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Mortality of workers employed in shoe manufacturing

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WALKER JT, BLOOM TF, STERN FB, OKUN AH, FINGERHUT MA, HALPERIN WE. Mortality of workers employed in shoe manufacturing. *Scand J Work Environ Health* 1993;19:89—95. A retrospective cohort mortality study was conducted among 7814 white shoe manufacturing workers followed from 1940 through 1982. The workers were potentially exposed to solvents (including toluene) and solvent-based adhesives. Benzene may have been present as an impurity of toluene. Mortality due to leukemia and aleukemia was not statistically significantly elevated. Statistically significant excess mortality due to cancer of the trachea, bronchus and lung was observed in the total cohort [standardized mortality ratio (SMR) 147, 95% confidence interval (95% CI) 120—180] and showed a statistically significant trend in standardized relative risk with increasing potential latency, but not with increasing duration of employment. Chronic nonmalignant respiratory disease was significantly elevated among the men (SMR 158, 95% CI 114—217) but was less than expected among the women (SMR 79), a finding suggesting a possible contribution of smoking to the mortality from respiratory cancer. However, adjustment for the potential effects of smoking did not completely eliminate the increased risk for lung cancer.

Key terms: acetone, hexane, leukemia, lung cancer, methyl ethyl ketone, occupational cancer, retrospective study, shoe industry, toluene.

The National Institute for Occupational Safety and Health (NIOSH) conducted a cohort mortality study in two shoe manufacturing factories to investigate whether workers exposed to toluene and other solvents experienced excess mortality due to leukemia or other causes of death.

Of the solvents frequently used in the shoe manufacturing industry, toluene was of particular interest because of the practice in recent years of substituting toluene for benzene in many industrial operations. The association of benzene with malignancies of hematopoietic tissue in a number of epidemiologic studies (1—3) has raised concern that toluene, a homologue of benzene, might also be carcinogenic. Experimental studies suggest that toluene is associated with skin cancer, leukemia, and hematosarcomas in rats and mice (4—5). However, these effects may have been due to the presence of benzene as an impurity (6).

Subjects and methods

Exposure data

The two plants, located in the state of Ohio in the United States, operate similar shoemaking processes. Plant 1 has been in operation since 1930, and plant 2 since 1939. The major departments and operations in the shoemaking process include the Cutting Department, where leather and other materials are cut to specific sizes; the Fitting Department, where the upper shoe is assembled; the Lasting Department, where the insole is glued to the upper shoe assembly; the Sole Leather Department, where the outsoles, insoles, and heels are prepared; the Bottoming Department, where the outsole, insole, and heel are glued onto the bottom of the upper shoe assembly; and the Packing Department, where the completed shoes are washed, cleaned, inspected, and packaged for shipment.

Study population and follow-up

All white employees who worked in either plant for one month or more during the period 1 January 1940—31 December 1979 were included in the study cohort. Employee identification data (name, social security number, date of birth, gender, and race) and general work history (first and last dates of employment) were coded into computer files. Vital status follow-up through 31 December 1982 was ascertained through the Social Security Administration, the Veterans Administration, the Internal Revenue Service, the National Death Index, and other sources. Employees whose vital status was unknown as of 31 December 1982 were considered to be alive as of that date. Death certificates were obtained, and the underlying cause of death was determined by a nosologist according to the revision of the International Classification of Diseases in effect at the time

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of death. Cause of death was classified as "unknown" for the deceased individuals for whom no death certificate was obtained.

Analysis

The members of the cohort contributed person-years at risk beginning 1 February 1940 or one month after their first day employed, whichever was later, and ending 31 December 1982. The total person-years at risk for the cohort were calculated for each five-year age and calendar-time interval beginning 1 February 1940 and ending 31 December 1982. Each worker ceased contributing to the total person-years at risk on the date of his or her death or on 31 December 1982, whichever was earlier. The duration of employment for each worker included all years employed up through 1979, including any years worked before 1940. Duration of employment excluded any time worked after 31 December 1979, the date on which the collection of detailed work history data began.

