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Health evaluation of employees occupationally exposed to methylene chloride

General study design and environmental considerations

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OTT MG, SKORY LK, HOLDER BB, BRONSON JM, WILLIAMS PR. Health evaluation of employees occupationally exposed to methylene chloride: General study design and environmental considerations. *Scand j work environ health* 9 (1983): suppl 1, 1–7. Recent concern regarding health hazards of methylene chloride stem primarily from the discovery of its metabolism to carboxyhemoglobin. In this report, a research program is described, the purpose of which was to assess potential health effects of methylene chloride exposure in an occupational setting. Particular attention was given to evaluating possible direct and carboxyhemoglobin-mediated effects on the hematopoetic and circulatory systems. The study involved one fiber production plant which used a methylene chloride/methanol mixture and acetone as solvents and a second fiber production plant that used acetone only. The research design included a retrospective cohort mortality study and several health evaluation studies, as well as an environmental assessment of the two plants. Industrial hygiene monitoring indicated that typical methylene chloride exposures ranged from an 8-h time-weighted average of 140 ppm in areas of low methylene chloride use to a corresponding average of 475 ppm in areas of high methylene chloride use and that methanol was present in about a one to ten ratio to methylene chloride. Acetone exposures in both plants ranged from 100 to over 1,000 ppm (time-weighted average).

Key terms: carboxyhemoglobin-mediated effects, circulatory system, environmental assessment, health evaluation, hematopoetic system, retrospective cohort mortality study.

Methylene chloride ($MeCl_2$) is an important commodity chemical with a variety of end uses as a nonflammable industrial solvent. Its toxicity has generally been regarded to be low in comparison to that of other chlorinated methanes, a principle concern being anesthetic effects at high concentrations (7).

In 1972 a finding of increased carboxyhemoglobin (COHb) was reported among persons exposed to the solvent in an experimental setting (10). This observation was subsequently confirmed and was determined to be due to the metabolism of methylene chloride to form carboxyhemoglobin (3, 8, 9). A second metabolic pathway for the degradation of methylene chloride has also been identified (1). Of the two routes of metabolism, the first-mentioned oxidative pathway has received more attention than the glutathione-dependent pathway to carbon dioxide. Further studies on the uptake, metabolism, and elimination of methylene chloride in humans have been reported by DiVincenzo & Kaplan (4, 5).

Discovery of the oxidative pathway led to a reconsideration of the potential hazards of methylene chloride exposure, particularly in regard to carboxyhemoglobin-related effects on the cardiovascular sys-

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tem. Increased carboxyhemoglobin has been associated with decreased maximal aerobic capacity, a decrease in time to onset of angina during exercise for men with ischemic heart disease, a decrement in visual function, and, at high levels, severe headaches (2, 6, 11). Although extensive literature exists regarding carbon monoxide toxicity, Turino recently indicated that adequate data were not yet available to assess the effects of chronic carbon monoxide exposure resulting in 5–10 % carboxyhemoglobin saturations (12).

The present research was undertaken to develop a better understanding of any effects of exposure to methylene chloride on an employee population, particularly effects that might be mediated through the metabolism of methylene chloride to form carboxyhemoglobin. This research included an industrial hygiene assessment of the work environment, a retrospective cohort mortality study, and several health evaluation studies.

Overall study design

Initially a search was made of industrial users of methylene chloride to identify a work setting in which the agent was present at concentrations approaching the existing standard of the Occupational Safety and Health Administration (OSHA), an 8-h time-weighted average (TWA) of 500 ppm (29 CFR Par 1910.1000, table Z-2), and for which multiple chemical exposures were not considered a major complicating factor. An additional consideration was that a reference plant in which methylene chloride was not present be available for comparison.

The plant selected for study in relation to methylene chloride exposure was located in Rock Hill, SC, and was part of a multiplant complex that had been in operation since 1948. Both cellulose diacetate (acetate) and cellulose triacetate (CTA) fibers were manufactured in adjacent work areas of the plant, CTA production having been initiated in 1954. Methylene chloride was the major component and methanol a lesser constituent of the solvent system used in the CTA production, whereas acetone was the only solvent used in the acetate production. Thus potential for exposure to methylene chloride, methanol, and acetone existed in the plant. The OSHA standard for acetone is a TWA of 1,000 ppm, and that for methanol is a TWA of 200 ppm (29 CFR par 1910.1000, table Z-1).

