total cohort		
	SMR	95% CI	Observed deaths (N)	SMR	95% CI	Observed deaths (N)	SMR	95% CI	Observed deaths (N)	SMR	95% CI	Observed deaths (N)	SMR	95% CI	Observed deaths (N)
All causes	88	81–96	593	106	100–112	1167	84	76–92	436	75	68–83	408	92	88–95	2714
Malignant neoplasms (140–207)	91	78–106	167	99	88–112	280	73	59–88	103	73	59–88	106	87	81–94	686
Buccal cavity and pharynx (140–149)	28	1–156	1	36	4–131	2	36	1–201	1	40	1–220	1	33	11–77	5
Esophagus (150)	181	87–334	10	83	27–193	5	24	1–131	1	..	0–93	—	82	47–131	17
Stomach (151)	107	61–174	16	117	71–180	20	79	38–145	10	92	48–161	12	95	72–123	58
Small intestine (152)	227	6–1266	1	0	0–414	—	645	78–2331	2	..	0–1317	—	150	31–438	3
Colon (153)	104	54–182	12	81	46–134	15	57	18–132	5	31	6–90	3	77	55–105	39
Rectum (154)	52	14–134	4	71	32–133	9	101	37–220	6	32	4–117	2	62	38–95	21
Liver and gallbladder (155–156)	26	1–146	1	99	40–204	7	29	1–163	1	34	1–190	1	61	31–110	11
Pancreas (157)	148	76–258	12	117	68–188	17	30	4–110	2	79	26–186	5	100	71–138	37
Unspecified digestive (159)	0	0–520	—	200	5–1114	1	164	4–913	1	..	0–709	—	80	10–289	2
Nose and nasal cavities (160)	0	0–946	—	175	4–977	1	0	0–1366	—	..	0–1419	—	64	2–357	1
Larynx (161)	155	32–452	3	118	32–302	4	59	1–328	1	132	16–475	2	111	53–205	10
Lung (162)	106	81–136	60	99	78–124	78	89	65–121	42	84	58–116	37	99	87–113	235
Connective and other soft tissue (171)	0	0–397	—	0	0–293	—	185	5–1032	1	0	0–738	—	59	7–214	2
Skin (172–173)	31	1–173	1	104	42–215	7	0	0–184	—	220	60–563	4	85	44–148	12
Breast (174)	55	11–161	3	101	43–198	8	0	0–251	—	23	3–85	2	52	28–89	13
Cervix uteri (180)	112	3–626	1	0	0–191	—	0	0–1604	—	61	2–342	1	40	5–146	2
Ovary (183)	261	71–669	4	109	22–319	3	0	0–802	—	150	41–385	4	140	70–251	11
Prostate (185)	89	36–184	7	143	90–217	22	84	34–174	7	70	23–163	5	102	74–139	41
Testis (186)	0	0–254	—	64	8–230	2	299	36–1078	2	0	0–802	—	68	19–174	4
Bladder (188)	56	12–164	3	145	81–239	15	62	13–180	3	85	23–217	4	95	61–140	25
Other urinary (kidney) (189)	90	25–232	4	75	30–154	7	29	1–161	1	69	8–251	2	77	44–125	16
Brain (191–192)	68	22–159	5	66	28–129	8	67	14–196	3	51	6–186	2	62	37–98	18
Thyroid (193)	227	6–1266	1	105	3–586	1	0	0–1085	—	0	0–946	—	91	11–330	2
Ill defined (195, 199)	34	7–101	3	128	66–224	12	78	25–183	5	158	76–290	10	96	65–136	31
Lymphatic and hematopoietic (200–207)	81	43–139	13	119	80–170	30	65	26–134	7	91	41–172	9	93	71–120	60
Non-Hodgkin's (200, 202)	140	56–288	7	55	15–139	4	30	1–167	1	101	21–294	3	77	43–128	15
Hodgkin's disease (201)	133	27–388	3	107	22–312	3	80	2–446	1	0	0–318	—	90	36–184	7
Multiple myeloma (203)	0	0–155	—	193	78–398	7	53	1–295	1	113	14–408	2	99	48–183	10
Leukemia (204–207)	48	10–139	3	140	79–228	16	94	26–240	4	99	27–254	4	104	69–150	28
Myeloid leukemia (205)	28	1–156	1	142	65–269	9	91	11–328	2	157	32–459	3	110	63–179	16
Circulatory disease (390–458)	91	80–103	257	97	88–107	394	96	84–109	223	79	69–92	190	92	87–97	1114
Respiratory disease (460–519)	70	48–98	34	99	75–130	54	69	47–99	30	79	57–106	44	79	67–92	169
Accidents, poisoning and violence (E800–E999)	89	69–112	70	128	113–145	256	88	63–120	39	76	50–112	26	110	99–121	402
Unknown cause	..	..	4	..	..	25	..	..	4	..	..	6	..	..	40