Expected deaths and standardized mortality ratios (SMR) were computed for specific causes of death with the use of the life-table analysis system developed by NIOSH (7—8). This program computes expected numbers of deaths and SMR values for 92 cause-of-death categories by applying age-, gender-, race-, and calendar-specific mortality rates for the United States to the appropriate accumulation of person-years at risk. Two-sided 95% confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution (9—10). For tests of overall trend with respect to potential latency or duration of employment, three exposure categories (1—2 months, 2 months-3 years, and ≥3 years) and three potential latency categories (<25 years, 25—34 years, and ≥35 years) were created, with approximately equal numbers of expected deaths within each category. Directly standardized mortality rate ratios (SRR) were calculated for each category with the use of the first category as the reference category for the ratios. Tests for overall trend in the SRR values were made according to methods suggested by Rothman (11) and Steenland et al (8).

In the absence of data on the smoking habits of the workers in the study cohort, the potential for confounding from excess smoking was evaluated through an examination of the mortality experience from nonmalignant respiratory diseases associated with smoking, as suggested by Steenland et al (12). A category of chronic nonmalignant respiratory disease was created which contained all of the nonmalignant respiratory diseases except deaths due to influenza, pneumonia, and other acute respiratory infections. In addition, the possible confounding effects from smoking were evaluated according to the methodology described by Axelson (13) and Steenland & Beaumont (14). Information on smoking was based on the 1970 national survey data for the men and women in the total population and for the male and female operatives, as reported by Sterling & Weinkam (15). We assumed that our cohort had smoking habits similar to those of machine operators, as reported in the 1970 United States survey. We then calculated the effect of confounding from smoking on cohort lung cancer rates, in comparison with the habits of the general population. The lung cancer mortality ratios used in the adjustment were based on the mortality ratios reported by Hammond (16).

Table 1. Personal solvent exposures measured in 1977—1979 by the Occupational Safety and Health Administration in the bottoming departments of plants 1 and 2. (TLV = threshold limit value, TWA = time-weighted average)

Substance	TLV[1] (ppm)	Number of samples	TWA exposures (ppm)	
			Mean	Range
Plant 1				
Toluene	100	4	50	38—72
Methyl ethyl ketone	200	4	133	63—250
Acetone	750	4	223	200—270
Hexane	500	2	55	30—80
Plant 2				
Toluene	100	6	22	10—43
Methyl ethyl ketone	200	6	153	48—330
Acetone	750	6	46	25—146
Hexane	500	6	22	13—45

[a] Source: reference 17.

Results

The two study plants operated similar shoemaking processes. In each plant, all of the departments and their associated work areas are contained in one large room. No significant changes in the manufacturing processes over time were reported at either plant. However, between 1977 and 1979, the company reported major ventilation additions in both plants to control vapor exposures. No other changes regarding exposure control mechanisms were reported.

Table 2. Vital status for the study cohort through 31 December 1982 by gender.

Vital status	Male		Female		Total	
	Number	Percent[a]	Number	Percent[a]	Number	Percent[a]
Alive	1674	66	4420	84	6094	78
Deceased	815	32	730	14	1545	20
Lost to follow-up (assumed alive)	40	2	135	3	175	2
Total	2529	100	5285	100	7814	100

[a] Percentages may not add to 100% due to rounding.

The industrial hygiene data available on the two plants were limited. Exposure measurements for toluene, methyl ethyl ketone (MEK), acetone, and hexane were made by the Occupational Safety and Health Administration (OSHA) in the Bottoming Department in 1977 for plant 1 and in 1978 for plant 2. Table 1 shows the results of the personal sampling conducted by OSHA. Exposures measured at both plants were less than the threshold limit values (17), except for methyl ethyl ketone in plant 2. Material safety data sheets indicated the presence of other solvents, including aliphatic petroleum naphtha, isopropyl alcohol, methyl alcohol, ethylene glycol monoethyl ether, mineral spirits, xylene, formaldehyde, methyl pyrrolidone, trichloroisocyanuric acid, and ammonia. No data were available describing potential airborne concentrations of benzene, leather dust, or dust from other natural or synthetic materials. However, NIOSH industrial hygiene surveys, conducted in each plant in 1979, indicated that the dust-producing operations were ventilated for removal of particulates.

