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Mortality of Workers Employed in Shoe Manufacturing: An Update

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Background *In the late 1970s, the National Institute for Occupational Safety and Health identified two shoe manufacturing facilities where workers experienced relatively "pure" exposures to toluene. A mortality study was conducted through December 31, 1982. An original study did not detect elevated leukemia mortality but did detect increased lung cancer mortality. The present study is an update of the mortality of the original cohort.*
Methods *The study cohort consisted of workers employed 1 month or more between 1940 and 1979 at two Ohio shoe manufacturing plants. Vital status was ascertained through December 31, 1999.*
Results *Seven thousand eight hundred twenty eight workers, contributing 300,777 person years, were available for analysis. An excess of lung cancer deaths persisted with additional years of follow-up (SMR = 1.36, 95% confidence interval (CI) = 1.19–1.54). Trend tests did not indicate a positive trend between lung cancer risk and duration of employment. Mortality from leukemia was not significantly elevated in the updated analysis.*
Conclusions *Results indicate a possible association between lung cancer mortality and exposure to chronic, low-levels of organic solvents. Although the strength of this conclusion was weakened by the lack of increasing lung cancer risk in relation to duration of employment, other studies have supported this association.* Am. J. Ind. Med. 49: 535–546, 2006. *Published 2006 Wiley-Liss, Inc.*†

KEY WORDS: toluene; solvents; lung cancer; leukemia; shoe manufacturing; xylene; methyl ethyl ketone; dementia

INTRODUCTION

This study updates the mortality experience of a cohort of shoe manufacturing workers employed at two plants located in Southwest Ohio [Walker et al., 1993]. The intent of the original study was to examine the hypothesis that toluene, a chemical structurally similar to benzene (a known leukemogen), increases leukemia mortality in exposed workers. These two plants were selected based on a search conducted by the National Institute for Occupational Safety and Health (NIOSH) in the late 1970s to identify facilities where workers experienced relatively ''pure'' exposures to toluene. As both plants operated at the same locations since the 1930s, maintained adequate employment records, and conducted similar shoemaking processes, the workers were combined into one cohort and statistical analyses were conducted on the aggregate number. Stratified analysis based on departments and operations was not conducted since the open plant layout did not provide adequate differentiation of exposures among workers in the different work areas. Vital status follow-up for the study cohort was conducted through December 31, 1982. Statistical analysis found no excess leukemia deaths but did find a statistically significant excess

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of death due to lung cancer. Further analysis found a statistically significant trend in standardized relative risk for lung cancer with increasing latency. The purpose of this update is to extend vital status follow-up through 1999 and to investigate potential associations between exposure to organic solvents and cause-specific mortality.

MATERIALS AND METHODS

Cohort Description

The original cohort included 7,814 white men and women who had worked at one of the study plants for 1 month or more during the period January 1, 1940–December 31, 1979. Workers having invalid or missing dates of birth were omitted from the analysis. For this update, the same cohort definition was used, with the addition of five black employees (four male and one female). Newly available tracing methods allowed us to locate additional demographic information for nine workers who were previously excluded from analysis due to inadequacy of key variables. Therefore, a total of 7,828 workers were available for this update.

Exposure Data

Historical exposure information for the plants is minimal, with no records existing prior to October, 1973. Nine sets of NIOSH, Occupational Safety and Health Administration (OSHA), and company industrial hygiene surveys were conducted at the study plants between 1973 and 1979. Even though toluene was the exposure of a priori interest, the surveys detected a variety of organic solvents, including toluene, hexane, acetone, and methyl ethyl ketone (MEK) in production department air samples. Survey findings are summarized in Table I. Benzene was not detected in these surveys and company management asserted that benzene had never been present in the solvents used at either of the plants. The highest toluene reading recorded was 119 parts per million (ppm) 8-hr time weighted average while three MEK samples obtained by OSHA in 1977 and 1978 exceeded 200 ppm. It is likely that worker exposures to solvents in these plants were much higher in the 1940s and 1950s when the majority of this cohort was employed. For example, in studies of workers employed in comparable industries, McConnell et al. [1942], Greenburg et al. [1942], and Wilson [1943] documented toluene exposures to workers at levels as high as 1,500 ppm. Engineering controls were installed in the plants in 1978 and 1979 and were apparently effective in reducing exposure levels based on measurements collected in October, 1978 and November, 1979 (Table I). These surveys also noted that exposure to leather dust,

TABLE I. Industrial Hygiene Surveys of Two Shoe Manufacturing Plants, Ohio, 1973–1979

Plant	Date	Source	Toluene (ppm)	Hexane (ppm)	Acetone (ppm)	MEK[a] (ppm)	Total hydrocarbon (ppm)
1	October 25, 1973	OSHA	61	28	—	>5	—
1	May 01, 1974	OSHA	67.7[b] (38–119)[c] n = 3	—	—	—	—
1	January 27, 1977	OSHA	50.5 (38–72) n = 4	55 (30–80) n = 2	223.5 (200–270) n = 4	132.8 (63–250*) n = 4	—
1	March 31, 1977	Company	(15–20) n = 2	(5–6) n = 2	(61–71) n = 2	(70–85) n = 2	—
1	May 02, 1979	NIOSH	(ND–20) n = 9	3.7 (2.6–4.5) n = 3	—	—	63.8 (20–120) n = 12
2	February 15, 1978	OSHA	22.0 (10–43) n = 6	18.2 (<25–45) n = 6	46.0 (<50–146) n = 6	152.7 (48–330*) n = 6	—
2	April 24, 1978	Company	13.5 (4–37) n = 6	5.0 (1–20) n = 6	23.8 (1–115) n = 6	46.1 (10–121) n = 6	—
2	October 01, 1978	OSHA	(28–34) n = 2		(50–129) n = 2	(29–79) n = 2	—
2	November 16, 1979	NIOSH	15.0 (ND–30) n = 10	16.7 (7–36) n = 3	36.3 (12–60) n = 3	45.5 (13–85) n = 4	—

[a]MEK, methyl ethyl ketone.
[b]Mean ± standard deviation.
[c]Range.

an exposure of concern in other studies of the shoe manufacturing industry, was virtually non-existent.

In our analysis, duration of employment was used as a proxy for cumulative exposure to organic solvents due to the scarcity of exposure and process data from the plants with no exposure, process, or production information available before 1973.

Follow-Up

Vital status updating was conducted through December 31, 1999. For deaths occurring on or before December 31, 1982, causes of death listed on death certificates were coded by a nosologist utilizing the International Classification of Diseases (ICD) revision in effect at the time of the worker's death. For deaths occurring after 1982, causes of death provided by the National Death Index (NDI) were used. Deaths occurring in 1999 were re-coded to the ninth revision of the ICD since mortality rate files were not yet available for the ICD tenth revision. Cohort members were considered to be alive as of the study end date (or date of NDI follow-up) as long as the individual was confirmed alive on January 1, 1979, had a valid (within assigned range) Social Security number and was not shown to be deceased on the NDI. Those lost to follow-up before January 1, 1979, with invalid Social Security numbers, and thus not able to be matched with the NDI, were considered ''lost to follow-up.'' As noted by Vena et al. [1987], this practice yields conservative standardized mortality ratio (SMR) results.