^a Statistics for subjects with unknown exposure are not shown.^b Code of the International Classification of Diseases, eighth revision, in parentheses.

Table 4 shows the rate ratios and 95% confidence intervals for cumulative and average exposure from the Poisson regression analysis. The rate ratios for neoplasms of the lymphatic and hematopoietic tissues are shown in figure 2 for both exposure models and also for the same models when a five-year lag time was applied. There was no indication of an increase in risk of neoplasms of the lymphatic and hematopoietic tissues with increasing cumulative exposure to styrene.

An increase in average exposure was related to a risk of neoplasms of the lymphatic and hematopoietic tissues (table 4, figure 3) and to risk of lympho-

mas (table 4, figure 4). Tests for linear trend were statistically significant in the models including age, gender, country, calendar period, and time since first exposure for neoplasms of the lymphatic and hematopoietic tissues (X^2 for linear trend = 5.45, $P < 0.05$) and marginally significant for lymphoma (X^2 for linear trend = 3.77, $0.05 < P < 0.1$).

Of a total of 50 exposed cases with neoplasms of the lymphatic and hematopoietic tissues, 24 were diagnosed in the Danish cohort. Mortality from these neoplasms was higher in Denmark (SMR 122, 95% CI 78–181, 24 deaths) than in the cohorts from Finland, Italy, Norway, Sweden, and the Unit-

Table 3. Mortality from all neoplasms and neoplasms of the lymphatic and hematopoietic tissue for workers exposed to styrene by time since first exposure and duration of exposure. (SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

Site ^a	Time since first exposure											
	< 10 years			10–19 years			≥ 20 years			Total		
	Observed deaths (N)	SMR	95% CI	Observed deaths (N)	SMR	95% CI	Observed deaths (N)	SMR	95% CI	Observed deaths (N)	SMR	95% CI
All neoplasms												
< 2 years' exposure	100	78	63–94	143	105	88–123	45	86	63–116	288	91	81–102
≥ 2 years' exposure	76	94	74–118	113	87	72–105	59	100	76–129	248	92	81–104
Total exposure	176	84	72–97	256	96	85–109	104	93	76–113	536	91	83–99
Lymphatic and hematopoietic (200–208)												
< 2 years' exposure	6	43	16–93	20	183	112–283	3	85	18–248	29	102	68–147
≥ 2 years' exposure	7	92	37–190	6	61	22–132	7	173	70–357	20	93	57–143
Total exposure	13	60	32–103	26	125	82–183	10	132	64–244	49	98	72–130
Non-Hodgkin's lymphoma (200–202)												
< 2 years' exposure	—	0	0–99	4	118	32–302	1	83	2–460	5	60	19–140
≥ 2 years' exposure	3	140	29–408	1	32	1–177	3	221	45–645	7	105	42–217
Total exposure	3	51	11–149	5	76	25–178	4	155	42–397	12	80	41–140
Hodgkin's disease (201)												
< 2 years' exposure	2	82	10–295	3	280	58–819	—	0	0–1844	5	134	44–313
≥ 2 years' exposure	1	83	2–460	—	0	0–419	1	500	13–2786	2	87	11–314
Total exposure	3	82	17–241	3	153	32–447	1	244	6–1359	7	116	47–239
Multiple myeloma (203)												
< 2 years' exposure	1	72	2–401	3	172	36–504	1	139	4–774	5	129	42–302
≥ 2 years' exposure	1	99	3–552	2	108	13–391	—	0	0–405	3	80	16–233
Total exposure	2	83	10–299	5	140	45–326	1	62	2–344	8	105	45–207
Leukemia (204–208)												
< 2 years' exposure	3	47	10–137	10	215	103–395	1	73	2–407	14	113	62–189
≥ 2 years' exposure	2	62	7–222	3	75	16–220	3	194	40–566	8	91	39–179
Total exposure	5	52	17–122	13	150	80–257	4	136	37–347	22	104	65–157

