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ORIGINAL CONTRIBUTIONS

Exposure to Styrene and Mortality from Nervous System Diseases and Mental Disorders

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Chronic low-dose exposure to solvents has been associated in epidemiologic studies with chronic neurotoxicity, but the evidence is not consistent. Styrene causes acute disturbances in the central and peripheral nervous systems. To determine if exposure to styrene may contribute to chronic diseases of the central nervous system, the authors examined mortality from nervous system diseases, mental disorders, and suicide in relation to styrene exposure in an international historical cohort study. The cohort involved 35,443 workers employed during 1945–1991 in the reinforced plastics industry, where high exposures to styrene occur. Indicators of exposure were reconstructed through job histories and environmental and biologic monitoring data. Poisson regression was used for internal comparisons. Mortality from diseases of the central nervous system (27 deaths) increased with time since first exposure, duration of exposure, average level of exposure, and cumulative exposure to styrene. A quadratic model described best the dose-response shape for cumulative exposure and duration of exposure with the highest risks at around 300 ppm-years and 5 years, respectively, and a subsequent decrease in risk in the highest exposure categories. Mortality from epilepsy increased monotonically with all styrene exposure indicators, while associations for degenerative diseases of the central nervous system were generally weaker. Mortality from mental disorders and suicide decreased with increasing duration of exposure and cumulative exposure, while there was no trend with time since first exposure and average exposure to styrene. These findings suggest that, in addition to the known acute effects, exposure to styrene may contribute to chronic diseases of the central nervous system. *Am J Epidemiol* 1996;144:623–33.

central nervous system; cohort studies; mental disorders; mortality; occupational health; styrenes; suicide

Styrene (C_8H_8, Chemical Abstracts Service Registry number 100–42–5) is an aromatic hydrocarbon produced in large quantities throughout the world. Global production of styrene in 1992 was over

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Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases*, Ninth Revision; RR, rate ratio; SMR, standardized mortality ratio.

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14,000 tons (906 kg) (1). The major uses for styrene are in the manufacture of plastics, latex paints and coatings, synthetic rubbers, polyesters, and styrene-alkyd coatings (2). Exposure occurs primarily in the workplace: during the production and polymerization of styrene; manufacture of plastics, resins, and synthetic rubber; and fabrication of products such as boats and containers made from glass-reinforced plastics (1).

Styrene is taken up through the lung (3) and to a lesser extent through the skin (4). It exhibits low-to-moderate acute toxicity in various organs in laboratory animals (5). In humans, it causes irritation of the skin, eyes, throat, and the respiratory tract and acute disturbances of the central and peripheral nervous system. A wide spectrum of barely detectable to severe adverse acute neurologic effects of occupational styrene exposure have been reported, such as decreased nerve conduction velocities and electroencephalographic, functional, and psychiatric impairments (6–11). Most neurologic effects have been observed at levels of about 100 ppm of styrene, although memory and neurobehavioral disturbances were seen at levels of 10–30 ppm and above. The underlying mechanism of styrene-induced neurotoxicity remains undetermined. Depletion of brain dopamine levels has been proposed as a potential mechanism of neurotoxicity (12). Styrene, like other solvents, has also been associated with chronic neurotoxicity (6, 7, 11, 13–16), but the evidence is not consistent. A full-blown clinical neurotoxic disease from long-term occupational exposure to styrene is seldom encountered or, at least, very rarely diagnosed. Chronic low-dose exposure to various solvents has been associated in epidemiologic studies with chronic neurotoxicity, but the evidence is not entirely consistent and the biologic mechanism is unknown (17–21).

We have previously reported the patterns of cancer mortality in an international cohort of workers exposed to styrene in the reinforced plastics industry (22–24), as well as mortality from other causes of death in one of the national cohorts (25). The international cohort, with well-characterized heavy exposure to styrene, offers an opportunity to explore the relation of solvent exposure to neuropsychiatric diseases. This paper examines mortality from diseases of the nervous system, mental disorders, and suicide in the same cohort.