Analysis

The mortality experience of the cohort was analyzed using the personal computer version of the NIOSH modified life table analysis system (LTAS) [Waxweiler et al., 1983; Steenland et al., 1998]. Each cohort member accumulated person-years-at-risk (PYAR) for each year of life after January 1, 1940 or completion of the 1-month eligibility period (whichever was later) until the date of death for deceased cohort members, the date last observed for persons lost to follow-up, or the ending date of the study (December 31, 1999) for cohort members assumed to be alive. A total of 300,777 PYAR were accumulated by this cohort. PYAR were stratified into 5-year intervals by age and calendar time and then multiplied by the appropriate US gender, race, and cause-specific mortality rates to calculate the expected number of deaths for that stratum. The resulting expected numbers were summed across strata to obtain cause-specific and total expected number of deaths. The ratio of observed to expected number of deaths was expressed as the SMR. Ninety-five percent confidence intervals were computed for the SMRs assuming a Poisson distribution for observed deaths [Rothman and Boice, 1979].

NIOSH has created standard mortality rate files (available beginning in 1940) for 92 cause-of-death categories that are used for LTAS analysis. Custom rate files that combine standard categories or further break-out single categories are created and used when appropriate to a particular study. For this study, we created a custom rate file to more closely examine the standard ''mental disorders'' death category. The reasons for creating this custom rate file are discussed later in this study.

The collection of work history records was conducted during January, 1980 at Plant 1 and April, 1980 at Plant 2. Duration of employment was calculated for each worker from date first employed through the respective record collection date, including any years worked before 1940. We stratified SMRs by gender, plant, duration of employment, time since first employment, and year of first employment. For tests of overall trend with respect to duration of employment, four categories (1–<6 months, 6 months–<2 years, 2–<10 years, and $\geq$10 years) were created, with approximately equal numbers of deaths within each category. The methods of Breslow and Day [1987] were used to test for trend in the SMRs. For selected mortality outcomes, internal comparisons were conducted using Poisson regression modeling. Rate ratios (RRs), adjusted for gender, age, calendar year, and time since first employment, were calculated for each duration of employment category relative to the lowest category.

Information on the smoking habits of the cohort was not available; however, the use of state and county referent rates can indirectly account for geographical differences in smoking prevalence, as well as other factors that influence cancer death rates. In analyses using state of Ohio or appropriate county referent rates, PYAR started to accumulate on January 1, 1960 (when the rates were first available), or completion of the 1-month eligibility period, whichever was later. Results derived from state and/or county rates are not shown in the tables since they rarely deviated significantly from results based on US rates. State and county results are referenced in the text where relevant. An indirect adjustment procedure was also used to estimate the RR for lung cancer that might be expected based on differences in smoking prevalence between the study cohort and the US population [Steenland et al., 1984; Axelson and Steenland, 1988]. As no quantitative smoking data are available for the study cohort, data on smoking prevalence in 1979 and 1980 [Weinkam and Sterling, 1987] for blue collar workers in the US was compared to data from the US population in 1980 [CDC, 1994]. Estimates of smoking prevalence for blue collar workers in the US in 1979–1980 were 0.291, 0.255, and 0.454 for males and 0.505, 0.134, and 0.361 for females for non-smokers, former smokers, and current smokers, respectively. Estimates of smoking prevalence in the US population in 1980 were 0.344, 0.281, and 0.376 for males and 0.555, 0.151,

and 0.293 for females for non-smokers, former smokers, and current smokers, respectively. Lung cancer relative risks were estimated to be 6.2 for former smokers relative to non-smokers and 10 for current smokers relative to non-smokers [Hammond, 1966]. These estimates were used to compute RRs for lung cancer separately for male and female workers.

Duration of employment was truncated for 624 workers who were actively employed when the records were obtained. A sensitivity analysis was performed by replicating the analysis under different assumptions regarding duration of employment for these workers. Active workers were assumed to have continued working at the plant until age 65, the date last observed, or the date the plant closed, whichever came first. Under this scenario, the exposure duration category remained unchanged for 7,533 (96.2%) of the 7,828 workers in the analysis. Of the 624 cohort members who were actively employed when records were obtained, 327 (52.4%) had already been employed 10 or more years. Results stratified by duration of exposure under the alternate scenario were essentially unchanged, suggesting that the impact of not updating the work histories is minimal.

Mortality differences between long- and short-term workers have been observed in many occupational studies. Often, mortality is highest among short-term workers [Steenland and Stayner, 1991; Kolstad and Olsen, 1999]. Consequently, additional analyses excluded workers with less than 1 year of employment.

RESULTS

As of December 31, 1999, 4,416 (56%) of the workers were alive, 3,135 (40%) were deceased, and 277 (4%) were lost to follow-up (Table II). The results of the mortality analysis for male workers, female workers, and all workers combined for selected causes of death are shown in Table III. Mortality is presented stratified by plant and year of hire (before 1950 vs. 1950 or later) in Table IV, and stratified according to duration of employment in Table V for causes of death that were either significantly elevated in the full cohort or of a priori interest based on the earlier study (leukemia and lung cancer).

TABLE II. Cohort Characteristics and Results of Follow-Up in a Retrospective Cohort Study of Shoe Manufacturing Workers, 1940–1999

Total number of workers	**7,828**
Plant	
Plant 1 only	3,197 (41)[a]
Plant 2 only	4,616 (59)
Both Plants 1 and 2	15 (<1)
Gender—race	
Male—white	2,541 (32)
Male—non-white	4 (<1)
Female—white	5,282 (67)
Female—non-white	1 (<1)
Age at first employment (years)	
Median, range	21, 11–83
Year of first employment	
Before 1950	4,676 (60)
1950 or later	3,152 (40)
Duration of employment	
<6 months	2,432 (31)
6 months–<2 years	2,037 (26)
2 years–<10 years	2,036 (26)
10 years or more	1,323 (17)
Time since first employment	
<20 years	674 (9)
20 years–<40 years	3,241 (41)
40 years or more	3,913 (50)
Vital status (as of December 31, 1999)	
Alive	4,416 (56)
Dead, cause of death known	3,030 (39)
Dead, cause of death unknown	105 (1)
Lost to follow-up	277 (4)
Age at death (years)	
Median, range	69, 17–104
Person-years-at-risk	300,777

[a]Number in parentheses is percent of total.

All Cause Mortality

Mortality from all causes (SMR = 1.04, 95% confidence interval (CI) = 1.01–1.08) was statistically elevated based on US referent rates (Table III). The use of state of Ohio referent rates (SMR = 1.00, 95% CI = 0.96–1.03) and county referent rates (SMR = 0.98, 95% CI = 0.95–1.02) produced similar results but were not statistically significant. Excess deaths from lung cancer and ischemic heart disease (IHD) were the main contributors to the overall mortality elevation.

All Malignant Neoplasms

Mortality from all malignant neoplasms was elevated (796 deaths, SMR = 1.05, 95% CI = 0.98–1.12), but varied inversely with duration of employment (Table V).

