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Health evaluation of employees occupationally exposed to methylene chloride

Mortality

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OTT MG, SKORY LK, HOLDER BB, BRONSON JM, WILLIAMS PR. Health evaluation of employees occupationally exposed to methylene chloride: Mortality. *Scand j work environ health* 9 (1983): suppl 1, 8–16. Methylene chloride is partially metabolized to form carboxyhemoglobin, the probable result being a reduction in oxygen availability to the myocardium. Thus, among exposed individuals, there could be a potential for an increased risk of ischemic events, particularly among those with advanced coronary artery disease. The present retrospective cohort study focused on ischemic heart disease deaths among employees of a fiber production plant in which methylene chloride was used as a general purpose solvent. The range of methylene chloride exposure was a time-weighted average of approximately 140–475 ppm. In comparison to the mortality of the general population of the United States, there was no significant increase in overall mortality or in deaths due to ischemic heart disease. Further analyses of ischemic heart disease mortality by employment status, duration of exposure, and follow-up interval did not reveal any exposure-related effect either. Thus, given qualifications relative to statistical power and possible confounding bias (eg, healthy worker effect) attendant with this study, no mortality effects attributable to methylene chloride exposure were found.

Key terms: death, ischemic heart disease.

Concerns regarding possible health hazards of methylene chloride ($MeCl_2$) have been raised on the basis of its metabolism to form carboxyhemoglobin (7, 14). Increased blood carboxyhemoglobin potentially reduces oxygen availability to the heart and thereby could increase the risk of ischemic events, particularly in persons with advanced coronary artery disease. The interest in adverse cardiovascular outcomes in relation to methylene chloride exposure also stems in part from the possibility that very high acute exposures to methylene chloride (eg, greater than 2 %) may directly sensitize the myocardium to epinephrine (13). However, excursion exposures of this magnitude are extremely unlikely.

The present cohort mortality study was conducted in conjunction with a detailed health evaluation offered to the current workforce of two fiber production plants. The plant of primary interest was one which used methylene chloride; the second plant was included for comparative purposes. For the aforestated reasons attention was focused on cardiovascular disease deaths, particularly those in which the underlying cause was ischemic heart disease and those which occurred among the active workforce. However, overall mortality and deaths due to malignant neoplasms and external causes were also investigated.

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In a prior study, Friedlander and his coworkers (5, 6) had found that mortality among men occupationally exposed to methylene chloride was consistent with that of industrial referents and was less than that of the general population. Furthermore, an examination of specific causes of death did not reveal excess risks for ischemic heart disease or site specific malignant neoplasms. The population studied was a moderately large male population, whose methylene chloride exposures were judged to have been in the range of 30 to 125 ppm. In contrast to the Friedlander study, the present cohort included both men and women. The methylene chloride exposure intensities were higher for the present cohort; however, the duration of exposure was generally less since methylene chloride use began in the plant of the present study in 1954, whereas its use in operations covered by the Friedlander study predates the 1950s.

Methods

The overall study design and objectives of this research, as well as environmental considerations, are contained in a prior report (11). The cohorts of interest consisted of production employees who worked for at least three months in the preparation or extrusion areas of either plant subsequent to 1 January 1954 and prior to 1 January 1977. The preparation and extrusion departments were chosen because of the high potential for exposure to the solvent system used at each location. In the plant with methylene chloride exposure, located in Rock Hill, SC, both cellulose diacetate (acetate) and cellulose triacetate (CTA) fibers were manufactured in adjacent work areas. Methylene chloride was the major component of the solvent system used in the CTA production, whereas acetone was the solvent of choice in the acetate production. Only acetone was present in the reference plant (located in Narrows, VA), as production was limited to acetate fibers.