^a Code of the International Classification of Diseases, eighth revision, in parentheses.**Table 4.** Mortality from neoplasms of the lymphatic and hematopoietic tissues by cumulative exposure, time since first exposure and average exposure to styrene, calculated on the basis of exposure model A, no lag — Poisson regression analysis.^a (RR = rate ratio, 95% CI = 95% confidence interval, ICD = international classification of diseases, 8th rev = eighth revision)

Variable	Lymphatic and hematopoietic neoplasms (ICD 200–208, 8th rev)			Leukemias (ICD 204–208, 8th rev)			Malignant lymphomas (ICD 200–202, 8th rev)		
	Observed deaths (N)	RR	95% CI	Observed deaths (N)	RR	95% CI	Observed deaths (N)	RR	95% CI
Cumulative exposure (ppm-years)									
< 75	20	1	—	11	1	—	5	1	—
75–199	8	0.98	0.43–2.26	2	0.46	0.10–2.09	5	2.63	0.74–9.32
200–499	10	1.24	0.57–2.72	3	0.69	0.19–2.53	5	2.99	0.82–10.91
≥ 500	9	0.84	0.35–2.02	5	0.86	0.26–2.83	3	1.64	0.34–7.82
Test for linear trend (P-value)	—	0.65	—	—	> 0.52	—	—	0.52	—
Time since first exposure ^a (years)									
< 10	13	1	—	5	1	—	6	1	—
10–19	25	2.90	1.29–6.48	12	3.01	0.90–10.08	8	2.43	0.69–8.49
≥ 20	9	3.97	1.30–12.13	4	3.79	0.70–20.59	4	5.16	0.90–29.47
Test for linear trend (P-value)	—	0.012	—	—	0.094	—	—	0.072	—
Average exposure ^b (ppm)									
< 60	7	1	—	3	1	—	3	1	—
60–99	9	1.68	0.59–4.79	4	1.58	0.32–7.79	4	2.51	0.49–12.87
100–119	10	3.11	1.07–9.06	8	4.43	0.98–20.03	1	1.65	0.15–18.57
120–199	13	3.08	1.04–9.08	3	1.36	0.22–8.48	8	7.15	1.21–42.11
≥ 200	8	3.59	0.98–13.14	3	2.16	0.29–16.24	2	4.40	0.42–45.99
Test for linear trend (P-value)	—	0.019	—	—	0.47	—	—	0.052	—

^a Models for cumulative and average exposure were adjusted by age, gender, country, calendar period, and time since first exposure.^b For the malignant lymphomas, the RR and 95% CI are presented for data from five countries, excluding Finland, because the model using the full data set did not converge.

Figure 2. Mortality from neoplasms of the lymphatic and hematopoietic tissues by cumulative exposure to styrene. Poisson regression analysis using different exposure models and models applying a five-year (5-yr) lag period.

Figure 3. Mortality from neoplasms of the lymphatic and hematopoietic tissues by average exposure to styrene — Poisson regression analysis using different exposure models.

ed Kingdom (SMR 81, 95% CI 53–118, 26 deaths). For ≥ 20 years since first exposure, the standardized mortality ratio for long-term workers (>2 years' duration of exposure) was 141 (95% CI 4–785, 1 leukemia death) in Denmark; in the cohorts from the other five countries the standardized mortality ratio was 181 (95% CI 66–392) mainly due to increased mortality from malignant lymphomas. The overall pattern observed for cumulative and average exposure reflected predominantly the pattern of the Danish cohort. An increase by cumulative exposure was observed in the cohorts from the other five countries, with rate ratios of 1, 1.7, 2.2, and 1.5 for each quartile, respectively (exposure model A, no lag), but no increase was observed for average exposure.