Leukemia and Aleukemia

Mortality from leukemia and aleukemia was not elevated (27 deaths, SMR = 1.01, 95% CI = 0.67–1.48). In general, female workers experienced increased mortality

TABLE III. Observed Numbers of Deaths and Standardized Mortality Ratios for Various Causes of Death Among Shoe Manufacturing Workers, Using US Referent Rates (1940–1999)[a]

	Male workers			Female workers			All workers combined		
Underlying cause of death (ICD-9)[b]	**O**	**SMR**	**95% CI**	**O**	**SMR**	**95% CI**	**O**	**SMR**	**95% CI**
All causes	1,367	1.08**	1.02–1.14	1,768	1.02	0.97–1.07	3,135	1.04*	1.01–1.08
All cancers (140–208)	314	1.09	0.98–1.22	482	1.02	0.93–1.12	796	1.05	0.98–1.12
Cancer of buccal cavity and pharynx (140–149)	8	1.11	0.48–2.18	1	0.17*	0.00–0.97	9	0.69	0.32–1.32
Cancer of digestive organs and peritoneum (150–159)	78	1.03	0.82–1.29	113	1.02	0.84–1.23	191	1.02	0.88–1.18
Stomach (151)	4	0.33*	0.09–0.84	6	0.50	0.18–1.09	10	0.41**	0.20–0.76
Biliary passages, liver, and gall bladder (155.0, 155.1, 156)	4	0.79	0.21–2.01	8	0.88	0.38–1.73	12	0.84	0.44–1.48
Liver, not specified (155.2)	3	1.40	0.29–4.08	3	1.01	0.21–2.96	6	1.17	0.43–2.55
Cancer of the respiratory system (160–165)	141	1.40**	1.18–1.66	115	1.28*	1.06–1.54	256	1.35**	1.19–1.52
Trachea, bronchus, and lung (162)	138	1.44**	1.21–1.70	110	1.26*	1.04–1.52	248	1.36**	1.19–1.54
Breast cancer (174–175)	1	2.69	0.07–14.9	76	0.81	0.64–1.02	77	0.82	0.65–1.02
Cancer of female genital organs (179–184)				69	1.11	0.86–1.41	69	1.11	0.86–1.41
Cancer of male genital organs (185–187)	25	0.94	0.61–1.39				25	0.94	0.61–1.39
Cancer of urinary organs (188–189)	15	0.98	0.55–1.61	14	1.03	0.56–1.73	29	1.00	0.67–1.44
Kidney (189.0–189.2)	6	0.86	0.31–1.86	8	1.05	0.45–2.07	14	0.96	0.52–1.61
Bladder and other organs (188, 189.3–189.9)	9	1.08	0.49–2.06	6	1.01	0.37–2.20	15	1.05	0.59–1.74
Cancer of other and unspecified sites (170–173, 190–199)	26	0.75	0.49–1.10	48	0.87	0.64–1.15	74	0.82	0.65–1.03
Neoplasms of lymphatic and hematopoietic tissue (200–208)	20	0.74	0.45–1.15	46	1.10	0.81–1.47	66	0.96	0.74–1.22
Leukemia and aleukemia (204–208)	8	0.72	0.31–1.42	19	1.22	0.74–1.91	27	1.01	0.67–1.48
Benign and unspecified neoplasms (210–239)	3	0.80	0.17–2.34	10	1.23	0.59–2.27	13	1.10	0.58–1.88
Tuberculosis (010–018)	12	1.44	0.74–2.52	1	0.13**	0.00–0.74	13	0.82	0.44–1.40
Diabetes mellitus (250)	19	0.90	0.54–1.41	61	1.35*	1.03–1.73	80	1.21	0.96–1.50
Diseases of the blood and blood-forming organs (280–289)	1	0.26	0.01–1.44	10	1.43	0.69–2.63	11	1.02	0.51–1.82
Alcoholism (303)	2	0.50	0.06–1.79	1	0.44	0.01–2.44	3	0.48	0.10–1.39
Mental disorders (excluding alcoholism) (290–302, 304–319)	8	1.40	0.60–2.75	23	1.50	0.95–2.25	31	1.47	1.00–2.09
Nervous system and sense organ diseases (320–389)	14	0.86	0.47–1.44	22	0.71	0.44–1.08	36	0.76	0.53–1.05
Diseases of the heart (390–398, 402, 404, 410–414, 420–429)	535	1.09*	1.00–1.19	572	1.02	0.94–1.10	1,107	1.05	0.99–1.12
Ischemic heart disease (410–414)	434	1.11*	1.01–1.22	423	1.05	0.96–1.16	857	1.08*	1.01–1.16
Other diseases of the circulatory system (401, 403, 405, 415–417, 430–459)	108	0.92	0.76–1.12	188	0.92	0.79–1.06	296	0.92	0.82–1.03
Respiratory system diseases (460–519)	114	1.20	0.99–1.44	110	0.86	0.71–1.04	224	1.00	0.88–1.14
Chronic and unspecified bronchitis (490, 491)	9	3.00**	1.37–5.70	3	0.95	0.20–2.79	12	1.95*	1.01–3.41
Digestive system diseases (520–579)	52	0.96	0.71–1.25	79	1.07	0.85–1.33	131	1.02	0.85–1.21
Genitourinary diseases (580–629)	20	1.04	0.63–1.60	24	0.76	0.49–1.13	44	0.87	0.63–1.16
Diseases of the skin and subcutaneous tissue (680–709)	0	0.00	0.00–3.59	4	1.47	0.40–3.75	4	1.07	0.29–2.73
Diseases of the musculoskeletal system and connective tissue (710–739)	3	1.27	0.26–3.73	6	0.70	0.26–1.53	9	0.83	0.38–1.57
Symptoms and ill-defined conditions (780–796, 798, 799)	4	0.34*	0.09–0.86	6	0.42*	0.15–0.92	10	0.38**	0.18–0.71
Accidents (E800–E949)	77	1.07	0.85–1.34	50	0.94	0.70–1.24	127	1.02	0.85–1.21
Transportation accidents (E800–E848, E929.0–E929.1)	54	1.39*	1.04–1.81	20	0.78	0.47–1.20	74	1.14	0.90–1.44
Suicide (E950–E959)	24	1.00	0.64–1.49	9	0.52*	0.24–0.99	33	0.80	0.55–1.12
Homicide (E960–E978)	1	0.15*	0.00–0.81	3	0.60	0.12–1.74	4	0.34*	0.09–0.86
Residual causes	18	0.79	0.47–1.25	40	0.93	0.66–1.27	58	0.88	0.67–1.14
Unknown causes	38			67			105		

[a]Person-years-at-risk and observed deaths began accruing in 1940.
[b]ICD-9, International Classification of Diseases, ninth revision; O, observed number of deaths; SMR, standardized mortality ratio; CI, confidence interval.
*Two-sided *P*-value less than 0.05.
**Two-sided *P*-value less than 0.01.

TABLE IV. Standardized Mortality Ratios for Selected Causes of Death Among Shoe Manufacturing Workers, Using US Referent Rates, by Plant and Period of First Employment (1940–1999)[a]

	Plant 1 only						Plant 2 only					
	Before 1950			1950 or later			Before 1950			1950 or later		
Underlying cause of death	O[b]	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI
All causes	847	0.98	0.92–1.05	201	1.01	0.87–1.15	1839	1.08**	1.03–1.13	237	1.06	0.93–1.20
All cancers	234	1.09	0.95–1.24	63	1.03	0.79–1.32	431	1.04	0.94–1.14	68	1.02	0.79–1.29
Trachea, bronchus, and lung cancer	63	1.25	0.96–1.60	18	1.19	0.70–1.88	150	1.50**	1.27–1.76	17	1.02	0.60–1.64
Leukemia and aleukemia	7	0.94	0.38–1.94	2	0.91	0.11–3.29	17	1.17	0.68–1.87	1	0.42	0.01–2.36
Ischemic heart disease	234	1.01	0.89–1.15	47	1.25	0.91–1.66	517	1.09	1.00–1.19	57	1.26	0.95–1.63
Chronic and unspecified bronchitis	1	0.57	0.01–3.19	0			6	1.64	0.60–3.57	4	10.38**	2.83–26.6
Mental disorders (excluding alcoholism)	15	2.32**	1.30–3.83	1	0.82	0.02–4.57	10	0.84	0.40–1.54	4	2.75	0.75–7.04

[a]Person-years-at-risk and observed deaths began accruing in 1940.
[b]O, observed number of deaths; SMR, standardized mortality ratio; CI, confidence interval.
**Two-sided *P*-value less than 0.01.