MATERIALS AND METHODS

Subjects

The original cohort comprised 41,167 subjects employed in 660 plants manufacturing reinforced plastics products during 1945–1991. These cohort members were identified through eight research centers in six countries (Denmark, Finland, Italy (two centers), Norway, Sweden, United Kingdom (two centers)). Because of unknown date of birth, unknown date of first employment, or unknown sex, 479 workers were subsequently excluded. In this analysis, we also excluded those unexposed to styrene or whose exposure was unknown (n = 5,245). Unexposed workers were excluded because they did not constitute a valid reference group for the international study, since in three centers (Denmark, Finland, United Kingdom (center 2)) information was only abstracted for exposed workers. The remaining 35,443 exposed workers comprised 30,682 men and 4,761 women ever employed in the reinforced plastics industry. For internal comparisons, we further excluded 2,641 exposed subjects with incomplete information on duration of exposure. This left 32,802 exposed subjects for the Poisson regression analysis.

A detailed description of recruitment to the cohort has been reported elsewhere (23). Information on employment was abstracted from company payrolls in five countries and from national pension scheme records in Denmark. Three categories of workers were distinguished on the basis of exposure measurements and job titles: 1) laminators (n = 10,629); 2) workers with "unspecified tasks" including predominantly workers with laminating tasks (n = 19,408); and 3) workers in "other exposed jobs" (n = 5,406).

The follow-up for mortality started at the first exposure to styrene or on the first date for which complete payrolls were available in the plant if later. The cohort members accumulated 446,784 person-years during an average of 12.6 years of follow-up (table 1). Workers lost to follow-up constituted 1.4 percent of the total cohort and those emigrated, 1.6 percent. In no national component did the proportion of workers lost to follow-up or emigrated exceed 8 percent. The cohort of 32,802 exposed subjects included in internal comparisons accumulated 405,975 person-years during an average of 12.4 years of follow-up.

Exposure assessment

A styrene exposure database was constructed on the basis of some 16,500 personal exposure measurements conducted during the period 1955–1990 and around 18,500 determinations of styrene metabolites in urine, conducted in the late 1980s (23, 26). Exposure decreased in all countries from recorded levels of around 200 ppm in the 1960s to levels of 20–40 ppm in the late 1980s (figure 1). Extensive exposure information for early periods of production (before 1970) was available for Denmark only (27). Exposures in early

TABLE 1. Description of exposed workers in the international cohort

Country and research center	No. of plants	Men (no.)	Women (no.)	Person-years	Period of follow-up
Denmark	287	13,682	2,185	175,640	1970–1990
Finland	157	1,652	433	30,726	1958–1989
Italy					
Center 1	3	1,106	60	13,847	1969–1991
Center 2	98	2,952	1,253	35,873	1956–1989
Norway	26	1,690		20,607	1956–1991
Sweden	30	2,787	238	42,599	1955–1987
United Kingdom					
Center 1	8	5,064	534	105,538	1945–1990
Center 2	51	1,749	58	27,164	1961–1988
Total	660	30,682	4,761	451,993	

production periods in the remaining five countries were estimated using national exposure data in conjunction with the exposure levels recorded in Denmark. The use of Danish data for the international cohort is justified by the similar production processes and materials used in plants under study, the similarity in time trends for exposure to styrene between countries after 1970, and limited information available for a few measurements that had been carried out in other countries before 1970 (28) (B. Pannett, Medical Research Council, Southampton, United Kingdom, personal communication, 1994). An exposure matrix was constructed by country and calendar period on job title, type of products, and methods of production. Estimates of individual exposure were reconstructed by aggregating this matrix and personal occupational histories.

Statistical analysis

For external comparisons, standardized mortality ratios were calculated with 95 percent confidence intervals based on the Poisson distribution, using the PERSONYEARS program (29). The World Health Organization mortality data bank was used to compute national mortality rates by sex, age (in 5-year groups), and calendar period (in 5-year periods, except when periods coincided with a revision of the *International*