Table 3. Person-years at risk, mean year first employed, mean years of employment, and mean years of follow-up for the cohort by gender.

Gender	Person-years at risk	Mean year first employed	Mean years of employment	Mean years of follow-up
Male	73 058	1949	5.7	28.6
Female	144 614	1954	6.0	27.4
Total	217 672	1952	27.4	27.8

Table 4. Observed (O) and expected (E) numbers of deaths and the standardized mortality ratio (SMR) and 95% confidence interval (95% CI) according to selected causes of cancer and nonmalignant respiratory diseases among the total cohort by gender.[a]

Cause of death[b]	Males				Females				Total			
	O	E	SMR	95% CI	O	E	SMR	95% CI	O	E	SMR	95% CI
All causes (000—999)	810	783.7	103	96—111	737	781.4	93	87—100	1540	1565.1	98	94—103
All malignant neoplasms	159	145.1	109	93—128	194	214.3	90	78—104	353	359.4	98	88—109
Buccal cavity and pharynx (140—149)	4	4.6	87	24—224	1	2.8	35	9—199	5	7.4	67	22—159
Digestive organs and peritoneum (151—159, 197.8)	39	42.8	91	65—125	51	52.9	96	72—127	90	95.7	94	76—116
Intestine except rectum (152—153)	18	13.6	131	78—208	28	22.8	122	82—177	46	36.5	126	92—168
Respiratory system (160—165)	68	46.1	147**	115—187	33	24.8	133	92—187	101	70.8	142**	116—173
Larynx (161)	—	2.1	0	0—173	2	0.6	334	40—1209	2	2.7	73	9—265
Trachea, bronchus and lung (162)	68	43.3	156**	122—199	31	23.7	130	89—186	99	67.0	147**	120—180
Other parts of the respiratory system (160, 163—165)	—	0.6	0	0—609	—	0.5	0	0—712	—	1.1	0	0—328
Urinary organs (188—1899)	10	8.0	124	59—228	6	5.6	107	39—234	16	13.6	117	67—191
Kidney (189—1892)	6	3.5	171	62—373	3	3.1	97	20—284	9	6.6	136	62—259
Bladder and other urinary organs (188, 1893—1899)	4	4.5	87	24—225	3	2.5	120	25—351	7	7.0	99	40—205
Neoplasms of lymphatic and hematopoietic tissue (200—208)	13	13.7	94	50—162	16	17.6	90	52—148	29	31.3	92	62—133
Lymphosarcoma and reticulosarcoma (200)	3	2.8	106	22—311	2	3.8	53	6—191	5	6.6	75	24—177
Hodgkin's disease (201)	2	1.7	119	14—432	2	1.9	106	13—383	4	3.6	112	31—288
Leukemia and aleukemia (204—208)	6	6.1	98	36—215	9	7.3	123	56—234	15	13.4	111	63—185
Nonmalignant respiratory disease (460—519)	56	45.9	122	92—158	20	35.5	56**	34—87	76	81.4	93	74—117
Acute respiratory, influenza, pneumonia (460—487)	16	20.7	77	44—125	7	19.0	37	15—76	23	39.7	58	37—87
Chronic nonmalignant respiratory disease (490—493, 470—478, 494—519)	40	25.1	158*	114—217	13	16.6	79	42—134	53	41.6	127	95—166
Bronchitis, emphysema, asthma (490—493)	19	12.9	147	88—230	9	7.4	122	56—231	28	20.3	138	92—199
Other respiratory diseases (470—478, 494—519)	21	12.2	172*	107—263	4	9.2	44	12—112	25	21.4	117	76—173

[a] For presentation, the standardized mortality ratios and confidence intervals have been rounded to the nearest whole number, and the expected numbers have been rounded to the nearest tenth.
[b] Code of the International Classification of Diseases (ninth revision) in parentheses.
* $P<0.05$ (2-sided Poisson), ** $P<0.01$ (2-sided Poisson).