(SMR = 1.22, 95% CI = 0.74–1.91), while male workers experienced reduced mortality (SMR = 0.72, 95% CI = 0.31–1.42). Leukemia mortality did not vary with duration of employment in the stratified SMR analysis nor in the Poisson regression analysis (Table V).

Malignant Neoplasms of the Trachea, Bronchus, and Lung

Mortality from malignant neoplasms of the trachea, bronchus, and lung was significantly elevated based on US referent rates for all workers combined (248 deaths, SMR = 1.36, 95% CI = 1.19–1.54), for male workers (SMR = 1.44, 95% CI = 1.21–1.70), and for Plant 2 workers (SMR = 1.43, 95% CI = 1.22–1.66). These mortality ratios decreased slightly when state and county referent rates were used, but remained significantly elevated. Lung cancer mortality was also significantly elevated for female workers based on US referent rates (SMR = 1.26, 95% CI = 1.04–1.52) and state of Ohio referent rates (SMR = 1.25, 95% CI = 1.03–1.59), but not based on county referent rates (SMR = 1.12, 95% CI = 0.92–1.36). When workers were stratified by plant and gender (not shown), mortality from lung cancer remained elevated for all four groups of workers. Men employed at Plant 2 before 1950 had the highest mortality (96 deaths, SMR = 1.66, 95% CI = 1.34–2.02).

Lung cancer mortality was highest among workers employed for less than 2 years (SMR = 1.55, 95% CI = 1.31–1.82). Results did not change when duration was lagged by 10 or 20 years, or when a 20-year minimum latency was specified (not shown). Internal analyses conducted using Poisson regression provided estimates of the RR for each duration of employment category relative to the lowest category after adjusting for gender, age, calendar year, and latency. A test for interaction between gender and duration of employment was used to determine if the relationship between lung cancer mortality and duration of employment was affected by gender. Evidence of interaction was observed between gender and duration of employment in Poisson regression modeling for lung cancer (interaction *P*-value = 0.048). Lung cancer for females decreased with duration of employment (trend test *P*-value = 0.029); RR estimates (95% confidence intervals) for female workers were 1, 1.13 (0.72–1.79), 0.50 (0.29–0.89), and 0.58 (0.33–1.03), for the four duration of employment categories, respectively. For male workers, mortality from lung cancer did not vary with duration of employment (trend test *P*-value = 0.65); RR estimates for male workers were 1, 1.01 (0.64–1.60), 1.02 (0.64–1.63), and 0.91 (0.56–1.50) for the four duration of employment categories, respectively. Results were essentially unchanged when workers with less than 1 year of employment were excluded (not shown).

In order to evaluate the potential confounding effect of smoking habits on lung cancer mortality, adjusted SMRs were calculated separately for male and female workers. The smoking adjustment factor was 1.097 for males and 1.119 for females, which means that differences in smoking habits between the cohort and referent population alone could account for an SMR of 1.10 for males and 1.12 for females. Using these factors to adjust the number of expected lung cancers resulted in adjusted SMRs of 1.31 for males and 1.13 for females.

Chronic and Unspecified Bronchitis

Mortality from chronic and unspecified bronchitis was elevated for the entire cohort (12 deaths, SMR = 1.95, 95% CI = 1.01–3.41) but did not increase with duration of

TABLE V. Mortality by Duration of Employment for Selected Causes of Death Among Shoe Manufacturing Workers (1940–1999)

	Duration of employment				
Underlying cause of death	1 month–<6 months	6 months–<2 years	2 years–<10 years	≥10 years	Trend *P*-value
All causes, O[a]	831	747	838	719	
SMR (95% CI)	1.04 (0.97–1.11)	1.02 (0.95–1.09)	1.09*(1.02–1.17)	1.02 (0.95–1.10)	0.70
All cancers, O	233	202	202	159	
SMR (95% CI)	1.14 (1.00–1.29)	1.08 (0.94–1.24)	1.03 (0.90–1.19)	0.92 (0.78–1.08)	0.046
Trachea, bronchus, and lung cancer, O	75	74	52	47	
SMR (95% CI)	1.50** (1.18–1.87)	1.61** (1.26–2.02)	1.13 (0.84–1.48)	1.16 (0.85–1.54)	0.11
RR (95% CI)[b]	1	1.07 (0.78–1.48)	0.78 (0.54–1.11)	0.76 (0.53–1.11)	0.094
Leukemia and aleukemia, O	8	4	9	6	
SMR (95% CI)	1.11 (0.48–2.18)	0.60 (0.16–1.55)	1.32 (0.60–2.505)	1.01 (0.37–2.21)	0.88
RR (95% CI)	1	0.55 (0.17–1.82)	1.19 (0.46–3.08)	0.85 (0.29–2.49)	0.99
Ischemic heart disease, O	211	196	222	228	
SMR (95% CI)	1.03 (0.89–1.18)	1.04 (0.90–1.19)	1.12 (0.98–1.28)	1.15* (1.00–1.31)	0.24
RR (95% CI)[c]	1	1.01 (0.83–1.22)	1.10 (0.91–1.33)	1.13 (0.94–1.37)	0.19
Chronic and unspecified bronchitis, O	4	2	3	3	
SMR (95% CI)	2.56 (0.70–6.56)	1.36 (0.16–4.91)	1.93 (0.40–5.63)	1.93 (0.40–5.65)	0.96
Mental disorders (excluding alcoholism), O	7	6	7	11	
SMR (95% CI)	1.30 (0.52–2.68)	1.18 (0.43–2.57)	1.42 (0.57–2.92)	1.93 (0.97–3.46)	0.28
RR (95% CI)	1	0.91 (0.31–2.71)	1.08 (0.38–3.08)	1.58 (0.61–4.13)	0.23
Non-cerebrovascular dementia, O[d]	7	6	5	6	
SMR (95% CI)	1.37 (0.55–2.83)	1.22 (0.45–2.66)	1.04 (0.34–2.43)	1.03 (0.38–2.24)	0.67
RR (95% CI)	1	0.96 (0.32–2.86)	0.83 (0.26–2.61)	0.99 (0.33–3.00)	0.95

[a]O, observed numbers of deaths; SMR, standardized mortality ratio based on US referent rates; CI, confidence interval; RR, rate ratio (obtained via Poisson regression and adjusted for gender, age, calendar year, and time since first employed).

