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Original Contribution

Associations of Occupational Styrene Exposure With Risk of Encephalopathy and Unspecified Dementia: A Long-Term Follow-up Study of Workers in the Reinforced Plastics Industry

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Exposure to industrial solvents has been associated with encephalopathy. Styrene is a neurotoxic industrial solvent, and we investigated the long-term risk of encephalopathy and unspecified dementia following styrene exposure. We followed 72,465 workers in the reinforced plastics industry in Denmark (1977–2011) and identified incident cases of encephalopathy ($n = 228$) and unspecified dementia ($n = 565$) in national registers. Individual styrene exposure levels were modeled from information on occupation, measurements of work place styrene levels, product, process, and years of employment. Adjusted analyses were performed using a discrete survival function. A positive trend for encephalopathy ($P < 0.01$) and a negative trend for unspecified dementia ($P = 0.03$) were seen with cumulative styrene exposure accrued during the recent period of up to 15 years. For unspecified dementia and the combination of unspecified dementia and encephalopathy, a positive trend was indicated when applying a 30-year exposure lag ($P = 0.13$ and $P = 0.07$). The risk patterns seen following recent exposure probably reflect diagnostic criteria for encephalopathy requiring recent industrial solvent exposure and referral bias rather than association with styrene exposure, while the increasing risk observed for unspecified dementia and the combination of encephalopathy and unspecified dementia following distant exposure indicates an increased risk of dementia following styrene exposure with a long latency period.

dementia; follow-up study; occupational diseases; occupational exposure; risk assessment; solvents

Abbreviations: CI, confidence interval; ICD-8, *International Classification of Diseases, Eighth Revision*; ICD-10, *International Classification of Disease, Tenth Revision*.

The reporting of a consistent pattern of symptoms belonging to the domains of mood, memory, and attention resembling those of mild to moderate dementia by workers with long-term industrial solvent exposure led to the definition of solvent-induced encephalopathy, in lay terms known as painter's syndrome (1, 2). Verified solvent exposure is a requirement for the diagnosis. The general opinion is that there is little lag between exposure and first symptoms and that symptoms do not progress upon cessation of exposure (3). In Denmark, a case of solvent-induced encephalopathy was reported in 1976 (4), and the diagnostic entity was quickly recognized as an occupational disease. A total of 19 cases were recognized as occupational diseases in 1979, increasing to 696 in 1984 in a population of 5.1 million and thereafter declining (5).

Styrene is an industrial solvent used worldwide in the manufacturing of synthetic rubbers and plastics (6). Styrene is a well-known neurotoxin affecting reaction time, color vision, and hearing threshold among workers with long-term exposure (7–9). There is also some evidence of associations with memory, attention, and nerve conduction velocity (10–12). We are not aware of studies that have examined the relationship with a syndrome consistent with solvent-induced encephalopathy.

In the present study, we examined the risk of encephalopathy and unspecified dementia in relation to cumulative styrene exposure in a large cohort of styrene-exposed workers in the Danish reinforced plastics industry. We include unspecified dementia because symptoms and clinical findings can overlap with those of encephalopathy.

METHODS

Study population

A cohort of 77,491 workers from 456 Danish companies producing reinforced plastics (1964–2007) was identified by means of the Danish Supplementary Pension Fund Register (13). The register provided annual information on employment in these companies and any other company since 1964. To have complete work histories, we excluded those with a registration in 1964 (3,496 persons), the year the pension register was established, resulting in a study population with employment histories starting between 1965 and 2007. Further exclusions due to death, disappearance, or emigration before start of follow-up (1,439 persons), missing vital status (25 persons), and diagnoses of encephalopathy or unspecified dementia before start of follow-up (66 persons) resulted in a final study population of 72,465 workers. Information on occupation during 1970–2007 was obtained from Statistics Denmark (14).