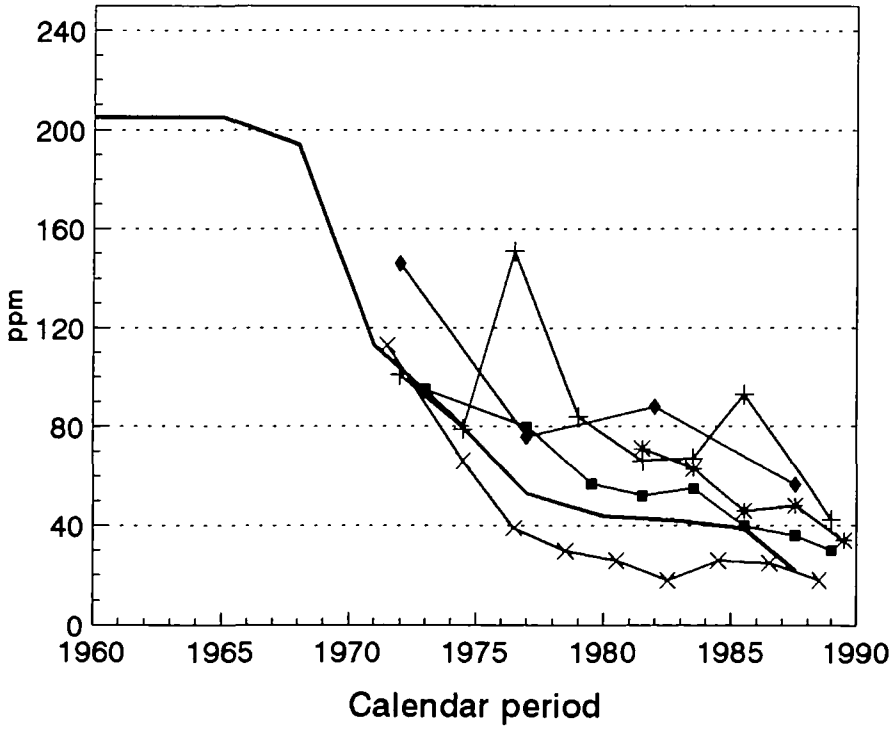

FIGURE 1. Recorded levels of exposure to styrene by calendar period among laminators in the reinforced plastics industry in an international cohort between 1960 and 1990. —, Denmark; +, Finland; *, Italy; ■, Norway; ×, Sweden; ♦, United Kingdom.

Classification of Diseases) from which expected numbers of death were derived. The list of diseases for which standardized mortality ratios could be calculated was limited by the availability of mortality rates in the World Health Organization data bank for the follow-up period. The underlying cause of death for deceased cohort members was retrieved from the national death certificate records.

For internal comparisons, calculation of exposure indices and allocation of person-years to the relevant exposure/confounder categories were performed using a SAS program (30). Country, sex, age (five levels: <35, 35–44, 45–54, 55–64, and ≥65 years), and calendar period (four levels: <1975, 1975–1979, 1980–1984, ≥1985) were included in all models as possible confounders. The time since first exposure was categorized in three levels (<10, 10–19, ≥20 years). Cumulative exposure (ppm-years) and average exposure (ppm, calculated as cumulative exposure divided by total duration of exposure) were derived and categorized. The cutpoints for cumulative (eight levels) and average (four levels) exposure and for duration of exposure (eight levels) were chosen a priori to give an even spread of the number of deaths across levels ensuring, however, that there was at least one death in each category. Poisson regression models were used for the internal comparisons among exposed subjects, and rate ratios and 95 percent confidence intervals were estimated for a more detailed list of diseases than was feasible when using external reference rates. Tests for linear trend were performed by entering an exposure term as a continuous variable into the model and comparing the deviance of the model before and after introducing the variable. The shape of the dose-response for duration of exposure and cumulative exposure was examined using spline regression models (31) on grouped data, with values in each category equal to their rank. First, a linear and a quadratic term were fitted. A second quadratic term was then added with the knot chosen at the maximum in the analysis of eight categories, that is, at category 5 for cumulative exposure (200–349 ppm-years) and category 6 (7–9 years) for duration (see table 3 and figure 2). The GLIM statistical package (32) was used for the analysis.

RESULTS

External comparisons

Mortality from all causes in the total cohort (n = 40,688) was lower than expected from national rates (2,714 observed deaths, standardized mortality ratio (SMR) = 0.92, 95 percent confidence interval (CI) 0.88–0.95). In exposed workers (n = 35,443) (table 2), there was a slight deficit (2,196 deaths, SMR = 0.96), due mainly to low mortality from malignant neoplasms (550 deaths, SMR = 0.91), respiratory diseases (118 deaths, SMR = 0.81), and circulatory diseases (874 deaths, SMR = 0.95). Mortality from mental disorders was around that expected (21 deaths, SMR = 1.01) and, from peripheral and central nervous system diseases, lower than expected (30 deaths,