[b]Interaction between gender and duration of employment was observed for trachea, bronchus, and lung cancer (*P*-value = 0.048). Rate ratio estimates (and 95% confidence intervals) were 1, 1.13 (0.72–1.79), 0.50 (0.29–0.89), and 0.58 (0.33–1.03) for female workers (trend test *P*-value = 0.029) and 1, 1.01 (0.64–1.60), 1.02 (0.64–1.63), and 0.91 (0.56–1.50) for male workers (trend test *P*-value = 0.65).

[c]Interaction between gender and duration of employment was observed for ischemic heart disease (*P*-value = 0.0091). Rate ratio estimates (and 95% confidence intervals) were 1, 1.05 (0.78–1.40), 1.24 (0.94–1.64), and 1.46 (1.12–1.90) for female workers (trend test *P*-value = 0.0037) and 1, 0.98 (0.75–1.27), 1.02 (0.79–1.33), and 0.88 (0.67–1.17) for male workers (trend test *P*-value = 0.33).

[d]Non-cerebrovascular dementia includes International Classification of Diseases ninth revision codes 290.0–290.3 and 331.0, eighth revision codes 290.0–290.1, and seventh revision codes 304–305. Person-years-at-risk and observed deaths began accruing in 1960 due to rate file restrictions.

*Two-sided *P*-value less than 0.05.

**Two-sided *P*-value less than 0.01.

employment. Further analysis found the highest mortality among those first employed in Plant 2 after 1950 (four observed deaths, SMR = 10.38, CI = 2.83–26.6) (Table IV).

Ischemic Heart Disease

Mortality from IHD was elevated in the cohort based on US referent rates (857 deaths, SMR = 1.08, 95% CI = 1.01–1.16), but not based on state (SMR = 0.98, CI = 0.92–1.06) or county (SMR = 1.00, 95% CI = 0.93–1.07) referent rates. The highest mortality results were found among those workers with 10 or more years of employment (SMR = 1.15, 95% CI = 1.00–1.31). Evidence of interaction between gender and duration of employment was observed in Poisson regression modeling for IHD (interaction *P*-value = 0.0091). For female workers, mortality from IHD increased with duration of employment (trend test *P*-value = 0.0037); RR estimates for female workers were 1, 1.05 (0.78–1.40), 1.24 (0.94–1.64), and 1.46 (1.12–1.90) for the four duration of employment categories, respectively. For male workers, mortality from IHD did not vary with duration of employment (trend test *P*-value = 0.33); RR estimates for male workers were 1, 0.98 (0.75–1.27), 1.02 (0.79–1.33), and 0.88 (0.67–1.17) for the four duration of employment categories, respectively. These results were essentially

unchanged when workers with less than 1-year of employment were excluded (not shown).

Mental Disorders

NIOSH rate files combine all ninth revision ICD codes in the 290–319 range, with the exception of alcoholism (ICD-9 303), into a standard ''mental disorders'' death category. This category covers a varied range of conditions, such as paranoia (ICD-9 297), depression (ICD-9 311), psychosis (ICD-9 293), and dementia (ICD-9 290). Mortality from mental disorders was elevated in the full cohort based on US referent rates (31 deaths, SMR = 1.47, 95% CI = 1.00–2.09), and state referent rates (SMR = 1.64, 95% CI = 1.11–2.34), but not based on county referent rates (SMR = 1.01, 95% CI = 0.68–1.46). The elevation was observed in both genders and largely among workers first employed at Plant 1 prior to 1950 (15 deaths, SMR = 2.32, 95% CI = 1.30–3.83). On average, when compared to the entire cohort, this group worked longer (8.8 years vs. 5.4 years) and died at an older age (79.7 years vs. 67.7 years). Mortality from mental disorders did not increase significantly with duration of employment in either the stratified SMR or the Poisson regression analyses; however, a RR of 1.58 (95% CI = 0.61–4.13) was observed in the 10 or more years of employment category.

To more precisely examine the mental disorders finding, we created special rate files that allowed us to conduct SMR analysis for deaths from cerebrovascular and non-cerebrovascular dementia occurring during the time period 1960–1999. No rates could be made prior to 1960 since electronic mortality data were not available. Cerebrovascular dementia was separated from other dementia because of the likelihood that neuronal death in these causes was due to the underlying cerebral vascular disease. Non-cerebrovascular dementia includes ICD codes for Alzheimer's disease, dementia (senile and pre-senile), and psychoses (senile and pre-senile). Cerebrovascular dementia includes ICD codes for arteriosclerotic dementia and psychosis associated with cerebral arteriosclerosis or other cerebrovascular disturbance. Mortality from cerebrovascular dementia was not elevated in any analysis conducted (results not shown). Results for non-cerebrovascular are shown in Table VI. Non-cerebrovascular dementia was significantly elevated only among women first employed at Plant 1 before 1950. No elevation was noted among males employed at either plant or for females employed at Plant 2. Non-cerebrovascular dementia mortality did not increase with duration of employment (Table V).

DISCUSSION

All Cancer

The International Agency for Research on Cancer (IARC) has determined that ''boot and shoe manufacture and repair entails exposures that are carcinogenic to humans'' [IARC, 1981, 1987]. This Group 1 determination (sufficient evidence of carcinogenicity in humans) was based

TABLE VI. Observed and Expected Numbers of Deaths and Standardized Mortality Ratios for Mortality From Non-Cerebrovascular Dementia[a] Among Shoe Manufacturing Workers, Using US Referent Rates (1960–1999)[b]

	Plant 1 only		Plant 2 only		Both plants combined		
Year first employed	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Total**
<1950							
O/E[c]	2/1.3	11/5.2	1/3.1	7/8.9	3/4.4	18/14.0	21/18.5
SMR	1.56	2.12*	0.32	0.79	0.68	1.28	1.14
95% CI	0.19–5.63	1.06–3.80	0.01–1.78	0.32–1.63	0.14–1.99	0.76–2.02	0.70–1.74
≥1950							
O/E	0/0.2	0/0.8	1/0.2	2/1.1	1/0.3	2/1.8	3/2.2
SMR	0	0	5.89	1.89	2.98	1.10	1.39
95% CI	—	—	0.15–32.7	0.23–6.83	0.08–16.5	0.13–3.96	0.29–4.06
Total							
O/E	2/1.4	11/6.0	2/3.3	9/9.9	4/4.7	20/15.9	24/20.6
SMR	1.39	1.85	0.61	0.91	0.84	1.26	1.16
95% CI	0.17–5.01	0.92–3.31	0.07–2.20	0.41–1.72	0.23–2.15	0.77–1.95	0.74–1.73

[a]Non-cerebrovascular dementia includes International Classification of Diseases ninth revision codes 290.0–290.3 and 331.0, eighth revision codes 290.0–290.1, and seventh revision codes 304–305.
[b]Person-years-at-risk and observed deaths began accruing in 1960 due to rate file restrictions.
[c]O, observed number of deaths; E, expected number of deaths; SMR, standardized mortality ratio; CI, confidence interval.
*Two-sided *P*-value less than 0.05.

on studies that observed nasal adenocarcinoma in workers exposed to leather dust, bladder cancer in workers exposed to chemicals used in leather tanning, and leukemia in workers exposed to benzene. Since this study population was not involved with leather tanning and dyeing, and since there was no evidence of any significant levels of leather dust, the exposure to organic solvents became the focus of this investigation.