We were not able to identify a reference plant that was both similar in operation, except for the presence of methylene chloride, and geographically close to the plant with methylene chloride exposure. However, it was possible to select a reference plant with similar operations. It was located in Narrows, VA (about 260 km from the other plant), was part of a similar, although older multiplant complex, and was owned by the same company as the other plant. The operations of this plant were of the same design as those of the other, except that no methylene chloride was used because only acetate fibers were manufactured.

There were five aspects to the research project: (i) a comprehensive industrial hygiene survey of both plants; (ii) a mortality study of both the exposed and reference populations using a retrospective cohort design including follow-up of employees who had left the company; (iii) a health evaluation offered to employees of the exposed and reference populations (the evaluation included a health history questionnaire, a physical examination, and laboratory assessment of blood and urine constituents); (iv) an analysis of continuous ambulatory electrocardiograms recorded from a subset of men over age 34; and (v) an evaluation of methylene chloride metabolism to form carboxyhemoglobin and related effects on the oxyhemoglobin dissociation curve.

Environmental considerations

Background

Comprehensive industrial hygiene surveys of the two plants were conducted from 12 September 1977 through 7 February 1978. An initial visit to each plant was undertaken to identify chemicals present in the work environment, establish exposure ranges (8-h TWA and peak concentrations), and lay the ground work for more-detailed personal sampling to be conducted in conjunction with later medical testing. The second visit included personal monitoring, with additional area and short-term excursion sampling. More than 350 personal, 170 area, and 20 excursion samples were obtained by industral hygienists during the 3.5-month survey period. A summary of the industrial hygiene methods is contained in appendix 1.

The environmental studies focused on the preparation and extrusion departments of both plants. These departments were selected because of the high potential for exposure to the solvent system used at each location. In the preparation area, the solvent is mixed with either acetate or CTA flakes. The mixture is then passed through a series of filtration steps to remove any undissolved polymer. Finally, polymer in solution is transferred to the extrusion areas where filaments are dried and wound on bobbins. The extrusion areas of both plants also included operations for producing cigarette tow (filter packing) from the acetate polymer.

Results

At both plants, carbon monoxide concentrations in the general work area samples (excluding cigarette smoking areas) were found to be less than 3 ppm, and, therefore, this agent was assumed to be a negligible factor in the exposure profile of the employees. Oil mist exposure in the extrusion area was also judged to be a negligible factor since measured exposures were less than a TWA of 5 mg/m^3. The oil mist was due to a finish oil, which contained mineral and vegetable oils, surfactants, and antifoam and antistatic agents.

As previously mentioned, the solvent system employed in CTA production was a mixture of methylene chloride and methanol. Personal monitoring showed that the ratio for methanol to methylene chloride concentrations in the air was less than 1 to 10 and, secondly, that methanol concentrations were predictable from and highly correlated with the methylene chloride concentrations. Thus the exposure profile for each employee could be described in terms of acetone and methylene chloride with the understanding that methanol accompanied methylene chloride in an approximate 1 to 10 ratio.

The categorization of exposure with respect to methylene chloride and acetone is given in table 1 for both the plants under study. In general the acetone levels in the plant with methylene chloride exposure were the lowest where the methylene chlo-

Table 1. Categorization of occupational exposure to methylene chloride and acetone.

Job category	Median time-weighted average	
	Methylene chloride (ppm)	Acetone (ppm)
Exposed population[a]		
Category 1 — Low methylene chloride and high acetone (most production jobs in block I extrusion and in preparation)[b]	140	1,080
Category 2 — Moderate methylene chloride and low acetone (jobs in tow extrusion and where time was spent in both block I and block I & block II (eg, service)[c]	280	110
Category 3 — High methylene chloride and low acetone (jobs in block II extrusion and one job in preparation)	475	110
Reference population		
Category 1 — Low acetone (supervisors, jobs in tow production and some jobs in preparation)	—	380
Category 2 — Moderate acetone (inspectors and service jobs in filament)	—	770
Category 3 — High acetone (operator jobs in filament extrusion)	—	1,070

[a] Eleven employees assigned to production support jobs had low exposure to both methylene chloride and acetone (median time-weighted average about 60 ppm for methylene chloride and 110 ppm for acetone); they were included in the health evaluation studies at their own request.

[b] One exception was a job in preparation which was categorized as low exposure to methylene chloride (140 ppm) and low rather than high exposure to acetone (110 ppm as opposed to 1,080 ppm).

