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Mortality update of cellulose fiber production workers

by Stephan F Lanes, PhD,¹ Kenneth J Rothman, DrPH,^{1,2} Nancy A Dreyer, PhD,¹ Kevin J Soden, MD³

LANES S, ROTHMAN KJ, DREYER NA, SODEN KJ. Mortality update of cellulose fiber production workers. *Scand J Work Environ Health* 1993;19:426—8. Mortality ascertainment was extended through 1990 for a cohort of 1271 workers involved in the production of cellulose triacetate fiber at a plant in Rock Hill, South Carolina. 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. Median exposures in 1977 ranged from 140 to 745 ppm (8-h time-weighted average). The observed numbers of deaths from specific causes were compared with the expected numbers of deaths computed from rates in York County, South Carolina. For most causes of death, there was little if any association with employment. Among causes of particular interest, no new deaths were observed from cancer of the liver and biliary tract, although the excess from the earlier study persisted (4 observed, 1.34 expected). No excess mortality was observed for cancer of the pancreas (2 observed, 2.42 expected) or for ischemic heart disease (43 observed, 47.8 expected).

Key terms: biliary tract cancer, carboxyhemoglobin, carcinogenicity, cardiovascular disease, follow-up study, liver cancer, methylene chloride, pancreatic cancer, solvent.

We have been monitoring mortality among workers involved in the production of cellulose triacetate fiber at a plant in Rock Hill, South Carolina in the United States (1). The cohort was assembled in 1977 for the purpose of investigating potential health effects of exposure to methylene chloride (dichloromethane) (2). It included all 1271 workers employed in the preparation or extrusion areas of the plant for at least three months between 1 January 1954 and 1 January 1977. Although methylene chloride was the principal solvent exposure in these areas, methanol and acetone were also used. Industrial hygiene monitoring in 1977 revealed 8-h time-weighted average (8-h TWA) concentrations of methylene chloride ranging from below detectable limits to 1700 ppm among employees in the extrusion and preparation areas (3). The median exposure levels (8-h TWA) for the workers in the three main areas were 140, 280, and 475 ppm (2). Details of the cohort have been described elsewhere (1, 2).

The cohort was initially assembled for a study of the possible effects of methylene chloride exposure on cardiovascular disease (2). Methylene chloride is metabolized to carboxyhemoglobin, and this metabolism reduces the arterial oxygen concentration,

which in turn is hypothesized to increase the risk of ischemic heart disease (2, 4). Another cohort exposed to smaller concentrations of methylene chloride showed no excess deaths from ischemic heart disease, but initial observations indicated an excess of pancreatic cancer (5) that has decreased with continued follow-up (6). In our previous report of mortality through September 1986, no excess deaths from ischemic heart disease or pancreatic cancer were observed, but four deaths in the category containing cancer of the biliary tract or liver exceeded the expectation of less than one death (1). Though based on small numbers, the excess appeared to be related to duration of employment and time since first employment. In a recent proposal to lower the standard for occupational exposure to methylene chloride, the earlier findings for biliary tract and liver cancer formed the basis for concern expressed by the Occupational Safety and Health Administration about the carcinogenicity of methylene chloride (7).

Materials and methods

Previous searches of the National Death Index and the Social Security Administration's Death Master Files identified 122 deaths through September 1986. We have now used the same sources to extend mortality ascertainment through December 1990 and have identified 50 new deaths, bringing the total to 172 deaths. We used the local population of York County, South Carolina, to compute the numbers of deaths expected in the cohort under the hypothesis that mortality is unrelated to employment at the plant. For each cause of death, the ratio of observed to expected number of deaths has been reported as a standardized mortality ratio (SMR), controlled for age,

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race, gender, and calendar period, along with its 95% confidence interval (95% CI).

Results

The overall SMR from all causes of death combined was 0.90, and the SMR for malignant neoplasms was 0.82 (table 1). There were 43 deaths from ischemic heart disease, with an SMR of 0.90 (95% CI 0.65–1.21). To investigate further the possibility that methylene chloride causes an acute increase in the risk of ischemic heart disease, we restricted the analysis of ischemic heart disease to active employees and included any deaths that occurred within one month of the date of termination. Eleven deaths were classified as occurring among active employees, producing an SMR of 0.67 (95% CI 0.34–12.0). If the period in which the deaths are considered to have occurred among active employees is extended to one year from the date of termination, only two additional deaths would be included.