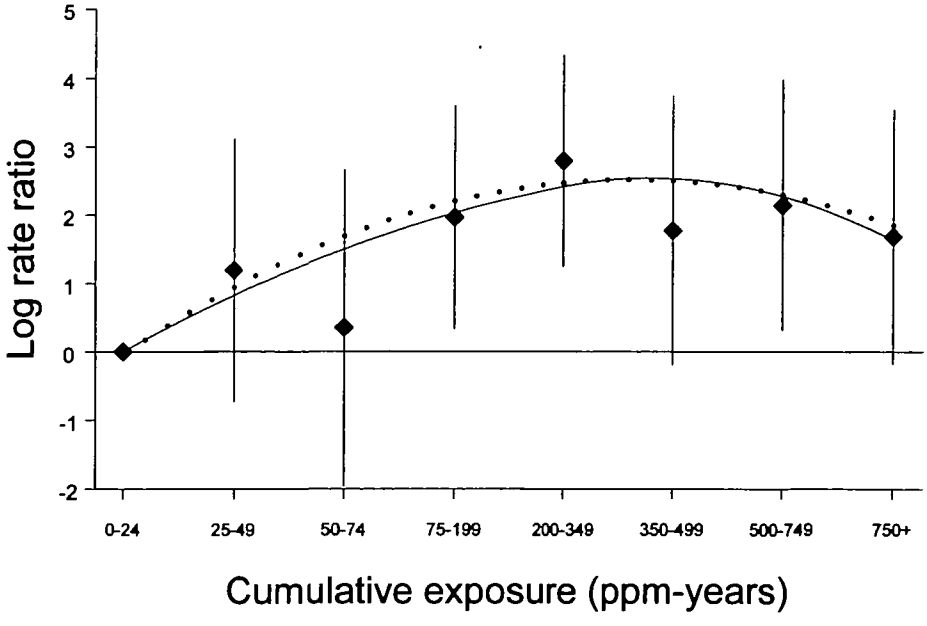

FIGURE 2. Log rate ratios for mortality from central nervous system diseases by cumulative exposure to styrene among international cohorts from 1945 to 1991. Categorical Poisson regression (dots, with bars indicating 95 percent confidence intervals), quadratic regression (solid line), and quadratic spline regression (dashed line). All models are adjusted for country, age, calendar year, and sex.

TABLE 2. Standardized mortality ratios by detailed cause of death for exposed workers in the international cohort, 1945–1991

Cause of death by ICD-9* codes	No. of observed deaths	No. of expected deaths	SMR*	95% CI*
All causes (codes 001–999)	2,196	2,293.1	0.96	0.92–1.00
All malignant neoplasms (codes 140–208)	550	607.3	0.91	0.83–0.98
Mental disorders (codes 290–319)	21	20.9	1.01	0.62–1.54
Diseases of nervous system (codes 320–389)	30	39.4	0.76	0.51–1.09
Diseases of circulatory system (codes 390–459)	874	920.1	0.95	0.89–1.08
Cerebrovascular diseases (codes 430–438)	121	144.9	0.84	0.69–1.00
Diseases of respiratory system (codes 460–519)	118	146.5	0.81	0.67–0.96
Diseases of digestive system (codes 520–579)	70	89.4	0.78	0.61–0.99
External causes of death (E800–E999)	365	323.1	1.13	1.02–1.25
Suicide and self-inflicted injury (E950–E959)	136	123.4	1.10	0.92–1.30
Other violent causes (E800–E918, E921–E949, E960–E999)	224	192.0	1.17	1.02–1.33

* ICD-9, *International Classification of Diseases*, Ninth Revision; SMR, standardized mortality ratio; CI, confidence interval.

SMR = 0.76). Accidents, poisoning, and violence constituted the only major category with a significantly raised standardized mortality ratio (365 deaths, SMR = 1.13), due to an excess of suicides and self-inflicted injuries (136 deaths, SMR = 1.10) and of deaths from other violent causes (224 deaths, SMR = 1.17).

