

Mortality of cellulose fiber production workers

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LANES SF, COHEN A, ROTHMAN KJ, DREYER NA, SODEN KJ. Mortality of cellulose fiber production workers. *Scand J Work Environ Health* 1990;16:247–51. Mortality was studied among 1271 employees of a cellulose fiber production plant in Rock Hill, South Carolina, in the United States. Each subject was employed for at least three months between 1 January 1954 and 1 January 1977 in jobs that entailed exposure to the highest concentrations of methylene chloride. In the cohort 122 deaths were identified through 1 September 1986, and mortality rates for the cohort were compared with mortality rates for York County, South Carolina. Deficit mortality was observed for cancers of the respiratory system, breast, and pancreas and from ischemic heart disease. Excess mortality was observed for cancers of the buccal cavity and pharynx and the liver and biliary tract, and for melanoma as well. The largest relative excess was for liver and biliary tract cancers. There were only four deaths in this category; however, three of the four deaths were cancer of the biliary tract (3 observed, 0.15 expected, standardized mortality ratio 20).

Key terms: buccal cavity, bile duct, ischemic heart disease, liver, melanoma, methylene chloride, neoplasms, pancreas, pharynx, solvents.

Methylene chloride (dichloromethane) is a chlorinated solvent with many industrial and commercial applications, including metal cleaning, paint stripping, chemical processing, and the decaffeination of coffee (1). In the early 1970s, inhalation of methylene chloride was found to decrease arterial oxygen content by increasing carboxyhemoglobin, and this finding stimulated interest in research on a possible relationship between methylene chloride and ischemic heart disease (2). More recently, bioassays have yielded evidence indicating that methylene chloride is carcinogenic in mice and rats (3). An epidemiologic study of workers exposed to methylene chloride in the production of photographic film found no excess of ischemic heart disease, but it did report an excess of pancreatic cancer (4). These studies have generated interest in the possible carcinogenic effect of methylene chloride on humans.

In this article we report an update of a study with a previously assembled cohort of textile workers exposed to methylene chloride in the production of cellulose triacetate fiber from 1954 until 1977 (5). Although exposure measurements for most of the study period are unavailable, existing data from the 1970s suggest that the exposure levels were substantially greater for this cohort (5, 6) than for a cohort of photographic film manufacturers (4).

Subjects and methods

We studied a previously assembled cohort of 1271 workers exposed to methylene chloride in the production of cellulose triacetate fiber at a fiber manufacturing plant in Rock Hill, South Carolina, in the United States (5). The plant produced cellulose triacetate fiber throughout the study period, but ceased production in 1986. The cohort was assembled in 1977 and comprised people employed in the preparation or extrusion areas for at least three months between 1 January 1954 and 1 January 1977 (5). Employment in the preparation and extrusion areas entailed the greatest exposures to methylene chloride (5). From previous investigators we obtained a data file for the cohort that included the following information for each employee: first and last name, social security number, date of birth, dates of hire and termination, sex, and race. We updated the information on employment status from personnel and benefits records.

Methylene chloride was the major solvent exposure to employees in the cellulose triacetate production process, but methanol was also used in a ratio of approximately one part methanol to ten parts methylene chloride, and acetone was used as well (5). An industrial hygiene survey conducted in 1977 reported 8-h time-weighted average (TWA) exposures ranging from below detectable limits up to 1700 ppm for methylene chloride, 1600 ppm for acetone, and 140 ppm for methanol among the workers in the extrusion and preparation areas (6). Respirators were not used until 1984. Detailed work history data are available only for 356 active employees and 119 employees who terminated their employment after 1979.

We ascertained vital status of the cohort for the period 1 January 1954 through 1 September 1986 by

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comparing the cohort roster with decedent records of the plant, the national death index, and the Social Security Administration (7, 8). A nosologist reviewed the death certificates and assigned codes to the underlying cause of death and contributing causes of death in accordance with the ninth revision of the International Classification of Diseases (ICD) (9). The 1149 employees not identified as deceased were assumed to be living at the end of the study period.

We compared the mortality of the cohort with the population of York County, South Carolina, which was the county of residence for 95 % of the cohort

members. During the study period, the cohort constituted less than 4 % of the York County population. Death rates for causes of death other than malignancies were unavailable for the reference population for years prior to 1962; therefore 1962 rates were used for the years 1954–1961. We used the occupational cohort mortality analysis program (OCMAP) to sum person-years within categories of age (five-year intervals), calendar period (five-year intervals), race (white/nonwhite), and sex and to compute standardized mortality ratio (SMR) values (10). We computed exact 95 % confidence limits for the SMR values using the mid-p method (11).

Table 1. Distribution of the cohort by vital status, sex, and race.