The relationship between exposure to organic solvents (other than benzene) and cancer in humans is unclear. IARC, the Environmental Protection Agency, the Agency for Toxic Substances and Disease Registry, and OSHA do not consider the organic solvents used in the study plants (toluene, hexane, acetone, and MEK) to be carcinogenic to humans [IARC, 1999a, 1999b]. National Toxicology Program studies found no evidence of carcinogenic activity in mice and rats that were exposed to organic solvents at high doses [NTP, 1986, 1990]. Nevertheless, there have been a number of occupational exposure studies that have found excess cancer risk to solvent-exposed workers including cancers of the nervous system [Anttila et al., 1998], respiratory tract [Svensson et al., 1990], bone [Wiebelt and Becker, 1999], and liver and biliary tract [Lynge et al., 1997]. Our study found an elevated, though not statistically significant (SMR = 1.05), risk of cancer death for this cohort. Virtually the entire elevation was due to lung cancer (SMR = 1.36, *P*-value <0.01).

Leukemia

We found no evidence to support the original study hypothesis relating solvent exposure to leukemia mortality. Mortality from leukemia and aleukemia, which was not statistically elevated in the original study (SMR = 1.11, 95% CI = 0.63–1.85), was not elevated in the updated cohort. In addition, mortality from leukemia and aleukemia was not related to duration of employment in the updated cohort.

Lung Cancer

The excess lung cancer mortality identified in the original study has persisted through this follow-up. The excess was consistently observed for both genders, both plants, and when using different referent populations. However, lung cancer mortality was not related to duration of employment among male workers and was inversely related to duration of employment among female workers.

Occupational epidemiology studies have long relied on the tenet of a duration of employment-increasing mortality risk relationship as a factor in establishing causality between an exposure and a health outcome. The lack of this relationship in our cohort weakens the conclusion that solvent exposure was a factor in an increased lung cancer risk of this cohort. However, higher than expected death rates in short-term employees have been observed in other mortality studies. In Gilbert [1982] study of Hanford nuclear plant workers, the highest relative risk was observed in workers who were employed for less than 2 years. The author reasoned that these ''transient'' workers might have certain characteristics, possibly socioeconomic in nature that distinguish them from longer term workers. Cone [1987] does not support the ''transient'' worker premise, finding that it is common for stable, consistently employed workers to have had periods of short-term and transitory employment in the past. Cone further notes that these short-term jobs have often presented the worker with the most dangerous and hazardous exposures of his working career that may result in cancer or other diseases many years later. Steenland and Stayner [1991] closely examined the results of 10 large occupational cohort studies conducted by NIOSH in which no occupational risk had been observed and found an inverse relationship between duration of exposure and mortality. The authors offered two alternative hypotheses to explain these results: (a) the reason for ending employment is unrelated to exposure, therefore workers leaving their jobs may be ill and thus will contribute to an inflated mortality rate, and (b) the reason for ending employment is related to exposure and workers leave due to irritation, noxious fumes, or other debilitating conditions. In a study of white males working in the phosphate industry, Checkoway et al. [1985] noted that with the exception of workers employed 30–39 years, the highest lung cancer SMR was for those employed 1–4 years, and suggested that the lack of trend between lung cancer mortality and duration of employment was an indication that the cancer was not related to occupational exposures, but possibly due to a higher smoking prevalence in the cohort compared to the referent population.

An attempt to account for the potential confounding effects of smoking on the lung cancer excess in two ways was made. First, as described previously, an adjustment for hypothesized differences in smoking habits between the cohort and the US population was calculated. This adjustment resulted in a lower, but still elevated, SMR for lung cancer of 1.31 for male workers and 1.13 for female workers. The smoking adjustment, however, must be interpreted cautiously since information on smoking habits in the cohort was not available. In addition, the adjustment relies on estimates of smoking habits in blue collar workers in the US at a single point in time and may not accurately describe the smoking habits of the cohort over the relevant time period. Siemiatycki et al. [1988] suggest that relative risks between lung cancer and occupation in excess of 1.4 are unlikely to be due to uncontrolled confounding. Thus, confounding cannot be ruled out as an explanation for the modest elevations in lung cancer mortality observed in this cohort. Second, state and county referent rates to account for possible local variations in smoking habits were used [Doll, 1985]. When state and county rates were considered, the lung cancer excess remained while the SMRs for other smoking-related

disease categories decreased. Overall, our analyses indicate that the lung cancer excess experienced by this cohort would not be solely explained by smoking and that occupational solvent exposures may be a contributing factor.

Other studies of shoeworker cohorts [Enterline and McKiever, 1963; Decoufle and Walrath, 1983; Garabrant and Wegman, 1984; NIOSH, 1984; Pippard and Acheson, 1985; Schoenberg et al., 1987; Walrath et al., 1987; Brownson et al., 1993; Fu et al., 1996; Jöckel et al., 1998] and solvent-exposed worker populations [Svensson et al., 1990; Chen and Seaton, 1996; Anttila et al., 1998; Gerin et al., 1998; Wiebelt and Becker, 1999] have provided inconclusive results relating solvent exposure to lung cancer mortality and incidence.

Chronic and Unspecified Bronchitis

In the original study, a cause of death category for bronchitis, emphysema, and asthma indicated elevated mortality (SMR = 1.38, 95% CI = 0.92–1.99). Mortality from bronchitis remains elevated in the updated cohort. Excess mortality from respiratory system diseases has not been reported in the literature for shoeworkers or for workers exposed to solvents [Decoufle and Walrath, 1983; Walrath et al., 1987; Svensson et al., 1990; Berlin et al., 1995; Fu et al., 1996; Wiebelt and Becker, 1999]. Since an elevation in mortality from bronchitis or from diseases of the respiratory system has not been linked to solvents or shoeworking, one possible explanation offered by Fox et al. [1974], among others, is that this may be an indication that the population under observation had a higher prevalence of smoking than the referent population.

Ischemic Heart Disease

Mortality from heart disease was not reported in the results of the original study. The updated cohort results found a low-level, statistically significant excess mortality from IHD when only national referent rates were used. Mortality from IHD was elevated in both plants and both genders. Mortality from IHD increased with duration of employment among females in internal analyses.

Death due to IHD has not been an a priori hypothesis of studies involving shoeworkers or workers exposed to solvents. Two proportionate mortality studies of shoeworkers and one cohort mortality study of solvent-exposed workers separately itemized IHD. Both PMR studies detected statistically significant excesses of IHD in both males and females. Walrath et al. [1987] reported PMRs of 1.17 for males and 1.25 for females while Decoufle and Walrath [1983] reported PMRs of 1.05 for males and 1.09 for females. However, both authors caution about over-interpreting the IHD findings, noting the standard limitations of the PMR methodology. The solvent cohort did not experience an excess risk of IHD (SMR = 0.83, CI = 0.57–1.16) [Lundberg, 1986].

Though the results of our study closely coincide with the results from the PMR studies there is no convincing evidence that the IHD elevation is related to solvent exposures. There may have also been other agents in the work environment that contributed to an increase in IHD that no longer existed at the time of the industrial hygiene surveys in the 1970s. One other possible explanation for this increase is that there may have been higher than expected smoking rates in the study cohort.

Mental Disorders

Our finding of elevated mortality due to mental disorders was not detected in the original study. In the update, 27 new deaths in this category were observed. The relationship between solvent exposure and increased risk of mental disorders and impairments has been documented in the scientific literature for many years [Axelson et al., 1976; Flodin et al., 1984; Ørbaek et al., 1985; Lundberg, 1986; Gregersen, 1988; Kukull et al., 1995; White et al., 1995; Schulte et al., 1996; Åbjörnsson et al., 1998], although it is important to note that a number of studies have not detected an increased risk [Heyman et al., 1984; Chandra et al., 1987; O'Flynn et al., 1987; Shalat et al., 1988; Graves et al., 1991].