Internal comparisons

The mortality from central nervous system diseases (table 3) increased with average exposure to styrene (p value for trend = 0.37), cumulative exposure (p value for trend = 0.01), duration of exposure (p value for trend = 0.02), and time since first exposure (p value for trend = 0.32). Workers with an average exposure higher than 120 ppm had an almost twofold risk compared with workers whose average exposure was less than 60 ppm, and those with a cumulative exposure of more than 75 ppm-years had risks ranging from six- to 16-fold compared with workers with less than 24 ppm-years. Adjustment for the time since first exposure did not materially affect the rate ratios for cumulative exposure and duration but reduced the rate ratios for average exposure (rate ratio (RR) = 1.0 for <60 ppm of styrene; RR = 1.1 for 60–119 ppm; and RR = 1.5 for ≥120 ppm). The shape of the dose-response for the duration of exposure and cumulative exposure was examined with spline regression models (figure 2). A first model included a linear and a quadratic term for both duration and cumulative exposure. For both variables, the linear and quadratic terms were above or close to statistical significance. The beta coefficients for duration were 1.091 ± 0.4193 (standard error) for the linear term and −0.1022 ± 0.0488 for the quadratic term. The corresponding values for cumulative exposure were 1.348 ± 0.435 and −0.1196 ± 0.0444. This simple quadratic equation fitted the data adequately, and the addition of a spline with one knot at the maximum (figure 2) did not improve the fit for cumulative exposure (difference in deviance, −0.2267, 1 df) or for duration (difference in deviance, −0.0022, 1 df).

Deaths from epilepsy constituted a quarter of all deaths from central nervous system diseases (table 4). This proportion is about that expected on the basis of national mortality statistics. No deaths from diseases of the peripheral nervous system were recorded. Mortality from epilepsy increased monotonically with all exposure indicators (table 5), but confidence intervals were wide because of small numbers. Of the seven deaths from epilepsy, six (86 percent) occurred below the age of 35 years. Two deaths from epilepsy occurred while the subjects were employed in the reinforced plastics industry or within half a year after having left the industry. Four subjects succumbed between half a year and 5 years after termination of employment.

Mortality from degenerative diseases of the central nervous system (cerebral degenerations, not in childhood, *International Classification of Diseases* (ICD-9) code 331; Parkinson's disease, ICD-9 code 332; and anterior horn cell disease, ICD-9 code 335) did not increase consistently with increasing exposure to styrene (table 5), although mortality tended to be higher among workers with a long duration of exposure or high cumulative exposure. Workers with higher than 200 ppm-years of cumulative exposure had an approximately fourfold statistically significant increased risk compared with workers with less than 200 ppm-years. Of 11 deceased subjects in this category, seven were diagnosed with anterior horn cell disease, which typically comprises mostly patients with amyotrophic lat-

TABLE 3. Mortality from central nervous system diseases* in the international cohort, 1945–1991, and indices of exposure to styrene†

	No. of deaths	RR‡	95% CI‡	*p* for linear trend
Time since first exposure (years)				
<10	9	1.00		0.32
10–19	14	1.98	0.73–5.35	
≥20	4	1.68	0.39–7.24	
Duration of exposure				
0–5 months	3	1.00		0.02
6–11 months	2	2.33	0.40–13.56	
1–2.4 years	7	4.97	1.29–19.15	
2.5–3 years	3	5.00	1.01–24.69	
4–6 years	5	6.46	1.50–27.78	
7–9 years	4	8.80	1.87–41.33	
10–14 years	2	4.75	0.75–30.14	
≥15 years	1	4.08	0.39–43.13	
Average exposure (ppm)				
<60	9	1.00		0.37
60–119	10	1.31	0.50–3.42	
≥120	8	1.72	0.57–5.13	
Cumulative exposure (ppm-years)				
0–24	2	1.00		0.01
25–49	2	3.29	0.48–22.65	
50–74	1	1.42	0.14–14.35	
75–199	5	7.14	1.39–36.59	
200–349	9	16.32	3.47–76.73	
350–499	2	5.90	0.82–42.69	
500–749	3	8.55	1.36–53.68	
≥750	3	5.40	0.83–35.06	

* *International Classification of Diseases*, Ninth Revision, codes 320–389. Occupational history (duration of exposure) was incomplete for three additional deceased exposed subjects.
† Internal comparisons (Poisson regression analysis), all models being adjusted for country, age, calendar year, and sex.
‡ RR, rate ratio; CI, confidence interval.