Methylene chloride exposure concentrations in the plant using methylene chloride were estimated to be an 8-h time-weighted average (TWA) of 140 ppm in areas of low methylene chloride use (mixed acetate and CTA production) (11). Some employees worked in intermediate exposure areas or intermittently in areas of both high and low methylene chloride use. Approximately 25 % of the workforce was assigned to a high use area. Methanol was a component of the solvent system in the CTA production and was present in a ratio of approximately 1 to 10 to methylene chloride. Acetone exposures in both plants ranged from a TWA of about 100 ppm to a TWA of over 1,000 ppm, depending on the work area. Generally the acetone exposure was the lowest in areas of high methylene chloride use. Details concerning the environmental exposure assessment may be found in our prior report (11).

Service employees (machine cleaners and janitors) were incuded in the exposed, but not in the reference, cohort. In the reference plant, service employees were assigned work throughout the plant complex, and therefore no records were available to determine which of these employees had worked in the preparation or extrusion departments.

The vital status of the employees in the two cohorts was established through company records, telephone and mail contact, motor vehicle registration searches, and, finally, through a submission of names to the Social Security Administration. The data obtained through the social security submission gave positive identification of decedents, but did not distinguish between alive and unknown status for other employees. In general, the social security identification of deceased men appears to have been reasonably complete since the 1950s (10, 12). In the present study, analyses were performed assuming the persons not identified as deceased by the Social Security Administration both to be living and to be lost to follow-up. The latter assumption would likely lead to a slight upward bias in risk ratios, while the former assumption leads to a slight downward bias.

The mortality experience of the two cohorts was followed from three months after the entry date through June 1977. Expected deaths were computed by the indirect method, United States white male, nonwhite male, and white female mortality data (five-year age intervals and five-year calendar periods of time) being used and 1975 being the most recent year with

national data available. Expected deaths were not computed for nonwhite women as no deaths were observed among the 108 nonwhite women in the study. Person-years were accumulated on a month-by-month basis, and comparisons in the ex-

Table 1. Vital and employment status of the exposed and reference cohorts as of 30 June 1977.

Population group	Working	Retired	Left employment			Total
			Deceased (company records)	Deceased	Alive per social security and/or personal follow-up	
Exposed cohort						
White						
Men	174	19	21	16	257	487
Women	195	10	1	10	399	615
Nonwhite						
Men	47	1	5	1	10	64
Women	97	–	–	–	8	105
Total	513	30	27	27	674	1,271
Reference cohort						
White						
Men	432	47	22	2	193	696
Women	148	15	1	2	82	248
Nonwhite						
Men	1	–	–	–	–	1
Women	3	–	–	–	–	3
Total	584	62	23	4	275	948

Table 2. Vital status follow-up of 980 employees who left employment prior to 30 June 1977.

Population group	Known deceased[a]	Known alive (personal contact)	Social security search only	Total
Exposed chort	27	448	226	701
Men				
Prior to 1960	7	39	38	84
1960–1969	9	59	45	113
In or after 1970	1	66	20	87
Women				
Prior to 1960	5	54	34	93
1960–1969	4	119	63	186
In or after 1970	1	111	26	138
Reference cohort	4	163	112	279
Men				
Prior to 1960	0	6	1	7
1960–1969	2	52	35	89
In or after 1970	0	59	40	99
Women				
Prior to 1960	2	6	10	18
1960–1969	–	29	15	44
In or after 1970	–	11	11	22

[a] Includes 15 deaths identified through personal follow-up and 16 deaths identified from Social Security Administration records.

posed cohort were based on Poisson distribution assumptions using the tables of Bailar & Ederer (1). Direct comparisons of standardized mortality ratios (SMRs) between the two cohorts were not made. Miettinen has pointed out the potential problems of such comparisons (9). In particular, SMR estimates are internally standardized to each subgroup and, therefore, are not mutually comparable when differences exist in the age-sex-race-specific distributions of the subgroups. The solution to this difficulty used in the present investigation was to compute stratum-specific numbers of observed and expected deaths for each subgroup and to compare the subgroups, conditioned on equating total observed and expected deaths within each stratum. Stratification was based on age at entry, years since entry, and length of employment. A summary statistic was calculated that is analogous to the Mantel-Haenszel statistic except that external information has been incorporated into the estimation procedure and a multinomial model replaces the hypergeometric one. Confirmatory analyses were also carried out based on Cox's regression model ignoring external information (2). Both approaches presume an underlying multiplicative hazard model.