	Dead	Alive	Total
Men			
White	81	406	487
Nonwhite	12	52	64
Women			
White	29	586	615
Nonwhite	—	105	105
Total	122	1149	1271

Table 2. Observed (O) and expected (E) numbers of deaths from selected causes. (SMR = standardized mortality ratio, 95 % CI = 95 % confidence interval)

	O	E	SMR	95 % CI
All causes	122	141.94	0.86	0.71–1.03
Neoplasms				
Buccal cavity pharynx	2	0.87	2.31	0.39–7.60
Biliary passages & liver	4	0.70	5.75	1.82–13.78
Melanoma	2	0.88	2.28	0.38–7.51
Bronchus, trachea & lung	8	10.11	0.79	0.37–1.50
Breast	2	3.32	0.60	0.10–1.99
Pancreas	1	1.54	0.65	0.03–3.20
Accidents	21	12.77	1.64	1.05–2.47
Hypertension without heart disease	2	0.62	3.20	0.54–10.66
Cerebrovascular disease	5	8.90	0.56	0.21–1.25
Ischemic heart disease	31	34.33	0.90	0.62–1.27
Nonmalignant respiratory disease	4	6.04	0.66	0.21–1.60
Suicide	3	4.86	0.62	0.16–1.68

Table 3. Characteristics of the four employees who died of liver and biliary tract cancer.

Sex	Age (years)	Cause ^a	Autopsy	Medical record confirmation
Male	59	Cholangiocarcinoma of ampulla Vater (156.2)	No	Yes
Male	67	Adenocarcinoma of liver (155.2)	Yes	No
Female	60	Cholangiocarcinoma of hepatic and common bile ducts (156.1)	No	Yes
Female	47	Cholangiocarcinoma of common bile duct (155.1)	No	Yes

^a Code of the International Classification of Diseases, ninth revision, in parentheses.

Results

The demographic composition of the cohort was predominantly white (87 %) with a slight majority of women (57 %) (table 1). Ninety-six percent of the employees were less than 40 years of age when they were hired. Fifty-three percent of the cohort was employed for at least 10 years, although only 34 % of the person-time was contributed to this category of duration of employment. Everyone was hired after 1 January 1948. The hiring rate was stable over the study period and resulted in only 26 % of the person-time contributed by the cohort to the category of 20 or more years since first employment.

We identified 122 deaths in 29 960 person-years, and we obtained death certificates for 97 % of the decedents (118 of 122). We computed effect estimates for 62 causes of death. For most causes of death, the SMR values were close to the null value and therefore indicated no association. Table 2 presents the SMR and 95 % confidence interval (95 % CI) for diseases for which we observed an excess or deficit of at least one death. We have also included the results for pancreatic cancer in table 2 because it was the only cause of death reported to occur in excess in a previous study of a cohort exposed to methylene chloride (4).

We observed excess mortality for the following types of cancer: cancer of the buccal cavity and pharynx, cancer of the liver and biliary passages, and melanoma (table 2). We observed deficit mortality for cancer of the respiratory system, breast, and pancreas. Among the noncancer causes of death, we observed excess mortality from accidents and hypertension without heart disease. We observed deficit mortality for cerebrovascular disease, ischemic heart disease, and nonmalignant respiratory disease.

Because of the strong association with cancer of the liver and biliary passages, we conducted further analyses for this cause of death in which we stratified by time since first employment at the plant (<20 years, ≥20 years) and duration of employment at the plant (<10 years, ≥10 years). We used employment as a marker for exposure in this analysis because complete

work histories were unavailable for the entire cohort. This approach can overestimate both the duration of exposure (if there was employment in unexposed areas) and time since first exposure (if the first job was not in an exposed area). All of the deaths from cancer of the liver and biliary passages occurred among the workers with ten or more years of employment and at least 20 years since first employment (4 observed/0.35 expected).

We investigated further the medical histories of the four employees who died of cancer of the liver and biliary tract (table 3). For three decedents, the tumor sites were confirmed by medical records as intrahepatic and common bile duct, common bile duct, and ampulla of Vater. For the remaining death, no medical record could be obtained. This person was, however, the only decedent in the group for whom an autopsy had been performed, and the death certificate diagnosis was adenocarcinoma of the liver. Fortunately, the three employees who died of biliary cancer were in the group of 119 employees for whom we obtained complete work histories. The approximate durations of employment in jobs entailing substantial exposure to methylene chloride for the three biliary cancer deaths were 28 years, 20 years, and less than 1 year.

In general, it is desirable to estimate effects separately for different diseases. Unfortunately, cancer of the liver is combined with cancer of the biliary passages in the mortality data from York County, South Carolina, and therefore we could not use these data to compute the number of deaths expected from cancer of the biliary tract. The surveillance, epidemiology, and end results (SEER) program, however, provides detailed vital statistics for selected areas of the United States, and these statistics are intended to be representative of the entire population of the continental United States (12). We obtained SEER mortality rates for biliary cancer [ICD (eighth revision) codes 155.5, 156.1–156.9] for the years 1973–1977. We used these data to estimate the number of deaths expected from biliary cancer while controlling for the effects of age, race, and sex. We could not control for the effect of calendar period because mortality rates for biliary cancer were unavailable for the 1950s and 1960s. For the three deaths from biliary cancer in the cohort, we computed an estimate of 0.15 expected deaths (SMR 20, 95 % CI 5.2–56).