Outcomes

We identified cases in the National Patient Register (1977–2011) (15) and the Psychiatric Central Research Register (1977–2011) (16). Diagnoses were coded according to the 8th (1977–1993) and 10th (1994–2011) revisions of the *International Classification of Diseases* (ICD-8 and ICD-10). We defined encephalopathy by ICD-8 codes 347.91, 347.99, and 781.79, as recommended for cases of solvent-induced encephalopathy by the Danish Association of Occupational and Environmental Medicine, and ICD-10 codes G92 and G934, and we identified unspecified dementia by ICD-8 codes 290.00 and 290.19 and ICD-10 code F03. From the National Patient Register, we also obtained diagnoses for chronic obstructive pulmonary disease (ICD-8 codes: 490–492; ICD-10 codes: J43–44) and alcohol-related diseases (ICD-8 codes: 291, 303, 571.0, and 571.10; ICD-10 codes: F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K85.2, and K86.0).

Exposure assessment

We modeled styrene exposure intensity from 1,122 personal styrene measurements and company characteristics (production process, product, and calendar year) obtained from 133 companies 1970–2011. We modeled styrene exposure probability from survey exposure information gathered in 2013 from 11,264 present and former employees of all companies linked with information on occupation, sex, product, production process, company size, and calendar year available for the entire population. For each year of employment in a study company since 1965, we computed styrene exposure level for each worker as the product of predicted exposure intensity and predicted exposure probability. These exposure estimates were added across all years of employment during styrene production to obtain a cumulative styrene exposure metric (expressed as mg/m^3-years). Detailed information on the study population and exposure assessment is described elsewhere (17).

The Danish Data Protection Agency approved the study (j.no: 1–16–02-01-07). Participants in the survey were informed that they could withdraw their consent to participate at any point in time.

Statistical analysis

We started follow-up at January 1, 1977, or January 1st of the year following first year of exposed employment in a study company, whichever was latest. We followed workers until the year of first diagnosis of encephalopathy or unspecified dementia, death, emigration, or end of follow-up at December 31, 2011, whichever came first.

We analyzed data with a discrete-time hazard model with person-years as unit of analysis, yielding incidence rate ratios and 95% confidence intervals (18). Styrene exposure metrics were categorized into tertiles in the initial analyses based on the person-year exposure distribution. Age was included in all models. Due to differences in age distribution we used slightly different age categorizations for encephalopathy (years: <40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, ≥70) and unspecified dementia (years: <50, 50–59, 60–69, 70–74, 75–79, 80–84, 85–89, ≥90). For combined analyses of encephalopathy and unspecified dementia, a combination of these age categorizations was used (years: <40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, ≥90). Models further included calendar year (1977–1989, 1990–1999, 2000–2011), sex, level of education, hospital diagnoses of chronic obstructive pulmonary disease and alcohol-related diseases as proxies of smoking and alcohol intake, and employment status.

Cumulative styrene exposure was the principal exposure metric. We also analyzed the separate exposure metrics combined in cumulative exposure: duration of employment during styrene production, mean styrene exposure intensity, and mean styrene exposure probability. Furthermore, we analyzed the association with cumulative styrene exposure accrued within the previous <15, 15–29, and ≥30 years. In these analyses cumulative styrene exposure within the window was dichotomized by the median while styrene exposure outside the window was classified as zero (19). We also analyzed the risk patterns for encephalopathy and unspecified dementia combined as well as the correlations between cumulative styrene exposure and age.

As a supplement, we investigated the incidence of Alzheimer disease and Parkinson disease following a diagnosis of encephalopathy or unspecified dementia.

In tests for linear trend we included cumulative styrene exposure as a categorized variable with 3 levels. Tests of significance were 2-sided. All statistical analyses were performed using Stata, version 13 (StataCorp LP, College Station, Texas).

RESULTS

The study population accumulated 1,496,594 person-years during follow-up, and we identified 228 incident cases

of encephalopathy and 565 incident cases of unspecified dementia.

For encephalopathy, we observed increasing rate ratios with increasing cumulative styrene exposure (P for trend < 0.01) in the model adjusting only for age (Table 1). The fully adjusting model also showed a positive trend ($P < 0.01$) and a rate ratio of 1.90 for the highest compared with the lowest exposure tertile (95% confidence interval (CI): 1.31, 2.77). Duration of employment showed rate ratios of encephalopathy that were comparable to the estimates for cumulative exposure while lower positive estimates were seen for styrene exposure probability and intensity. No association was observed for unspecified dementia in either model. When we pooled cases of encephalopathy and unspecified dementia, we observed an increasing trend by cumulative styrene exposure accrued during the total work history ($P = 0.11$) with a rate ratio of 1.17 for the highest compared with the lowest exposure tertile (95% CI: 0.96, 1.42).