Among the malignant neoplasms, the largest SMR was recorded for cancer of the biliary passages and liver, with four observed deaths (SMR 2.98, 95% CI 0.81–7.63). Each of these deaths occurred among employees with at least 10 years of employment and at least 20 years since first employment, yielding an SMR of 5.83 (95% CI 1.59–14.92) for this subgroup. For one of these cases, the work history indicated less than one year of employment in an area involving exposure to methylene chloride. There were two deaths from pancreatic cancer and 2.42 expected, for an SMR of 0.83 (95% CI 0.10–2.99). The observed numbers of deaths from other forms of cancer were also close to their expected values.

Discussion

We observed no excess deaths from ischemic heart disease (SMR 0.90). One possible limitation in this regard is that we used a general population comprising both unemployed and employed individuals as the comparison group. Since mortality from cardiovascular disease in occupational cohorts is typically approximately 20–30% less than in general populations (the "healthy worker" effect), the SMR could be an underestimate.

The inhalation of methylene chloride increases the level of carboxyhemoglobin and is hypothesized to increase the risk of ischemic heart disease. This increased risk is expected to be transient, lasting approximately as long as the carboxyhemoglobin concentration remains elevated, just as a smoker's risk of ischemic heart disease begins to decline upon cessation of smoking. This mechanism implies that a direct effect of methylene chloride on ischemic heart disease should be concentrated among active employees. When we restricted the analysis to active employees, the SMR for ischemic heart disease decreased to 0.67. Although restricting the analysis to

Table 1. Data on deaths from selected causes. (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio, 95% CI = 95 % confidence interval)

Cause of death	O	E	SMR	95% CI
All causes	172	192.18	0.90	0.77–1.04
Malignant neoplasms	39	47.7	0.82	0.58–1.52
Buccal cavity	2	1.34	1.50	0.18–5.40
Biliary passages and liver	4	1.34	2.98	0.81–7.63
Melanoma	2	1.03	1.94	0.24–7.00
Bronchus, trachea and lung	13	16.21	0.80	0.43–1.37
Breast	3	5.59	0.54	0.11–1.57
Pancreas	2	2.42	0.83	0.10–2.99
Accidents	24	15.94	1.51	0.97–2.28
Cerebrovascular disease	7	13.00	0.54	0.22–1.11
Ischemic heart disease	43	47.77	0.90	0.65–1.21
Nonmalignant respiratory disease	8	8.29	0.97	0.42–1.90
Suicide	4	5.21	1.19	0.39–2.77

active employees should identify the employees at greatest risk from methylene chloride, it would also amplify the healthy worker effect. Thus the decrease in the SMR of the active employees does not rule out the possibility that methylene chloride increases the risk of mortality from ischemic heart disease.

If there is an effect of methylene chloride on mortality from ischemic heart disease, however, it must be so small that it is completely overshadowed by the healthy worker effect. A design that would be more sensitive to this small effect, should it exist, would be to compare incidence rates of ischemic heart disease among active employees who are and who are not exposed to methylene chloride. Unfortunately, we cannot make these comparisons in this cohort because unexposed employees were excluded from the cohort when it was assembled (2).

Previously we reported four deaths from cancer of the biliary passages and liver with 0.70 deaths expected (SMR 5.75, 95% CI 1.82–13.8) (1). In this update, an additional 0.64 deaths were expected, but none was observed. We used a likelihood approach to evaluate the consistency of the new data with the estimate obtained previously (SMR 5.75) and with the null hypothesis of no effect (SMR 1.0). If it is assumed that the true value of the SMR is 5.75, then 3.68 deaths should have been observed during the current follow-up period, in which 0.64 deaths were expected. With the use of the Poisson distribution, the likelihood that we would actually observe zero deaths under these assumptions can be computed as $e^{-3.68} = 0.025$ (8). Alternatively, if the true value of the SMR were 1.0, the likelihood of observing zero deaths is $e^{-0.64} = 0.527$. The ratio of the likelihoods for these two hypotheses ($0.527/0.025 \approx 21$) indicates that the new data are 21 times more likely if the SMR is equal to the null value (SMR 1.0) than if the SMR is equal to the previously reported estimate. According to the overall data collected, there is still a small excess of cancer of the liver and biliary passages, but the wide confidence interval indicates that the find-

ing remains statistically unstable and warrants continued monitoring.

To date, most of the effect estimates have been close to the null value, consistent with the absence of any adverse effects of methylene chloride on mortality. The main limitation of this analysis is that the cohort is young. As the cohort ages, estimates of potential effects will become more precise and more informative about delayed effects.

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