[c] Several service jobs were classified as methylene chloride (280 ppm) and acetone (1,080 ppm).

ride levels were the highest. Solvent exposure was less variable in the extrusion than in the preparation areas of each plant. However the ambient air concentrations of the solvents were generally higher during extrusion because of the continuous nature of the operation.

The extrusion area of the plant using methylene chloride was divided into two blocks: block I, mixed acetate and CTA extrusion, and block II, CTA extrusion only. In block I the median TWA concentration of methylene chloride (84 personal samples) was about 140 ppm with a range of 60–350 ppm. Individuals who worked in tow production were exposed to somewhat higher methylene chloride concentrations because of the proximity of these operations to block II. Based on 19 personal samples, a range of 50 to 470 ppm of methylene chloride was observed. In block II the TWA concentrations of methylene chloride ranged from 210 to 690 ppm (63 samples). The median TWA exposure was approximately 475 ppm.

Acetone exposures in the extrusion department of the plant using methylene chloride were the lowest for individuals whose work assignments were in block II or involved tow production. For example, 59 of 63 personal samples for acetone had a TWA below 300 ppm in block II and 14 of 19 samples had a TWA below 300 ppm in tow production. The acetone exposures were much higher in block I extrusion and were comparable to those found in the extrusion areas of the reference plant. The respective ranges were TWAs of 250 to 1,600 ppm (84 samples) in block I extrusion and TWAs of 260 to 1,750 ppm (83 samples) in the reference plant.

Personal sampling in the preparation area of the plant using methylene chloride (26 samples) revealed 8-h TWA concentrations of methylene chloride of 5 to 380 ppm with two uncharacteristically high readings of 860 and 900 ppm. The TWA concentrations depended both on job assignment and whether or not the mixture being prepared was for use in CTA or acetate extrusion. Peak concentrations occurred during the stripping and redressing of filter presses and the charging of CTA and acetate residue tanks. The TWA concentrations of acetone ranged from 10 to 800 ppm in the plant using methylene chloride. In the preparation area of the reference plant, acetone TWAs (16 samples) varied from 50 to 980 ppm with one sample of 1,470 ppm.

On the basis of a review of process changes and the limited prior sampling data, exposures measured during the surveys were believed to be representative of exposure throughout the history of the plant.

To summarize, the exposure profile across both plants included acetone alone at low and high TWA concentrations, low methylene chloride TWAs in the presence of high acetone TWAs, and intermediate and high methylene chloride TWAs concomitant with low acetone exposure intensities.

General design of the mortality study

The target population for the mortality study consisted of production and service employees who had worked for at least three months in the preparation or extrusion areas of either of the plants in question subsequent to 1 January 1954 and prior to 1977. In the plant using methylene chloride, service employees (eg, machine cleaners and janitors) were specifically assigned to preparation or extrusion areas and, therefore, were included in the study. In contrast many service employees from the reference plant were assigned work throughout the plant complex rather than in specific departments; thus, since no record was kept of the day-by-day assignments, there was no mechanism for identifying these employees and including them in the study. All work history records at each plant location were reviewed in an effort to identify the individuals who satisfied the target population definition. A total of 1,271 employees from the plant with methylene chloride exposure and 948 employees from the reference plant met these criteria and were included in the mortality study.

The following items of information were obtained for each individual: name, employee identification number (and other information pertinent to tracing former employees), sex, race, birthdate, employment status, a listing of each job held, and the employment dates on each job. Vital status of former company employees was established through telephone and mail contact, a search of motor vehicle registrations, and a submission of names to the Social Security Administration.

Causes of death were determined from copies of death certificates obtained through company insurance records or state vital statistics agencies. They were coded by a nosologist according to the Revision of the International Classification of Diseases in force at the time of death. Mortality within the exposed cohort was compared with that of both the corresponding United States population and the reference population. Outcomes of a priori interest were deaths due to ischemic heart disease and malignant neoplasms.

General design of the health evaluation studies

The health evaluation portion of the overall surveillance program included a general health examination that was offered to personnel currently assigned to the preparation or extrusion work areas and several additional studies undertaken for subsets of the employee population. After verbal and written explanations of the study objectives, self-administered "intent to participate" forms were completed by employees of both plants and returned voluntarily. On the basis of the replies, examination dates were then scheduled. The evaluation was conducted from October 1977 to February 1978, specifically from October 25th through December 19th in the plant with methylene chloride exposure and from November 7th through February 13th in the reference plant.