TABLE 4. Underlying causes of death from central nervous system diseases in exposed workers in the international cohort, 1945–1991

Cause of death by ICD-9* code	No. of deaths
Meningitis (code 320)	3
Intracranial and intraspinal abscess (code 324)	1
Cerebral degenerations, not in childhood (code 331)	1
Parkinson's disease (code 332)	3
Anterior horn cell disease (code 335)	7
Epilepsy (code 345)	7
Other conditions of brain (code 348)	4
Other disorders of nervous system (code 349)	1
All	27

* ICD-9, *International Classification of Diseases*, Ninth Revision.

eral sclerosis. Mortality from amyotrophic lateral sclerosis was not consistently associated with exposure, although the risk tended to increase with cumulative exposure (RR = 1.0 for <50 ppm-years, referent category; RR = 3.14, 95 percent CI 0.39–25.5, for 50–199 ppm-years; RR = 6.90, 95 percent CI 0.92–51.8, for 200–499 ppm-years; RR = 2.47, 95 percent CI 0.21–29.11, for ≥500 ppm-years; *p* value for trend, 0.29) and was highest in the longest duration category (RR = 6.69, 95 percent CI 0.53–85.08 for ≥10 years of duration).

We also examined mortality from cerebrovascular diseases (ICD-9 codes 430–438), since this group of diseases may be of relevance when examining mortality from central nervous system diseases. A small but statistically significant increase in mortality from cerebrovascular diseases was observed by the time since first exposure (*p* value for trend = 0.0042) and with average exposure (*p* value for trend = 0.013). No trend in risk was seen for the duration of exposure or cumulative exposure (table 6).

The mortality from mental disorders, in particular from psychosis (seven deaths) and neurotic disorders (12 deaths), was highest among short-term workers (<1 year of employment) and decreased with increasing duration of employment (table 7). A similar pattern was seen for suicide, with a clearly higher risk among workers with a short duration of exposure (RR = 1.0 for <1 year of duration; 0.42 for 1–3 years; 0.31 for 4–9 years; and 0.44 for ≥10 years). For all

TABLE 5. Mortality from epilepsy* and degenerative central nervous system diseases in the international cohort, 1945–1991, and indices of exposure to styrene†

	Epilepsy				Degenerative central nervous system diseases			
	No. of deaths	RR‡	95% CI‡	*p* for trend	No. of deaths	RR	95% CI	*p* for trend
Time since first exposure (years)								
<10	3	1.00		0.008	3	1.00		0.75
10–19	3	5.64	1.03–30.9		5	1.02	0.20–5.15	
≥20	1	485.9	1.19–9,999		3	1.22	0.16–9.19	
Duration of exposure (years)								
<1	1	1.00		0.03	1	1.00		0.16
1–3	3	1.37	0.08–23.2		5	8.85	1.06–73.9	
4–9	1	8.28	0.76–90.4		4	9.88	1.09–89.9	
≥10	2	28.4	2.11–381.5		1	4.74	0.28–79.8	
Average exposure (ppm)								
<60	3	1.00		0.32	4	1.00		0.32
60–119	2	1.20	0.16–9.21		2	0.43	0.07–2.44	
≥120	2	3.35	0.32–35.4		5	1.30	0.31–5.42	
Cumulative exposure (ppm-years)								
<50	1	1.00		0.07	1	1.00		0.16
50–199	2	2.95	0.25–34.3		2	3.09	0.28–33.8	
200–499	2	5.33	0.44–64.9		7	14.4	1.75–119.2	
≥500	2	9.63	0.71–131.1		1	1.87	0.11–31.1	

* Epilepsy: *International Classification of Diseases*, Ninth Revision (ICD-9), code 345; degenerative central nervous system diseases: ICD-9 codes 331, 332, and 335.
† Internal comparisons (Poisson regression analysis), all models being adjusted for country, age, calendar year, and sex.
‡ RR, rate ratio; CI, confidence interval.

these causes of death, the pattern for the other exposure indices was similar: no trend for the time since first exposure or average exposure, with the highest risk associated with the lowest cumulative exposure. The pattern of risk for traffic accidents was similar to that observed for suicide with the highest risk among short-term workers (RR = 1.0 for <1 year of duration; 0.55 for 1–3 years; 0.39 for 4–9 years; and 0.37 for ≥10 years).

Of the 27 deaths from central nervous system diseases, 13 occurred in the Danish cohort. The pattern of risk for central nervous system diseases by time since first exposure, duration of exposure, and cumulative exposure was fairly similar between the Danish and the cohorts in the other five countries. An inconsistently increasing risk by average exposure was observed in Denmark, while there was no increase in the other five countries.