Discussion

We identified 122 deaths in an occupational cohort exposed to methylene chloride in the production of cellulose triacetate fiber. Since we did not verify the vital status of the 1149 employees not identified as deceased, we may have underestimated the total number of deaths in the cohort. Studies have shown that the national death index and the records of the Social Security

Administration may fail to ascertain mortality by approximately 10–20 % (7, 8).

For most causes of death, the results do not indicate an effect of exposure. In particular, this cohort experienced no excess mortality from ischemic heart disease, which is in agreement with the results reported for a cohort of photographic film manufacturers (4). Thus, within the limits of these two studies, any reduction in arterial oxygen content caused by methylene chloride being metabolized to carbon monoxide does not appear to have an adverse effect on mortality from ischemic heart disease.

Our study did not corroborate the association between methylene chloride exposure and death from pancreatic cancer that was found earlier for the photographic film manufacturers (4). Seven of the eight deaths from pancreatic cancer observed among the photographic film manufacturers occurred, however, more than 30 years after first employment. In our textile cohort only about 6 % of the total person-time was contributed by workers for whom at least 30 years had elapsed since first employment. This cohort, therefore, has not yet been followed long enough to be informative about exposure-disease relations with induction periods as long as 30 years. For this reason, the absence of a pancreatic cancer excess in this cohort is not inconsistent with the findings from the cohort of photographic film manufacturers.

We observed an excess of approximately three deaths from cancer of the biliary tract. Biliary cancer has not been previously reported to be associated with exposure to methylene chloride, acetone, or methanol. Bioassays have shown, however, that the inhalation of 2000 ppm of methylene chloride over a period of two years produces lung and liver tumors in mice and mammary tumors in rats (1, 3). Included among the non-neoplastic effects on the rats was fibrosis of the biliary tract (3). There is little information with which to compare the pharmacokinetics of methylene chloride in the biliary tracts of rats with that in the biliary tracts of humans. Thus the implications of the bioassays for the potential carcinogenicity of methylene chloride in the human biliary tract are unclear.

A study of Swedish painters revealed excess cancer of the intrahepatic bile ducts (13), and an excess of biliary cancer also has been reported for rubber workers (14). These cohorts were exposed to many solvents, however, and the results are difficult to interpret with regard to the effects of specific agents.

In the most recent follow-up of the cohort of photographic film manufacturing workers, Hearne et al (4) found no deaths from cancer of the liver or biliary tract (0.8 deaths were expected for these sites combined on the basis of New York State death rates) (T Hearne, personal communication). Eastman Kodak researchers are currently verifying the cause of death for all digestive cancers recorded for this cohort. The methylene

chloride exposures of the present study population appeared to have been considerably higher than the exposure levels experienced by the photographic film manufacturers, whose exposure was reported to average 26 ppm (TWA) over 22 years (4). If methylene chloride causes biliary tract cancer, it may do so at levels of exposure experienced by the cohort of textile production workers but not at the levels experienced by the cohort of photographic film workers. Another important difference between these cohorts is that the photographic film manufacturers were all men, whereas our cohort of textile workers was mostly women. Two of the biliary cancer decedents in this study were women. In this regard, a recent study revealed an association between solvent exposure and biliary cancer in women but not in men (15).

The excess deaths from bile duct cancer in our cohort might have been caused by other risk factors for these cancers. But biliary cancer has not been the subject of much study, and few risk factors have been identified. The use of oral contraceptives is associated with liver tumors (16), and there have been two reports of biliary cancer in women aged 21 and 29 years with a recent history of oral contraceptive use (17, 18). Oral contraceptive use is common among young women, however, and a possible relation between oral contraceptives and biliary cancer has not been studied epidemiologically. Two of the three deaths from biliary cancer in this cohort occurred in women; their ages (47 and 60 years), however, are not typically associated with recent use of oral contraceptives. It is possible that, if oral contraceptives cause biliary cancer, they do so only after a long induction period; the case reports, however, would suggest otherwise. Cancer of the bile ducts is associated with a medical history of chronic ulcerative colitis and gallstones (19), but neither of these factors was noted in the medical records.

In this cohort the excess deaths from accidental causes were of interest in light of the neurobehavioral effects of methylene chloride (20). This study did not take into account the effects of many other risk factors for accidental death (eg, alcohol consumption, amount of automobile driving, etc), however, and cannot be assumed to measure accurately the effect of methylene chloride on accidental deaths.

In summary, we did not observe a previously reported excess of mortality from pancreatic cancer (4). If methylene chloride causes pancreatic cancer, it may do so after long induction times not yet experienced by this cohort. The strongest association observed in this study was an excess of mortality from cancer of the bile ducts, an association that was not observed in a study made in the photographic industry (4). If the excess of cancer of the bile ducts is a direct result of methylene chloride exposure, then the absence of such an excess in the study by Hearne et al (4) may indicate a threshold dose below which there is no effect.

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