Table 5. Standardized mortality ratios (SMR) for leukemia and aleukemia in the total cohort by duration of employment and potential latency.

Potential latency (years)	Duration of employment													
	1 month—<1 year		1—4 years		5—9 years		10—14 years		15—19 years		≥20 years		Total	
	Observed deaths (N)	SMR	Observed deaths (N)	SMR	Observed deaths (N)	SMR	Observed deaths (N)	SMR	Observed deaths (N)	SMR	Observed deaths (N)	SMR	Observed deaths (N)	SMR
<5	1	0	—	0	.	.	.	.	.	.	.	.	—	0
5—9	2	459	—	0	1	273	.	.	.	.	.	.	3	271
10—14	—	0	1	285	—	0	1	316	.	.	.	.	2	153
15—19	—	0	—	0	—	0	—	0	—	0	.	.	—	0
20—24	—	0	—	0	—	0	—	0	—	0	—	0	—	0
≥25	4	176	2	101	2	329	—	0	—	0	2	173	10	150
Total	6	120	3	75	3	209	1	116	—	0	2	141	15	112

Table 6. Standardized mortality ratios (SMR) for malignant neoplasms of the trachea, bronchus and lung in the total cohort by duration of employment and potential latency.

Potential latency (years)	Duration of employment													
	1 month—<1 year		1—4 years		5—9 years		10—14 years		15—19 years		≥20 years		Total	
	Observed deaths (N)	SMR	Observed deaths (N)	SMR	Observed deaths (N)	SMR	Observed deaths (N)	SMR	Observed deaths (N)	SMR	Observed deaths (N)	SMR	Observed deaths (N)	SMR
<5	1	0	1	130	.	.	.	.	.	.	.	.	1	68
5—9	—	0	—	0	1	119	.	.	.	.	.	.	1	43
10—14	—	0	—	0	—	0	—	0	.	.	.	.	—	0
15—19	3	162	1	76	—	0	—	0	—	0	.	.	4	78
20—24	4	138	2	96	3	418	—	0	1	301	1	74	11	141
≥25	22	140	22	218**	8	186	7	331**	2	132	11	128	82	175
Total	29	125	36	178**	12	179	7	180	3	104	12	120	99	147**

** P<0.01, 2-sided Poisson.

Table 7. Standardized relative risks (SRR) for malignant neoplasms of the trachea, bronchus and lung in the total cohort by potential latency.

Potential latency	Observed deaths (N)	SRR
<25 years	17	100
25—29 years	36	135
≥30 years	46	231
P-value*		<0.001

* P-value for Rothman trend test.

Since it is common practice for OSHA to collect samples from employees who are thought to have the highest exposure, the employees working in the Bottoming Department may have had the highest levels of exposure to the aforementioned solvents. While no exposures were measured in the Packing Department, the pattern of usage of solvents for washing and cleaning purposes suggests that this department also involved significant potential for solvent exposure. The other departments — cutting, fitting, lasting, and sole leather — probably had relatively lower exposures to organic vapors.

The vital status of the cohort members through 31 December 1982 is shown in table 2, with 98% of the follow-up complete, and the person-years at risk, mean year first employed, mean years of employment, and mean years of follow-up are given in table 3 by gender. Table 4 shows the standardized mortality ratios (SMR) for selected causes of death. The all-causes SMR was 103 (95% CI 96—111) for white males and 93 (95% CI 87—100) for white females.