Results

The vital and employment status of both the exposed and reference cohorts are presented in table 1. The exposed cohort was larger than the referent one (1,271 vs 948 persons) and differed in sex and racial composition. There were more women and nonwhites in the exposed cohort and more white men in the reference cohort. Of the 1,271 individuals in the exposed cohort, 701 (55 %) left employment between 1954 and 1977, whereas 279 (29 %) persons in the reference cohort left employment during the same years.

Vital status ascertainment for the 980 employees who left the company is summarized in table 2. The initial follow-up through personal contact with former employees or their relatives led to verification of 611 living persons and 15 dece-

Table 3. Number of deaths and number of men at risk in the exposed and reference cohorts by year of first exposure and duration of exposure.

Year of first exposure	Duration of exposure								Total	
	< 1 year		1–4 years		5–9 years		≥ 10 years			
	Deaths	Risk	Deaths	Risk	Deaths	Risk	Deaths	Risk	Deaths	Risk
Complete exposed cohort										
1954–1959	3	40	4	60	6	27	5	88	18	215
1960–1969	–	8	1	34	–	14	–	19	1	75
1970–1976	2	40	1	60	–	–	..	..	3	100
1954–1976	5	88	6	154	6	41	5	107	22	390
Service employees in the exposed cohort										
1954–1959	–	6	4	22	4	13	9	54	17	95
1960–1969	–	6	–	10	1	10	3	22	4	48
1970–1976	–	2	–	15	–	1	..	..	–	18
1954–1976	–	14	4	47	5	24	12	76	21	161
Reference cohort[a]										
1954–1959	–	4	1	12	3	13	18	218	22	247
1960–1969	–	39	1	98	–	77	1	95	2	309
1970–1976	–	53	–	85	–	3	..	..	–	141
1954–1976	–	96	2	195	3	93	19	313	24	697

[a] Year of first exposure is the earliest date subsequent to 1953 that the employee worked in the preparation or extrusion area of the reference plant. Solvent exposure was only to acetone.

dents. A list of the remaining 354 former employees was submitted to the Social Security Administration for further follow-up. Positive identification of 16 additional decedents was obtained. Thus, although exception reporting was complete for both cohorts, confirmative information on vital status was not available for 226 (18 %) persons in the exposed cohort and 112 (12 %) individuals in the reference cohort. However, previous experience with social security follow-up indicates that few deaths

Table 4. Number of deaths and number of women at risk in the exposed and reference cohorts by year of first exposure and duration of exposure.

Year of first exposure	Duration of exposure								Total	
	< 1 year		1–4 years		5–9 years		≥ 10 years			
	Deaths	Risk	Deaths	Risk	Deaths	Risk	Deaths	Risk	Deaths	Risk
Complete exposed cohort										
1954–1959	2	37	3	69	1	41	4	113	10	260
1960–1969	–	40	1	101	–	73	–	56	1	270
1970–1976	–	39	–	120	–	23	..	..	–	182
1954–1976	2	116	4	290	1	137	4	169	11	712
Service employees in the exposed cohort										
1954–1959	–	–	–	–	–	2	–	–	–	2
1960–1969	–	–	–	1	–	–	–	–	–	1
1970–1976	–	–	–	4	–	1	..	..	–	5
1954–1976	–	–	–	5	–	3	–	–	–	8
Reference cohort[a]										
1954–1959	–	9	2	18	–	18	–	46	2	91
1960–1969	–	10	–	15	–	13	–	12	–	50
1970–1976	–	28	1	77	–	5	..	..	1	110
1954–1976	–	47	3	110	–	36	–	58	3	251

[a] Year of first exposure is the earliest date subsequent to 1953 that the employee worked in the preparation or extrusion area of the reference plant. Solvent exposure was only to acetone.