In time-window analyses, we observed an increasing trend for encephalopathy with cumulative styrene exposure accrued during the prior 1–14 years ($P < 0.01$, Table 2). The rate ratio was 1.67 in the highest relative to the null exposure category (95% CI: 1.17, 2.37). The trend was less pronounced for the 15–29-years exposure window, and no trend was observed for the ≥30-years window (for the highest vs. the null exposure category, rate ratio = 0.80; 95% CI: 0.45, 1.44). For unspecified dementia, a decreasing trend was observed for the 1–14-years window (for the highest vs. the null exposure category, rate ratio = 0.65; 95% CI: 0.45, 0.94). On the other hand, an increasing trend ($P = 0.13$) was seen for the ≥30-years exposure window (for the highest vs. the null exposure category, rate ratio = 1.19; 95% CI: 0.95, 1.48). For combined encephalopathy and unspecified dementia, time window analyses showed no clear trends for the 1–14- and 15–29-years exposure windows, but for the ≥30-years window an increasing trend was suggested ($P = 0.07$) with a rate ratio of 1.21 for the highest versus the null exposure category (95% CI: 0.98, 1.49).

The correlation coefficients between age and cumulative styrene exposure, examined for different combinations of both continuous and categorical variables for age and exposure, varied between 0.13 and 0.16 and were similar across occupations and educational levels.

A total of 91 participants (16%) initially diagnosed with unspecified dementia were later diagnosed with Alzheimer disease and 21 (4%) with Parkinson disease. Only <5 participants (<2%) initially diagnosed with encephalopathy were later diagnosed with Alzheimer disease, and the same was the case for Parkinson disease.

DISCUSSION

We observed increasing risks of encephalopathy and combined encephalopathy and unspecified dementia with cumulative styrene exposure accrued during the complete work history. In analyses considering the timing of exposure, we observed increasing risk of encephalopathy and decreasing risk of unspecified dementia with cumulative exposure accrued during recent years. Risk of unspecified dementia and of combined encephalopathy and unspecified dementia increased with cumulative exposure accrued 30 years or more prior.

Increasing risk of central nervous system diseases with increasing styrene exposure has been reported in a cohort of styrene exposed workers of the European reinforced plastics industry that partly overlapped with the current study population (20). A recent study of styrene-exposed workers in the US reinforced plastics industry reported no excess mortality in the category of "nervous system disorders other than multiple sclerosis" (21). Encephalopathy or dementia diseases were, however, not evaluated specifically in either study.

Our observation of an increased risk of encephalopathy is in accord with a number of cross-sectional studies showing associations between industrial solvent exposure, impairment in neuropsychological functioning (22–24), and disability pension due to neuropsychiatric diseases (25, 26). Inconsistencies among the findings have, however, been noted (27). This might be due partly to differences in diagnostic criteria, given that only few studies have followed the 2 sets of diagnostic criteria defined in the 1980s (the World Health Organization and Raleigh classifications) (28). A recent Dutch study of nonvascular dementia observed a positive exposure-response relationship with cumulative exposure to chlorinated solvents in men but observed no association in women (29).

We defined encephalopathy using ICD-8 diagnoses specified by the Danish Association of Occupational and Environmental Medicine to be used for cases of solvent-induced encephalopathy. The Danish version of the ICD-10 code G934, valid since 1994, is labeled "painter's syndrome." Except for this, the other encephalopathy diagnoses are expected to include some cases not attributed to industrial solvent exposure by the diagnosing physician. However, the very high rates of workers who received compensation in the early 1980s (5) suggest solvent-induced encephalopathy is predominant in our encephalopathy case category.

We identified case information from Danish health registers with high coverage. The public health-care system in Denmark is universal, with no user payment, but only patients seen in hospitals are registered. A concomitant history of recent industrial solvent exposure and dementia symptoms might increase the likelihood of referral (e.g., to a hospital department of occupational medicine).