DISCUSSION

This historical cohort study of workers exposed to styrene was initially formed to examine the risk of leukemia and lymphoma. Very little information is available, however, on mortality from other diseases associated with exposure to styrene, despite the fact that acute and chronic exposures to the compound have been shown to affect physiologic parameters and cause morbidity in various systems.

Chronic low-dose exposure to various solvents has been associated with neurotoxicity, but the epidemiologic evidence is not consistent (17–20). The validity of some of the findings has been questioned, particularly concerning the definition of the disease and of the exposure, the lack of specificity of the effects, the lack of dose-response relations, and the absence of a biologically plausible mechanism (21). In this international study, the exposure to solvents and the outcome were well characterized, and positive dose-response relations were observed. Inaccuracy of diagnoses from death certificates, confounding by other chemical exposures in the workplace, and a biased comparison group particularly due to the healthy worker effect may, however, have influenced the validity of our results. We discuss these issues in turn.

Erroneous diagnoses or coding of death certificates may have affected analyses for specific diseases within the wider category of central nervous system diseases. This is reflected, for example, in the relatively high number of deaths (n = 5) coded as other conditions/disorders of the nervous system (table 4). All effect estimates were adjusted for calendar period and country, and this should, at least, reduce any errors

TABLE 6. Mortality from cerebrovascular diseases* in the international cohort, 1945–1991, and indices of exposure to styrene†

	No. of deaths	RR‡	95% CI‡	*p* for trend
Time since first exposure (years)				
<10	27	1.00		0.0042
10–19	52	1.71	1.01–2.91	
≥20	31	2.66	1.37–5.15	
Duration of exposure (years)				
<1	49	1.00		0.75
1–3	21	0.65	0.39–1.08	
4–9	26	0.95	0.57–1.57	
≥10	14	0.82	0.43–1.55	
Average exposure (ppm)				
<20	4	1.00		0.013
20–59	20	1.08	0.37–3.19	
60–119	38	1.38	0.48–3.95	
120–199	30	2.11	0.72–6.18	
≥200	18	2.15	0.70–6.62	
Cumulative exposure (ppm-years)				
<10	20	1.00		0.57
10–74	22	0.68	0.37–1.24	
75–199	21	0.84	0.45–1.57	
200–499	19	0.69	0.36–1.30	
≥500	28	0.77	0.42–1.42	

* *International Classification of Diseases*, Ninth Revision, codes 430–438. Occupational history (duration of exposure) was incomplete for 11 additional deceased exposed subjects.

† Internal comparisons (Poisson regression analysis), all models being adjusted for country, age, calendar year, and sex.

‡ RR, rate ratio; CI, confidence interval.

due to temporal variation in coding or diagnostic practices, as well as differences among countries. An associated issue is possible misdiagnosis between diseases of the central nervous system and cerebrovascular diseases. Mortality from cerebrovascular diseases was not associated with cumulative exposure or duration of exposure, and consequently it is unlikely that the positive trends observed for central nervous system diseases are due to a transfer of diagnoses between the two disease groups.

Among the industries using styrene, manufacture of reinforced plastics involves by far the highest recorded levels of exposure to the chemical (26–28). Acetone and glass fiber are among other agents used in large quantities in this industry. Also used, although in much lower quantities, are various other solvents including agents with known or suspected neurotoxicity, such as toluene, *n*-hexane, and gasoline (27). A confounding effect of such solvents cannot be ruled out, although given the relatively low levels of exposure, we would expect any such effect to be small.

The healthy worker effect is of special relevance in this study, since many neurologic deaths follow chronic disabling disease. Selection of healthy individuals into employment affects predominantly external comparisons using national mortality rates as the reference and may have contributed to the low standardized mortality ratios observed in this study for central nervous system diseases. This type of bias should not affect internal comparisons within the cohort. Decline of health status with time may lead to an increase in risk with time since first exposure (as observed in this cohort) but also may affect the results by duration of exposure and cumulative exposure. Selection out of employment of ill individuals was potentially a more important problem in the internal comparisons in this study because of the prolonged duration of central nervous system diseases. This aspect of the healthy worker effect tends to attenuate dose-response relations. Thus, the increased mortality from central nervous system diseases in this study with exposure to styrene indicates that, if anything, the association between styrene and central nervous system mortality may be even stronger than suggested in our analysis.