Table 5. Observed and expected deaths[a] in the exposed cohort by cause, sex and race, 1954 – June 1977.

Cause of death category	White men			Nonwhite men			White women		
	Observed	Expected[b]	Expected[c]	Observed	Expected[b]	Expected[c]	Observed	Expected[b]	Expected[c]
All causes	37	34.9	30.4	6	6.4	5.6	11	15.9	13.5
Malignant neoplasms	5	6.3	5.6	–	0.9	0.9	2	5.2	4.5
Diseases of circulatory system	11	14.0	12.4	4	2.2	2.0	3	3.7	3.2
Ischemic heart disease	10	10.5	9.4	2	1.1	1.1	2	1.6	1.4
Symptoms, senility and ill-defined conditions	2	0.5	0.5	–	0.2	0.2	–	0.3	0.2
All external causes	12	7.9	6.5	2	1.6	1.3	4	2.9	2.4
Accidents	9	5.4	4.4	1	0.8	0.6	3	1.7	1.4
Suicide	2	1.7	1.4	–	0.1	0.1	1	0.9	0.7
Residual	4	6.2	5.4	–	1.5	1.2	1	3.8	3.2
Unable to locate death certificate	3	0.0	0.0	–	0.0	0.0	1	0.0	0.0

[a] Expected deaths calculated from United States death rates for white men, nonwhite men, and white women, respectively. There were no deaths among the 107 nonwhite women in the exposed cohort.
[b] Individuals presumed living through the end of the follow-up period if not identified in the social security records as deceased.
[c] Individuals presumed lost to follow-up if not contacted and known to be living.

were apt to have been missed.

The distribution of deaths relative to the number of persons at risk is given by year of first exposure and duration of exposure for the men (table 3) and women (table 4) in both cohorts. Data for service only employees of the exposed plant are presented separately, since employees in the reference plant with similar work assignments were not included in the study.

Observed and expected deaths are summarized by cause for the exposed cohort in table 5. Expected deaths were computed under two separate assumptions: first, by assuming individuals not identified as deceased by the Social Security Administration to be alive and, second, by assuming these same individuals were lost to follow-up although accepting identification of deaths by the Social Security Administration. Overall mortality was comparable to that of the corresponding United States population. There was a relative excess of deaths due to external causes in each of the three sex-by-race subgroups of the cohorts. When the observed and expected deaths were summed across the three subgroups, and the conservative estimates of expected deaths were used for comparison, a significant difference was attained for "all external causes" (18 observed vs 10.2 expected, $p < 0.05$) and the subcategory "accidents" (13 observed vs 6.4 expected, $p < 0.05$). A review of the 10 deaths due to accidents among the men revealed that four involved automobile collisions; one each was described as a pedestrian-automobile accident, an industrial accident (past employee of the plant with methylene chloride exposure who was working for another company at the time of the accident), a house fire, a drowning, and a home accident; and, finally, there was one death in which the circumstances of the accident were unknown. Four of the men had left employment at least two years prior to death, and a fifth man had been working in another area of the plant complex. The three accidental deaths among the women occurred at least 10 years after the last methylene chloride exposure.

Among the exposed employees, seven deaths due to malignant neoplasms were observed compared to 12.4 expected deaths. The site-specific distribution of cancer deaths was also similar to the expected value. Among the men the sites were lung (2 cases), pancreas, bladder and blood-forming organs (acute monocytic leukemia), and among the women they were lung and primary unknown.

Mortality contrasts between the exposed and reference cohorts are shown in table 6. For white women, there were no differences in cause-specific mortality between the two. Among white men, statistical differences in risk were observed for "all causes," risk ratio 2.2 ($p < 0.01$), "diseases

Table 6. Mortality contrasts between the exposed and reference cohorts by cause of death category — White men and women.