Other neoplasms

No significant excess risk for other cancers was observed among the exposed workers (table 2). Among the female exposed workers, a small increase in risk was found for ovarian cancer (SMR 147, 95% CI 59–304, 7 deaths). Significantly decreased risks were observed for cancers of the esophagus, colon, and female breast in the unexposed group. Among the exposed workers, mortality was highest at ≥ 20 years since first exposure for cancers of the esophagus (SMR 166, 6 deaths), pancreas (SMR 170, 9 deaths), larynx (SMR 268, 3 deaths), and for some other rare neoplasms. The rate ratios and 95% confidence intervals for cumulative exposure (using exposure model A) are shown in table 5 for all neoplasms and also for cancers of the esophagus, pancreas, lung, and kidney. Mortality rates from all neoplasms and from laryngeal and lung cancer were not related to cumulative exposure to styrene. Mortality from kidney cancer increased with cumulative exposure (RR 6.04 in the ≥ 500 ppm-years category) but decreased with time since first exposure (RR 0.72, 5 deaths, 10–19 years since first exposure; RR 0.31, 1 death, ≥ 20

Figure 4. Mortality from malignant lymphomas by average exposure to styrene — Poisson regression analysis using different exposure models.

years since first exposure). The mortality rates from esophageal cancer increased slightly with cumulative exposure and were highest at ≥ 20 years since first exposure (RR 5.82, 95% CI 1.0–33.91, 6 deaths). The mortality rates from cancer of the pancreas were highest at ≥ 20 years since first exposure (RR 2.05, 95% CI 0.58–7.29, 9 deaths) and increased with cumulative exposure (table 5).

Discussion

Exposure to styrene has been associated with the occurrence of lymphomas and leukemias in epidemiologic studies, but the overall evidence is inconsistent (9). Most studies have examined mortality from cancer in industries where exposure to styrene is, on the average, fairly low. This international study was conducted in the reinforced plastics industry because there are high levels of styrene in that occupational environment and there is no or minimal exposure to other identified carcinogenic agents, such as benzene or 1,3-butadiene, which have been associated with the occurrence of lym-

Table 5. Mortality from all neoplasms and selected cancers by cumulative exposure, estimated on the basis of exposure model A, no lag — Poisson regression analysis.^a (RR = rate ratio, 95% CI = 95% confidence interval)

Cancer	Observed deaths (N)	RR	95% CI
All neoplasms			
<75 ppm-years	206	1.0	·
100—199 ppm-years	83	0.89	0.69—1.16
200—499 ppm-years	96	1.00	0.78—1.28
≥500 ppm-years	119	1.01	0.78—1.29
Test for trend (P-value)	·	0.92	·
Esophagus			
<75 ppm-years	5	1.0	·
100—199 ppm-years	2	1.01	0.20—5.23
200—499 ppm-years	3	1.67	0.39—7.18
≥500	4	1.76	0.42—7.30
Test for trend (P-value)	·	0.31	·
Pancreas			
<75 ppm-years	9	1.0	·
100—199 ppm-years	5	1.44	0.48—4.34
200—499 ppm-years	6	1.90	0.65—5.53
≥500 ppm-years	10	2.56	0.90—7.31
Test for trend (P-value)	·	0.068	·
Lung			
<75 ppm-years	73	1.0	·
100—199 ppm-years	25	0.75	0.47—1.19
200—499 ppm-years	26	0.74	0.47—1.16
≥500 ppm-years	37	0.90	0.58—1.38
Test for trend (P-value)	·	<0.43	·
Kidney			
<75 ppm-years	2	1.0	·
100—199 ppm-years	3	4.40	0.71—27.15
200—499 ppm-years	2	3.30	0.42—25.60
≥500 ppm-years	3	6.04	0.74—49.45
Test for trend (P-value)	·	0.12	·

^a All of the models were adjusted by age, gender, country, calendar period, and time since first exposure.

phomas or leukemias (9, 10). The most frequent other chemical exposure in this industry is acetone (18) which, however, has not been associated with an increased cancer risk.