The nervous system has been shown to be one of the most sensitive target systems for styrene. Epilepsy was among the most frequent causes of death from central nervous system diseases in this population and was positively associated with all exposure indicators in the internal comparisons. Case reports and epidemiologic studies of workers exposed to organic solvents

TABLE 7. Mortality from mental disorders and suicide in the international cohort, 1945–1991, by duration of exposure to styrene (in years)*

	No. of deaths	RR†	95% CI†	*p* for trend
Mental disorders (ICD-9† codes 290–319)				
Duration of exposure (years)				0.01
<1	14	1.00		
1–3	3	0.37	0.10–1.31	
4–9	1	0.16	0.02–1.26	
≥10	1	0.22	0.02–1.89	
Psychosis (ICD-9 codes 290–299)				
Duration of exposure (years)				
<1	3	1.00		0.48
1–3	2	0.94	0.15–5.80	
4–9	1	0.48	0.05–4.91	
≥10	1	0.56	0.05–6.58	
Neurotic disorders (ICD-9 codes 300–316)				
Duration of exposure (years)				
<1	11	1.00		
≥1	1	0.10	0.01–0.78	
Suicide (ICD-9 codes E950–E959)				
Duration of exposure (years)				
<1	95	1.00		<0.001
1–3	22	0.42	0.26–0.68	
4–9	9	0.31	0.15–0.62	
≥10	6	0.44	0.18–1.07	

* Internal comparisons (Poisson regression analysis), all models being adjusted for country, age, calendar year, and sex.

† RR, rate ratio; CI, confidence interval; ICD-9, *International Classification of Diseases*, Ninth Revision.

and of subjects sniffing organic solvents have associated these exposures with the occurrence of epileptic seizures (33–38). The mechanisms through which exposure to solvents might lead to higher mortality from epilepsy are unknown. The information available in this study did not allow a distinction to be made between epilepsy that developed before working age and during working life. Of note is that six of seven deaths from epilepsy occurred among subjects below the age of 35 years. Head injuries and alcohol abuse are well-recognized risk factors for epilepsy, particularly in young adults. Death certificates of the seven deceased subjects were reviewed but in only one subject was a contributing cause (intracerebral hemorrhage, *International Classification of Diseases*, Ninth Revision, code 431) perhaps indicative of a central nervous system trauma. The associations between exposure to styrene and mortality from degenerative disorders of the central nervous system (Parkinson's disease, unspecified degenerative disorders of the brain, and anterior horn cell disease/amyotrophic lateral sclerosis) were generally weaker than those found for epilepsy but are interesting, since they may imply a long-term effect of styrene on the central nervous system. A small increase in mortality from degenerative disorders of the nervous system was also found in a large Danish study of workers employed in industries producing reinforced plastics, which partly overlaps with this international cohort (25).

Among all major nonneoplastic disease groups, the only increased standardized mortality ratio in this cohort was observed for deaths from accidents, poisoning, and violence, including suicide and self-inflicted injuries and other violent causes. Biases in recording suicide over time and across communities and socioeconomic strata can arise from different cultural and operational conventions of diagnosis and classification. Internal comparison among workers of similar socioeconomic status should, however, be minimally affected by biases in diagnostic practices, if the specificity of diagnostic classification (supposedly nondifferential with regard to exposure) remains reasonably high. Internal comparisons indicated that the highest risk for suicide and mental disorders was concentrated in short-term workers. Health patterns of short-term workers have frequently been shown to differ from those of long-term workers (39, 40). This has been attributed to differences in work conditions (with supposedly higher exposure of short-term workers to hazards), differences in lifestyle, and a selection effect, the so-called healthy worker survivor effect (41). The absence of a positive association with exposure indicators suggests that lifestyle factors may be more important in explaining differences in risk by duration

of exposure than a direct effect of styrene. No lifestyle data were available in this study. However, mortality from cirrhosis of the liver, which has been highly correlated with the use of alcohol, was inversely associated with duration of employment: 20 (71 percent) of 28 subjects who died from cirrhosis had been employed for less than 1 year.

In conclusion, in this large cohort of workers, mortality from central nervous system diseases, and especially from epilepsy, tended to increase with exposure to styrene. Lifestyle factors and a selection effect rather than a direct effect of styrene appear the most likely causes of the higher mortality from mental disorders and suicide in short-term compared with long-term workers. Although these results have to be interpreted with caution because of small numbers, the findings indicate that, in addition to known acute effects, exposure to styrene may contribute to chronic disease from the central nervous system.

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