Even with an added refinement of narrowing our analysis to non-cerebrovascular dementia mortality (Table VI), it is not clear that any elevated risk results for any sub-cohort was related to occupational factors. The types and intensity of the solvent exposures among the workers is unknown and it has not been established that those with elevated mortality were a highly exposed group. The reasons for the widely differing SMRs between Plant 1 and Plant 2, and between male and female workers, are also unknown. Since the manufacturing processes at the plants were similar, we would have expected to see similar SMRs if the excess mortality was related to occupational exposure. We did not observe a trend of increasing mortality with increasing duration of employment.

CONCLUSION

There continues to be no evidence from this study to support the a priori hypothesis that solvent exposure may be linked to excess risk of leukemia mortality. The lung cancer excess identified in the original study has persisted through 17 additional years of vital status follow-up. Interpretation of this finding is limited due to the two chief study limitations: lack of smoking data and the lack of quantitative exposure data prior to 1973. The elevated risk could be due to a higher than expected smoking prevalence within the cohort, despite our efforts to control for confounding through indirect methods. Conversely, smoking is a risk factor for causes of death other than for lung cancer. Smoking has been attributed to elevated mortality from cardiovascular disease (not just IHD), chronic bronchitis, kidney, bladder, and buccal cavity/

pharynx cancers. If the smoking prevalence of our cohort was truly higher than that in an overall US population, we would expect to see elevated mortality for those smoking-related causes as well. Mortality was elevated for IHD and chronic bronchitis but not for the other causes. This weakens any argument to attribute the lung cancer excess solely to the smoking habits of the cohort. One other possibility is that there were non-solvent occupational exposures within the study plants that could have contributed to the excess lung cancer risk. As noted, exposure records are only available beginning in 1973.

The elevated IHD mortality observed in our cohort is contrary to what is expected in an occupational cohort. Most occupational mortality studies report lower than average mortality from IHD. This ''healthy worker effect'' (HWE) has been well-documented in the literature. An absence of an HWE in our cohort may be due to an unexpectedly high smoking rate. However, the HWE requires a closer examination when a cohort, such as ours, nears retirement age. McMichael [1976] and others have shown that while an apparent HWE does exist for younger workers, the HWE virtually disappears by age 65, and actually exceeds the mortality of the general population by age 75. In our population, the average year of birth is 1926 and the average age at death or date last observed is 64.4 years. The overall SMR of our cohort closely resembles the mortality pattern described by McMichael [1976]. The trend in IHD mortality with increasing duration of employment observed among female workers in this study should be examined in future studies of solvent-exposed workers. To date, there is little information in the scientific literature confirming that such a relationship exists.

Finally, there are notable plant-specific differences in mortality patterns. The statistically significant lung cancer and respiratory disease elevations were limited to Plant 2 while the statistically significant elevation for non-cerebrovascular dementia was limited to Plant 1. As is clearly presented by Table I, one of the study limitations is the lack of adequate exposure data. The few exposure readings that are available were conducted during a 6-year period of time in the 1970s. Although our assumption that production methods and resultant exposures were similar between the plants is supported by this survey data, the observed morality differences could be explained by plant-specific exposures that were not documented.

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REFERENCES

Åbjörnsson G, Pålsson B, Bergendorf U, Karlson B, Österberg K, Ørbaek P. 1998. Long-term follow-up of psychological distress, social functioning, and coping style in treated and untreated patients with solvent-induced chronic toxic encephalopathy. J Occup Environ Med 40(9):801–807.

Anttila A, Pukkala E, Riala R, Sallmen M, Hemminki K. 1998. Cancer incidence among Finnish workers exposed to aromatic hydrocarbons. Int Arch Occup Environ Health 71(3):187–193.

Axelson O, Steenland K. 1988. Indirect methods of assessing the effects of tobacco use in occupational studies. Am J Ind Med 13(1):105–118.

Axelson O, Hane M, Hogstedt C. 1976. A case-referent study on neuropsychiatric disorders among workers exposed to solvents. Scand J Work Environ Health 2(1):14–20.

Berlin K, Edling C, Persson B, Ahlborg G, Hillert L, Hogstedt B, Lundberg I, Svensson BG, Thiringer G, Ørbaek P. 1995. Cancer incidence and mortality of patients with suspected solvent-related disorders. Scand J Work Environ Health 21(5):362–367.

Breslow N, Day N. 1987. Statistical Methods in Cancer Research, Vol II. International Agency for Research on Cancer Sci. Pub. No. 82. Lyon, France: IARC.

Brownson R, Alavanja M, Chang J. 1993. Occupational risk factors for lung cancer among non-smoking women: A case-control study in Missouri. Cancer Causes Control 4(5):449–454.

Centers for Disease Control and Prevention. 1994. Surveillance for selected tobacco-use behaviors—United States, 1900–1994. MMWR 43(S–3):1–27.

Chandra V, Philipose V, Bell PA, Lazaroff A, Schoenberg BS. 1987. Case-control study of late onset ''probable Alzheimer's disease''. Neurology 37(8):1295–1300.

Checkoway H, Mathew RM, Hickey JL, Shy CM, Harris RL Jr, Hunt EW, Waldman GT. 1985. Mortality among workers in the Florida phosphate industry: I. Industry-wide cause-specific mortality patterns. J Occup Med 27(12):885–892.

Chen R, Seaton A. 1996. A meta-analysis of mortality among workers exposed to organic solvents. Occup Med (Lond) 46(5):337–344.

Cone J. 1987. Occupational lung cancer. Occup Med 2(2):273–295.

Decoufle P, Walrath J. 1983. Proportionate mortality among US shoeworkers, 1966–1977. Am J Ind Med 4(4):523–532.

Doll R. 1985. Occupational cancer: A hazard for epidemiologists. Int J Epidemiol 14(1):22–31.

Enterline PE, McKiever MF. 1963. Differential mortality from lung cancer by occupation. J Occup Med 5(6):283–290.

Flodin U, Edling C, Axelson O. 1984. Clinical studies of psychoorganic syndromes among workers with exposures to solvents. Am J Ind Med 5(4):287–295.

Fox AJ, Lindars DC, Owen R. 1974. A survey of occupational cancer in the rubber and cablemaking industries: Results of five-year analysis, 1967–71. Br J Ind Med 31(2):140–151.

Fu H, Demers P, Constantini A, Winter P, Colin D, Kogevinas M, Boffetta P. 1996. Cancer mortality among shoe manufacturing workers: An analysis of two cohorts. Occup Environ Med 53(6):394–398.

Garabrant DH, Wegman DH. 1984. Cancer mortality among shoe and leather workers in Massachusetts. Am J Ind Med 5(4):303–314.

Gerin M, Siemiatycki J, Desy M, Krewski D. 1998. Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene: Results of a case-control study in Montreal. Am J Ind Med 34(2):144–156.

Gilbert ES. 1982. Some confounding factors in the study of mortality and occupational exposures. Am J Epidemiol 116(1):177–188.