The SMR for leukemia and aleukemia was 123 (9 observed, 95% CI 56—234) for the women, 98 for the men (6 observed, 95% CI 36—215), and 111 for the total cohort (95% CI 63—185) (table 4). Of the 15 leukemia deaths in the total cohort, eight were lymphatic leukemia, five were myeloid leukemia, and two were monocytic leukemia. The SMR values for leukemia in the total cohort were evaluated by duration of employment (table 5). There was no systematic increase in mortality with duration of employment when examined for the whole cohort or when duration of employment strata were examined within categories of potential latency. In addition, no pattern of increased leukemia mortality risk with potential latency (time since first employment) was observed.

Excess mortality from cancer of the trachea, bronchus and lung was statistically significant for the total cohort (SMR 147, 95% CI 120—180) and for the men (SMR 156, 95% CI 122—199) (table 4). Can-

cer of the trachea, bronchus and lung was increased among the women (SMR 130, 95% CI 89—186), but the increase was not statistically significant. Two cancers of the larynx occurred, both in women, resulting in an SMR of 334 (95% CI 40—1209).

The SMR values by duration of employment were evaluated for cancer of the trachea, bronchus and lung for the total cohort. There was no systematic increase with duration of employment when examined for the whole cohort. However, an apparent increase in mortality risk with potential latency for cancer of the trachea, bronchus and lung was observed for the total cohort (table 6). Since SMR comparisons across subgroups can be problematic if there is confounding by age, we examined the apparent trend seen in table 6 directly using SRR values for three potential latency categories containing approximately equal numbers of expected deaths. A trend test for the SRR values showed a statistically significant linear trend for latency ($P < 0.001$) (table 7).

After adjustment for smoking according to methods suggested by Axelson (13) and Steenland & Beaumont (14), the SMR for lung cancer among the men was somewhat reduced but remained statistically significantly elevated at 139 (95% CI 108—176), compared with the unadjusted value of 156, while the SMR for lung cancer among the women was reduced to 124 (95% CI 84—176) from the unadjusted value of 130.

The overall mortality from nonmalignant respiratory disease in the total cohort was slightly less than expected (SMR 93, 95% CI 74—117) (table 4). However, mortality from chronic nonmalignant respiratory disease, which is generally associated with smoking, was elevated in the total cohort (SMR 127, 95% CI 95—166). Mortality in this category was statistically significantly elevated among the men (40 observed, SMR 158, 95% CI 114—217), but was statistically nonsignificantly lower than expected among the women (13 observed, SMR 79, 95% CI 42—134). A review of the causes of death recorded on the death certificates revealed that no cases of pneumoconioses had been recorded.

Discussion

Leukemia was of interest in this cohort because it was initially believed that only toluene-based solvents were used in shoe making at these facilities. The study found that the SMR for leukemia and aleukemia was not elevated for the men, although there was a slight statistically nonsignificant elevation for the women. In addition, there was no relationship of mortality with either increasing potential latency or duration of employment. However, the study only had sufficient power (90%) to find a twofold or higher excess as statistically significant.

Examination of the data showed that the 15 workers who died from leukemia worked predominantly before 1956, when benzene exposure was potentially an impurity in toluene (18). However, the period of employment of the total cohort was predominantly before 1956. There were no leukemia deaths among the members of the cohort employed only after 1 January 1956, with 0.7 expected.

Several studies of shoe workers have reported excess deaths due to leukemia, and these deaths were linked to benzene exposure (19—21). Managers of the facilities in our study reported at the time of the 1979 NIOSH surveys that no benzene-based adhesives or solvents had ever been used in the plants since they began operation in 1930 (plant 1) and 1939 (plant 2). Information pertaining to the chemical contents of tradename products and organic solvent cleaners in use in both plants in 1986 did not indicate that benzene was a constituent. Thus there was no clear evidence that benzene had ever been used in the plants, although there was historical evidence that benzene was an impurity in industrial-grade toluene in the United States before the mid-1950s (18).

The SMR for mortality from trachea, bronchus and lung cancer in the total cohort and among the male shoe workers was statistically significantly increased (SMR 147 and 156, respectively). When potential latency and duration of employment were used to explore variation in the mortality from cancer of the trachea, bronchus and lung, the mortality for neoplasms of the trachea, bronchus and lung showed no apparent association with duration of employment, but it did show a statistically significant association with potential latency (table 6).