Cause of death category	Deaths								Risk estimates (exposed cohort : reference cohort)			
	Exposed cohort				Reference cohort				Conditional risk		Cox regression analysis	
	Men		Women		Men		Women					
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Men	Women	Men	Women
All causes	37	34.9	11	15.9	24	53.8	3	6.7	2.2**	1.3	2.1**	1.5
Malignant neoplasms	5	6.3	2	5.2	5	10.0	2	2.3	1.2	NC[a]	1.3	NC
Diseases of circulatory system	11	14.0	3	3.7	9	23.0	1	1.9	2.2*	NC	1.9	NC
Ischemic heart disease	10	10.5	2	1.6	6	17.4	1	0.9	3.1*	NC	2.6	NC
Symptoms, senility and ill-defined conditions	2	0.5	–	0.3	1	0.8	–	0.1	NC	NC	NC	NC
All external causes	12	7.9	4	2.9	5	10.6	–	1.0	2.5*	NC	2.6*	NC
Accidents	9	5.4	3	1.7	4	7.2	–	0.6	2.5	NC	2.7	NC
Suicide	2	1.7	1	0.9	1	2.3	–	0.3	NC	NC	NC	NC
Residual	4	6.2	1	3.8	4	9.4	–	1.4	NC	NC	NC	NC
Unable to locate death certificate	3	0.0	1	0.0	–	0.0	–	0.0	0.0	0.0	0.0	0.0

[a] NC = not computed due to small number of deaths.
* $p < 0.05$, ** $p < 0.01$.

Table 7. Observed and expected deaths due to ischemic heart disease in the exposed cohort by duration of exposure, subsequent follow-up interval and employment status, 1954 – June 1977.

Duration of exposure	Total cohort						Actively working for company					
	White men		Nonwhite men		White women		White men		Nonwhite men		White women	
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
< 5-year exposure												
< 5-year follow-up	1	0.9	–	0.2	–	0.2	–	0.7	–	0.2	–	0.1
5 – 9-year follow-up	–	0.4	–	0.1	–	0.1	–	0.1	–	0.0	–	0.0
≥ 10-year follow-up	1	2.2	1	0.1	–	0.3	–	0.1	–	0.0	–	0.0
5 – 9-year exposure												
< 5-year follow-up	2	1.1	–	0.2	–	0.2	2	1.1	–	0.2	–	0.1
5 – 9-year follow-up	–	0.2	–	0.1	–	0.1	–	0.0	–	0.0	–	0.0
≥ 10-year follow-up	–	0.3	–	0.1	–	0.1	–	0.0	–	0.0	–	0.0
≥ 10-year exposure												
< 5-year follow-up	2	1.6	–	0.1	–	0.2	2	1.5	–	0.1	–	0.1
5 – 9-year follow-up	3	2.1	–	0.2	2	0.2	3	1.5	–	0.2	–	0.2
≥ 10-year follow-up	1	1.6	1	0.1	–	0.2	–	0.8	1	0.1	–	0.1
Total	10	10.5[a]	2	1.1	2	1.6	7	5.9	1	0.8	–	0.7

[a] Expected numbers of deaths may not be additive due to round-off errors and the presumption that the social security follow-up was complete.

of the circulatory system," risk ratio 2.2 ($p < 0.05$), and "all external causes," risk ratio 2.5 ($p < 0.05$), based on conditional risk estimates incorporating external information. Similar risk estimates were obtained based on Cox regression analyses using age at entry as the only covariate. A significant risk ratio was also observed for the subcategory "ischemic heart disease" ($p < 0.05$), but not for "accidents" ($p = 0.08$). Observed deaths were considerably less than expected (United States mortality experience) in the reference group for each of the categories in which significant differences between cohorts had been found.

Mortality due to ischemic heart disease among the exposed participants is presented by duration of exposure, length of follow-up, and employment status in table 7. Overall, there were 14 observed compared to 13.2 expected deaths. With a subcategorization of this detail, the expected numbers of deaths in any given cell of the table were small, and thus weak associations would be difficult to detect. There were, however, no definite trends in the data with respect to duration of exposure, follow-up interval, or employment status. Of particular interest was the relationship between employment status and ischemic heart disease. Eight of the 14 deaths due to ischemic heart disease had occurred among actively working employees. This value compares with 7.4 expected deaths based on United States mortality experience. Similar analyses with respect to the "all causes" of death and other cause of death categories revealed no trends indicative of an exposure effect.