Graves AB, van Duijn CM, Chandra V, Fratiglioni L, Heyman A, Jorm AF, Kokmen E, Kondo K, Mortimer JA, Rocco WA, Salat SL, Soininen H, Hofman A. 1991. Occupational exposures to solvents and lead as risk factors for Alzheimer's disease: A collaborative re-analysis of case-control studies. Int J Epidemiol 20(Suppl 2):S58–61.

Greenburg L, Mayers M, Heiman H, Moskowitz S. 1942. The effects of exposure to toluene in industry. JAMA 122(4):573–578.

Gregersen P. 1988. Neurotoxic effects of organic solvents in exposed workers: Two controlled follow-up studies after 5.5 and 10.6 years. Am J Ind Med 14(6):681–701.

Hammond E. 1966. Smoking in relation to the death rates of one million men and women. Epidemiological approaches to the study of cancer and other chronic diseases. Natl Cancer Inst Monogr 19:127–204.

Heyman A, Wilkinson WE, Stafford JA, Helms MJ, Sigmon AH, Weinberg T. 1984. Alzheimer's disease: A study of epidemiological aspects. Ann Neurol 15(4):335–341.

International Association for Research on Cancer. 1981. Boot and shoe manufacture and repair. IARC monographs on the evaluation of carcinogenic risk to humans.

International Association for Research on Cancer. 1987. Boot and shoe manufacture and repair. IARC monographs on the valuation of carcinogenic risk to humans. Supplement 7.

International Association for Research on Cancer. 1999a. Toluene. IARC monographs on the evaluation of carcinogenic risk to humans.

International Association for Research on Cancer. 1999b. Xylenes. IARC monographs on the evaluation of carcinogenic risk to humans.

Jöckel KH, Ahrens W, Jahn I, Pohlabeln H, Bolm-Audorff U. 1998. Occupational risk factors for lung cancer: A case-control study in West Germany. Int J Epidemiol 27(4):549–560.

Kolstad HA, Olsen J. 1999. Why do short term workers have high mortality? Am J Epidemiol 149(4):347–352.

Kukull WA, Larson EB, Bowen JD, McCormick WC, Teri L, Pfanschmidt ML, Thompson JD, O'Meara ES, Brenner DE, van Belle G. 1995. Solvent exposure as a risk factor for Alzheimer's disease—A case-control study. Am J Epidemiol 141(11):1059–1071.

Lundberg I. 1986. Mortality and cancer incidence among Swedish paint industry workers with long-term exposure to organic solvents. Scand J Work Environ Health 12(2):108–113.

Lynge E, Antilla A, Hemminki K. 1997. Organic solvents and cancer. Cancer Causes Control 8(3):406–419.

McConnell WJ, Fehnel JW, Ferry JJ. 1942. Potential health hazards of the leather industry. J Ind Hygiene Toxicol 24(5):93–108.

McMichael A. 1976. Standardized mortality ratios and the "healthy worker effect": Scratching beneath the surface. J Occup Med 18(3):165–168.

National Institute for Occupational Safety and Health. 1984. Occupational characteristics of cancer victims in Massachusetts, 1971–1973, DHHS (NIOSH) Pub. No. 84-109. Cincinnati, OH: NIOSH.

National Toxicology Program. 1986. Toxicology and carcinogenesis studies of xylenes in F3441n rats and B6C3F$_1$ mice. NTP TR 327. Research Triangle Park, NC.

National Toxicology Program. 1990. Toxicology and carcinogenesis studies of toluene in F344/N rats and B6C3F$_1$ mice (inhalation studies). NTP TR 371. Research Triangle Park, NC.

Ørbaek P, Risberg J, Rosen I, Haeger-Aronsen B, Hagstadius S, Hjortsberg U, Regnell G, Rehnstrom S, Svensson K, Welinder H. 1985. Effects of long-term exposure to solvents in the paint industry: A cross-sectional epidemiologic study with clinical and laboratory methods. Scand J Work Environ Health 11(Suppl 2):1–28.

O'Flynn RR, Monkman SM, Waldron HA. 1987. Organic solvents and presenile dementia: A case referent study using death certificates. Br J Ind Med 44(4):259–262.

Pippard EC, Acheson ED. 1985. The mortality of boot and shoe makers, with special reference to cancer. Scand J Work Environ Health 11(4):249–255.

Rothman K, Boice J. 1979. Epidemiologic analysis with a programmable calculator. Washington, DC: U.S. Government Printing Office.

Schoenberg JB, Stemhagen A, Mason TJ, Patterson J, Bill J, Altman R. 1987. Occupation and lung cancer risk among New Jersey white males. J Natl Cancer Inst 79(1):13–21.

Schulte PA, Burnett CA, Boeniger MF, Johnson J. 1996. Neurodegenerative diseases: Occupational occurrence and potential risk factors, 1982 through 1991. Am J Public Health 86(9):1281–1288.

Shalat SL, Seltzer B, Baker EL. 1988. Occupational risk factors and Alzheimer's disease: A case-control study. J Occup Med 30(12):934–936.

Siemiatycki J, Wacholder S, Dewar R, Cardis E, Greenwood C, Richardson L. 1988. Degree of confounding bias related to smoking, ethnic group, and socioeconomic status in estimates of the associations between occupation and cancer. J Occup Med 30(8):617–625.

Steenland K, Stayner L. 1991. The importance of employment status in occupational cohort mortality studies. Epidemiology 2(6):418–423.

Steenland K, Beaumont J, Halperin W. 1984. Methods of control for smoking in occupational cohort mortality studies. Scand J Work Environ Health 10(3):143–149.

Steenland K, Spaeth S, Cassinelli R, Laber P, Chang L, Koch K. 1998. NIOSH life table program for personal computers. Am J Ind Med 34(5):517–518.

Svensson B, Nise G, Englander V, Attewell R, Skerfving S, Moller T. 1990. Deaths and tumours among rotogravure printers exposed to toluene. Br J Ind Med 47(6):372–379.

Vena JE, Sultz HA, Carlo GL, Fiedler RL, Barnes RE. 1987. Sources of bias in retrospective cohort mortality studies: A note on treatment of subjects lost to follow-up. J Occup Med 29(3):256–261.

Walker JT, Bloom TF, Stern FB, Okun AH, Fingerhut MA, Halperin WE. 1993. Mortality of workers employed in shoe manufacturing. Scand J Work Environ Health 19(2):89–95.

Walrath J, Decoufle P, Thomas TL. 1987. Mortality among workers in a shoe manufacturing company. Am J Ind Med 12(5):615–623.

Waxweiler RJ, Beaumont JJ, Henry JA, Brown DP, Robinson CF, Ness GO, Wagoner JK, Lemen RA. 1983. A modified life-table analysis system for cohort studies. J Occup Med 25(2):115–124.

Weinkam JJ, Sterling TD. 1987. Changes in smoking characteristics by type of employment from 1970 to 1979/80. Am J Ind Med 11(5):539–561.

White RF, Proctor SP, Echeverria D, Schweikert J, Feldman RG. 1995. Neurobehavioral effects of acute and chronic mixed-solvent exposure in the screen printing industry. Am J Ind Med 28(2):221–231.

Wiebelt H, Becker N. 1999. Mortality in a cohort of toluene exposed employees (rotogravure printing plant workers). J Occup Environ Med 41(12):1134–1139.

Wilson RH. 1943. Toluene poisoning. JAMA 123(17):1106–1109.