The potential effect of smoking on lung cancer was assessed through an examination of the results for other smoking-related diseases and through indirect adjustment of the results for the potential effects of smoking. Chronic nonmalignant respiratory disease has been reported to be elevated along with lung cancer when smoking is a contributory factor (12, 22). In this study, mortality for chronic nonmalignant respiratory disease (bronchitis, emphysema, and other nonmalignant respiratory disease) was statistically significantly increased among the men (SMR 158), an indication of a possible confounding effect of smoking in the cohort. However, the excess was confined to the men, since mortality was lower than expected among the women (SMR 79). Plant officials stated in 1982 that smoking had always been prohibited in each facility, although employees might have smoked more away from work to make up for this time.

When the SMR values for lung cancer were indirectly adjusted according to methods suggested by Axelson (13) and Steenland & Beaumont (14) for the potential effects of hypothesized higher levels of smoking, the SMR values for lung cancer were lowered among the men and women, but the statistically significant excess mortality due to lung cancer among the men remained. This finding is consistent with the results of Siemiatycki et al (23), who con-

cluded that a relative risk between lung cancer and occupation for blue-collar workers in excess of 1.2 is unlikely to be due to confounding by smoking.

We considered using the Ohio population as the comparison population in addition to that of the United States. However, inspection of the Ohio death rates for the causes of primary interest showed that, for most of the study period, they were virtually the same as those of the United States, and therefore no separate analyses were conducted (24).

There is inconsistent information in the literature concerning the relationship between shoe manufacturing employment and respiratory cancer. A previous retrospective cohort mortality study of shoe workers reported a statistically significant deficit in deaths from lung cancer among male boot and shoe makers in Great Britain (25). On the other hand, six other studies found elevations of lung cancer. A proportional mortality study by DeCoufle & Walrath (26) of a cohort of shoe workers found a statistically significant excess of lung cancer (observed 155, expected 129.5, $P<0.05$) although the authors stated that the results may have been biased due to incomplete ascertainment of deaths. Five population-based surveillance-type studies among shoe makers and repairers in Massachusetts (27), the United States (28—30), and England and Wales (31) revealed proportionate mortality ratios (PMR) for lung cancer of 120, 140 ($P<0.05$), 130, 190 ($P<0.05$), and 170. However, these studies lacked lifetime occupational histories and, with the exception of two studies, could not control for smoking or other lung cancer risk factors except for age, gender, and race. The Massachusetts study by Dubrow & Wegman (PMR 120) (27) controlled for smoking and social class, and the England and Wales study by the Registrar General (PMR 170) (31) controlled for social class. In addition, all of the six studies were surveillance-type studies, and the large number of statistical comparisons made in each may have resulted in chance lung cancer findings.

In summary, this study was undertaken to determine if shoe workers potentially exposed to toluene and other solvents experience excess mortality due to leukemia and other causes of death. The mortality experience showed a slight statistically nonsignificant elevated SMR for leukemia only for the women, and it was based upon small numbers of observed and expected deaths. No trend was observed with increasing duration of employment or latency. Although our study had low statistical power and little detailed exposure data, it does not provide evidence for an association between toluene and leukemia. For the total cohort we also found a statistically significant excess of mortality due to cancer of the trachea, bronchus and lung, which showed a statistically significant linear trend with increasing potential latency, but not with duration of employment. Although the women had elevated mortality due to cancer of the trachea, bronchus and lung, a statistically significant excess was observed only for the men, who also had a statistically significant excess of mortality for smoking-related chronic nonmalignant respiratory disease. An indirect adjustment for smoking indicated that, for this cohort, smoking probably would not fully account for the excess mortality due to cancer of the trachea, bronchus and lung. Future studies with better exposure information are needed to examine the relationship further between shoe manufacturing and the risk of cancer of the trachea, bronchus and lung.

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