Study population

The data base contained information on about 40 000 workers, most of whom were involved in lamination and were thus exposed to high levels of styrene. About 60% of the workers in the study had been employed for less than two years, a period reflecting the typical employment pattern in the industry. Of the workers employed for more than two years, around 11 500 had been followed for longer than 10 years, contributing 87 577 person-years after the 10th year. At present, it is that subgroup of workers which was most informative of cancer risk. Information was collected by similar procedures in five of the six participating countries. In Denmark, however, it was not possible to contact all plants in the study or to retrieve production records and job records of workers. Of the Danish workers currently classified as exposed to styrene, a proportion, possibly as much as 25%, could actu-

ally have had no exposure to styrene (15). In Finland, workers were identified through a cross-sectional survey. As a result, a lower percentage of short-term workers were included in this cohort when compared with those of other countries. In this study, data were abstracted from 660 plants, including numerous small workplaces. In early periods of production payroll records were not complete in many small plants or were not available because of the relatively frequent changes in plant ownership in the industry. The observation period for each subject in the study started on the date of first exposure to styrene or on the first date for which complete payroll records were available in the plant (whichever later). An unknown number of workers employed in early periods were, therefore, not included in the study. Although the estimates of the risk should not be biased by the lack of inclusion of these workers, it has inevitably resulted in the exclusion of workers who had been heavily exposed and who potentially could have been followed for a long period of time.

Exposure assessment

The levels of exposure to styrene in the reinforced plastics industry decreased considerably during the study period (figure 1). Although the decrease occurred over different periods in each country, the overall pattern is similar. In Denmark, where measurements are available from 1955 on, recorded levels of exposure among laminators were about 200 ppm in the 1950s, about 100 ppm in the late 1960s, and about 20 ppm in the late 1980s (18). In most other participating countries measurements were available only after the early 1970s. In all countries, recorded levels of exposure provide more reliable estimates of the 8-h time-weighted average exposures for periods after 1980, and for the United Kingdom after 1985. For most analyses, exposure in early periods of production were estimated on the basis of the Danish data. The extrapolation from the Danish data seems justified because of the similarity in time trends for exposure to styrene between countries, the existence of limited data suggesting that high exposure levels occurred not only in Denmark (25, Pannett unpublished observations), the similar production processes and materials used in European plants, and the similar climatic conditions in northern countries, although not in Italy. The use of alternative exposure models in the analysis provided a means for examining the dependency of results on the various assumptions made when past exposures were estimated. The results indicated that the overall pattern of risk for neoplasms of the lymphatic and hematopoietic tissues did not depend critically on the exposure model applied or on the use of a lagged period when the total length of exposure was estimated. In any case, even if past exposures levels based on the Danish data are overestimated,

rate ratios based on quartiles of cumulative exposure are not likely to be seriously affected and will probably underestimate the carcinogenic potency of styrene.

Neoplasms of the lymphatic and hematopoietic tissues

In this cohort, time since first exposure was the variable most strongly related with the occurrence of lymphomas and leukemias. Among the exposed workers, especially those with more than two years of exposure, mortality from lymphomas and leukemias increased considerably with time since first exposure. No similar increase was seen among the unexposed workers with time since first employment. No clear association was observed with duration of exposure or job categories. As the levels of styrene decreased sharply during the study period in all countries, duration of exposure may be a poor surrogate for cumulative exposure.

Only small differences in mortality were observed between worker groups, even though the levels of styrene to which laminators were exposed were, on the average, three times higher than those in the other exposed jobs category (16). Several factors could attenuate any difference in risk between workers in different exposure groups. First, misclassification of individual exposure could have occurred, especially because in Denmark and Finland all subjects were placed into one group. Second, individual exposure levels varied widely within each group. This problem is exemplified in an analysis of biological monitoring data from plants included in one of the Italian cohorts, which indicated that the job categories used in the study accounted for only 25% of the interindividual variability in exposure (17). Third, although subjects in the other jobs category had lower overall exposures than the laminators, they had actually been exposed in the past to high levels of styrene, frequently reaching levels above 50 ppm. Finally, most subjects in the other exposed jobs category were skilled manual workers having a longer average length of employment than laminators or workers with unspecified tasks.