Symptoms and psychometric findings of encephalopathy and early stages of unspecified dementia are interchangeable. However, the higher incidence of a later diagnosis of Alzheimer or Parkinson disease in participants diagnosed with unspecified dementia compared with those diagnosed with encephalopathy suggests that this interchangeability is not complete in our study population. Nevertheless, patients recently exposed to solvents might be more likely to be diagnosed with encephalopathy rather than unspecified dementia with no suspected cause, resulting in spurious associations with styrene exposure. This is an inherent problem of diagnoses that require a postulated cause and ultimately precludes a meaningful investigation of the association between the disease and its postulated cause. We interpret the increased risk of encephalopathy and the decreased risk of

Table 1. Rate Ratios of Encephalopathy, Unspecified Dementia, and Combined Encephalopathy and Unspecified Dementia Following Styrene Exposure Among 72,465 Workers in the Danish Reinforced Plastics Industry, 1977–2011

Styrene Exposure Metric	Person-Years	Encephalophathy					Unspecified Dementia					Combined Encephalopathy and Unspecified Dementia				
		Cases	RR[a]	95% CI	RR[b]	95% CI	Cases	RR[a]	95% CI	RR[b]	95% CI	Cases	RR[a]	95% CI	RR[b]	95% CI
Cumulative exposure, mg/m^3-years																
<18	498,700	40	1.00		1.00		124	1.00		1.00		164	1.00		1.00	
18–71	498,987	70	1.56	1.06, 2.31	1.26	0.85, 1.86	187	0.97	0.77, 1.22	1.03	0.81, 1.29	257	1.11	0.91, 1.36	1.09	0.90, 1.34
>71	498,907	118	2.55	1.77, 3.66	1.90	1.31, 2.77	254	0.86	0.69, 1.07	0.98	0.78, 1.23	372	1.17	0.97, 1.41	1.17	0.96, 1.42
P for linear trend			<0.01		<0.01			0.13		0.78			0.12		0.11	
Mean exposure probability																
<0.23	497,945	66	1.00		1.00		224	1.00		1.00		290	1.00		1.00	
0.23–0.58	497,489	70	1.14	0.81, 1.60	0.88	0.63, 1.25	205	1.05	0.87, 1.27	0.98	0.80, 1.19	275	1.07	0.91, 1.26	0.94	0.79, 1.12
>0.58	501,160	92	1.67	1.21, 2.30	1.41	1.01, 1.96	136	0.99	0.80, 1.22	0.89	0.71, 1.11	228	1.19	1.00, 1.41	1.03	0.86, 1.23
P for linear trend			<0.01		0.03			0.98		0.32			0.06		0.81	
Mean exposure intensity, mg/m^3																
<12	498,858	50	1.00		1.00		108	1.00		1.00		158	1.00		1.00	
12–40	497,914	73	1.25	0.87, 1.80	0.88	0.60, 1.27	217	1.08	0.85, 1.36	1.11	0.87, 1.41	290	1.13	0.93, 1.38	1.05	0.86, 1.29
>40	499,822	105	1.83	1.31, 2.58	1.18	0.82, 1.68	240	0.98	0.77, 1.23	1.05	0.82, 1.34	345	1.17	0.96, 1.42	1.08	0.88, 1.33
P for linear trend			<0.01		0.21			0.64		0.90			0.13		0.47	
Duration of employment, years																
1	686,337	90	1.00		1.00		248	1.00		1.00		338	1.00		1.00	
2–4	552,064	66	0.89	0.65, 1.22	0.98	0.71, 1.35	193	0.89	0.74, 1.08	0.96	0.79, 1.16	259	0.89	0.76, 1.05	0.95	0.81, 1.12
≥5	258,193	72	1.80	1.32, 2.46	2.19	1.58, 3.02	124	0.73	0.59, 0.91	0.83	0.66, 1.03	196	0.94	0.79, 1.13	1.06	0.88, 1.27
P for linear trend			<0.01		<0.01			<0.01		0.10			0.40		0.68	

Abbreviations: CI, confidence interval; RR, rate ratio.

[a] Adjusted for age.

[b] Adjusted for age, calendar year, sex, level of education, hospitalizations related to chronic obstructive pulmonary disease, alcohol-related hospitalizations, and employment status.