Discussion

The mortality experience of the exposed cohort was comparable to that of the corresponding United States population with the possible exception of deaths due to external causes. A review of the deaths in the exposed cohort did not reveal a pattern suggestive of an occupational etiology.

Since there were apparent differences in the mortality experience of white men in the exposed and reference cohorts, possible reasons for these differences were explored. We first examined available mortality data and population characteristics for the counties in which the two plants were located. Population characteristics, as determined in the 1960 United States census, confirmed our impression of urban-rural differences between the two counties (exposed plant county 48 % rural, reference plant county 85 % rural). An investigation of the geographic patterns of cardiovascular disease mortality (1968–

1971) found the Southeastern United States (area includes the exposed plant county) to have the highest standardized death rates due to cardiovascular disease of any area of the country (3). On the basis of further communications with the authors of that report, cardiovascular disease mortality in the exposed plant county was determined to have been 31 % above the national average. Cardiovascular disease mortality in the reference plant county was 11 % above the national average. In light of these data, the mortality trends observed for the exposed plant are in a consistent direction with the expected geographic differences in mortality, namely, higher cardiovascular disease mortality in the exposed plant county in comparison to the reference plant county, and in the exposed plant county in comparison to the United States population. Furthermore, a mortality study of two cotton mills, involving similar operations but not methylene chloride exposure, in the neighboring state of North Carolina reported standardized mortality ratios of 98 for men and 84 for women, the cause-specific standardized mortality ratio for arteriosclerotic heart disease being 103 for white men and 128 for white women (8). These ratios are similar to those of the exposed plant but not those of the reference plant. The low death rates for the reference cohort are not explained by either the geographic mortality patterns or other occupational data.

Selection factors (eg, hiring practices) and employee recordkeeping procedures were also investigated in relation to the mortality differences between white men in the two cohorts. As both plants belonged to the same parent company, no differences were anticipated in the record retention policy between the two locations. Discussions with the respective personnel managers from each plant did not uncover any differences in the retention of work history records for former employees. Hiring practices were indirectly examined through the comparison of the distribution of white men by age at the time of hiring. Of the 696 white men in the reference cohort, 497 (71.4 %) were under the age of 25 at the time of hiring and only 35 (5.0 %) were at least 35 years of age. In contrast only 217 of 491 (44.2 %) of the white men in the exposed cohort were under the age of 25 at the time of hiring, and 80 (16.3 %) were 35 years of age or older. These differences, together with the higher employee turnover rates in the exposed plant, indicate that hiring practices were dissimilar in the two plants. The apparent lack of comparability in hiring practices also indicates a need for caution in the comparison of mortality between the two cohorts. One possible explanation for the very low death rates in the reference plant is that the company, being the only large-scale employer in that area, was able to be more selective in hiring.

Mortality data from the present study do not indicate that exposure to methylene chloride, low concentrations of methanol, and variable concentrations of acetone has had an adverse impact on the health of exposed employees. This interpretation requires qualification, in part, because of the small numbers of observed and expected deaths for contrasts of particular interest. For example, on the basis of United States death rates only 7.4 deaths due to ischemic heart disease were expected among active employees of the exposed plant. Eight deaths were actually observed. Thus, the healthier than average status of typical working populations (4) and the low power for detecting moderately elevated risks being considered, our results do not exclude the possibility of increased health risks in this population. With this qualification in mind, the findings of the present study are in agreement with those of the Friedlander study previously discussed, but they do not preclude the need for mortality studies of other working populations exposed to methylene chloride. The present study extends the coverage of exposed populations to both men and women, and the conditions of exposure to higher TWA concentrations of methylene chloride than in the previously reported study.

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