The analysis of mortality from neoplasms of the lymphatic and hematopoietic tissues indicated that there was no trend in risk with increasing cumulative exposure. An increasing trend in mortality with increasing average exposure was seen for neoplasms of the lymphatic and hematopoietic tissues and for malignant lymphomas. Exposure indices based on some measure of the intensity of exposure have been shown to yield monotonically increasing exposure-response relationships and high relative risks more often than those based on duration of exposure (26). These results, although they possibly could be due to chance, may indicate that very high exposures, even for periods of only a few years, increase the risk of cancer. Even in recent years, when average ex-

posure levels have been considerably lowered, environmental peak exposures of 200–300 ppm are regularly recorded in lamination processes, especially in spray lamination (1). The importance of peak exposures on long-term health effects is poorly understood (27). Studies on styrene metabolism in rodents and humans indicate that the metabolism of styrene appears to be nonlinear and becomes saturated at levels between 100 and 250 ppm (28). Levels of styrene oxide may, therefore, not be expected to be proportional to environmental levels of exposure to styrene.

The increase in mortality from neoplasms of the lymphatic and hematopoietic tissues observed in the international cohort partly reflects the findings in the Danish cohort. The increase in the other cohorts was of smaller magnitude although more consistent in the analysis by cumulative exposure to styrene. The variation in mortality between the cohorts is unlikely to reflect different chemical exposures in the reinforced plastics industry in Europe and may be, to an extent, a chance finding. It may also partly reflect the different method of cohort assembly in Denmark in comparison with that used in the other countries and, specifically, a more complete enumeration of workers employed in small workplaces.

Other neoplasms

Among the exposed workers, no increased risk was observed for mortality from all causes or from major diseases. As in other occupational cohorts, mortality rates from all causes and from all neoplasms were initially lower than expected and increased gradually with time since first exposure. In the total study population, no increased risk was observed for cancers of any site. Increased risks, frequently based on small numbers, were observed for individual cohorts for a variety of cancers, including those of the pancreas, ovary, testis, and prostate, most of which have not previously been associated with exposure to styrene. In the international study, the most consistent results for neoplasms other than leukemias and lymphomas in relation to styrene exposure were seen for cancer of the pancreas. Mortality from this cancer increased with time since first exposure and cumulative exposure. Excess risk for cancer of the pancreas has been related to various occupational exposures, including exposures in the chemical and petroleum industries, the aluminum production industry, and the rubber industry, and with exposure to organochlorine compounds and asbestos, but the results of the numerous epidemiologic studies have generally been inconsistent (29). Inaccuracies in death certification pose serious problems in studies on cancer of the pancreas, although they are unlikely to have affected considerably the findings from internal comparisons in this study. A small increased risk was seen for cancer of the esophagus. This cancer has mainly been associated with life-style fac-

tors, such as tobacco and alcohol consumption, and occasionally with occupational exposures (30). In an updated mortality study of workers in the reinforced plastics industry in the United States (12), an increased risk for cancer of the kidney was reported (Wong, personal communication). A similar increase in mortality from cancer of the kidney with cumulative exposure was seen in our study, but most cases occurred during the 10 years after first exposure.

Concluding remarks

In the total study population, exposure to styrene was not associated with an excess risk of mortality from major neoplasms or, specifically, with an excess risk of mortality from neoplasms of the lymphatic and hematopoietic tissues. Nevertheless, mortality from neoplasms of the lymphatic and hematopoietic tissues increased with time since first exposure and average level of exposure to styrene. Increases in risk were also seen for cancer of the pancreas and some other neoplasms which have not previously been related with exposure to styrene. In conclusion, these findings leave the question open of whether an excess risk of neoplasms of the lymphatic and hematopoietic tissues occurs among workers exposed to styrene.

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