Table 2. Rate Ratios of Encephalopathy, Unspecified Dementia, and Combined Encephalopathy and Unspecified Dementia According to Cumulative Styrene Exposure Accrued During Different Exposure Time Periods Among 72,465 Workers of the Danish Reinforced Plastics Industry, 1977–2011

Exposure Period and Cumulative Styrene Exposure	Person-Years	Encephalopathy			Unspecified Dementia			Combined Encephalopathy and Unspecified Dementia		
		Cases	RR[a]	95% CI	Cases	RR[a]	95% CI	Cases	RR[a]	95% CI
<15 years prior, mg/m^3-years										
0	635,123	93	1.00		466	1.00		559	1.00	
<26	430,989	46	1.36	0.94, 1.98	56	0.89	0.66, 1.21	102	1.07	0.85, 1.34
≥26	430,482	89	1.67	1.17, 2.37	43	0.65	0.45, 0.94	132	1.09	0.86, 1.39
P for linear trend			<0.01			0.03			0.43	
15–29 years prior, mg/m^3-years										
0	872,793	117	1.00		273	1.00		390	1.00	
<46	311,893	31	0.61	0.41, 0.93	125	1.01	0.81, 1.25	156	0.81	0.67, 0.98
≥46	311,908	80	1.42	1.04, 1.93	167	0.82	0.67, 1.01	247	0.87	0.73, 1.03
P for linear trend			0.05			0.07			0.08	
≥30 years prior, mg/m^3-years										
0	1,305,496	201	1.00		296	1.00		497	1.00	
<45	95,303	13	0.75	0.41, 1.37	106	1.08	0.85, 1.38	119	1.10	0.88, 1.38
≥45	95,795	14	0.80	0.45, 1.44	163	1.19	0.95, 1.48	177	1.21	0.98, 1.49
P for linear trend			0.35			0.13			0.07	

Abbreviations: CI, confidence interval; RR, rate ratio.

[a] Adjusted for age, calendar year, sex, level of education, hospitalizations related to chronic obstructive pulmonary disease, alcohol-related hospitalizations, and employment status.

unspecified dementia seen following recent styrene exposure as the partial result of such misclassification. Diagnostic misclassification and referral bias are, on the other hand, less likely interpretations of the increasing risk seen for combined encephalopathy and unspecified dementia following styrene exposure accrued more than 30 years prior.

Our study population included prevalent hires starting employment in the reinforced plastics industry in 1965–1976, and results might have been biased toward the null because of left truncation bias (30). We also defined an inception population, but this reduced the number of cases of encephalopathy and unspecified dementia to 29 and 27, respectively, which were too few for meaningful analyses.

Our principal exposure metric was cumulative styrene exposure, which was a combination of styrene exposure intensity, probability, and duration. Each component was estimated with considerable uncertainty, which can cause truly increased risks to be overlooked and exposure-response relationships to be attenuated. On the other hand, grouping of exposure should mainly lead to Berkson-type error, causing little or no bias to risk estimates (31).

The risk of dementia diseases increases with age (32), but we found no strong association between age and cumulative styrene exposure. Furthermore, we adjusted all analyses for age. We included level of education in the adjusted analyses, because an inverse association between level of education and dementia diseases has been suggested (33, 34). Smoking has also been associated with risk of dementia, while the evidence for alcohol consumption is conflicting (35). We adjusted for hospitalizations for chronic obstructive pulmonary disease and alcohol-related diseases as proxies of smoking and alcohol consumption, but this should capture only severe abuse. We have, however, earlier shown declining smoking prevalence by increasing duration of employment (and thus by increasing cumulative styrene exposure) in this population, which does not indicate that our results are inflated by smoking (36). We were not able to account for possible genetic or lifestyle factors, electromagnetic fields, or other occupational factors that have been suggested as being implicated in the causation of dementia diseases (32).

In conclusion, we observed increasing risk of encephalopathy, decreasing risk of unspecified dementia and no risk of the 2 diseases combined with increasing cumulative styrene exposure during recent years. This risk pattern probably reflects diagnostic criteria requiring recent industrial solvent exposure and referral bias and not causal association. The increasing risk observed for combined encephalopathy and unspecified dementia following styrene exposure $\geq$30 years prior is less likely to be influenced by such biases and indicates a real association with a long latency period.

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