Because the program was voluntary, we sought to estimate participation in the health evaluation through knowledge of the actively employed population defined in the mortality study. According to comparable job classifications, 61 and 55 % of the workforce in the methylene chloride and reference plants, respectively, took part in the program. Participation was highest among the nonwhite men and women (76 %), most of whom worked in the plant using methylene chloride. Among the white women, participation was 60 % in the plant using methylene chloride and 57 % in the reference plant; the corresponding values for the white men were 43 and 54 %, respectively. Acceptance in both plants was slightly higher among whites under the age of 45 than over that age, 60 versus 48 % in the plant with methylene chloride exposure and 57 versus 52 % in the reference plant. Thus similar participation rates, albeit lower than desirable, were obtained for both plants. Nonwhites were somewhat overrepresented and white males underrepresented in relation to the total exposed population. The questionnaire portion of the health evaluation included information on environmental exposures (alcohol and cigarette smoking history, medications, part-time jobs, and prior job history). These data were used, in conjunction with selected laboratory tests, to determine evidence or lack of evidence of liver injury and to determine if certain hematologic changes observed in cigarette smokers and attributed by some researchers to carbon monoxide exposure were also seen with methylene chloride exposure.

Additional studies were performed for several subsets of the health evaluation participants. In one study, 24-hour electrocardiographic monitoring was conducted on 50 older men, 24 of the exposed group and 26 of the referents. The objective of this monitoring was to determine whether or not the methylene chloride exposure concentrations existing in the present work environment were associated with increased ventricular or supraventricular ectopic activity or ST-segment depression.

In a second investigation, measurements of blood carboxyhemoglobin saturation, alveolar carbon monoxide and P_{50} (the partial pressure at which hemoglobin is 50 % saturated with oxygen), both before and after a shift, were made in conjunction with the personal monitoring of methylene chloride exposure. This evaluation was performed for 268 employees, 136 exposed employees and 132 referents. The objective was to quantitate the relationships between these variables in a large employee population and to provide an additional perspective for interpreting the overall study findings.

Summary

The primary objective of the present research was to assess the potential health effects of methylene chloride exposure in an occupational setting with

particular attention given to possible carboxyhemoglobin-related effects on the cardiovascular system.

Recognizing that evaluation of the current workforce alone would leave important questions regarding selection in and out of the studied population unanswered, a retrospective cohort mortality study was incorporated into the overall study design.

Industrial hygiene monitoring of the plant using methylene chloride and the reference plant was carried out over a 3.5-month period. The industrial hygiene surveys were scheduled, in part, to coincide with the biological monitoring and medical testing to detect shifts in the oxyhemoglobin dissociation curve. Continuous ambulatory electrocardiographic monitoring was conducted for a subset of 50 male employees. Finally, selected blood constituents obtained during the health evaluation were examined to determine the presence or absence of hematologic changes or liver dysfunction relative to exposure.

The environmental studies indicated that, on the whole, acetone exposures were similar in both plants. In the plant using methylene chloride, about 25 % of the personnel were assigned to jobs for which typical methylene chloride exposure was a TWA of 475 ppm. Most of the other employees in the exposed population were exposed to a TWA methylene chloride level of about 140 ppm. However, some individuals were either assigned to jobs of intermediate exposure or were intermittently working in areas of relatively high (475 ppm) and low (140 ppm) exposure. The acetone exposure in this plant was, in general, inversely correlated with the methylene chloride exposure.

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Appendix

Industrial hygiene methods

During the initial visit, personal samples for acetone, methanol, and methylene chloride were collected with two hand-packed 700-mg silica gel tubes and one Pittsburg coconut base (PCB) 1-g charcoal tube in series. At the reference plant, two PCB 1-g charcoal tubes in series were employed for the collection of acetone. The sampling times were 4 h at a flow rate of about 50 ml/min on Mine Safety Appliance (MSA), SKC and Sipin equipment; thus, employees were monitored with a second sampling train during the last 4 h of the shift. Onsite testing indicated that one silica gel tube was adequate for the second visit sampling at the plant using methylene chloride and that 8-h sampling could be conducted at the reference plant. Acetone and methylene chloride were adsorbed on both the silica and activated charcoal and, therefore, were analyzed from both media with two different columns. Methanol was collected on the silica gel tube. Measurements were based on flame-ionized detection chromatography. The area and excursion samples were collected with high-flow Bendix and MSA pumps at a rate of 240 ml/min for 15 min with adsorbent configurations similar to those of the personal sampling.

Background carbon monoxide concentrations were measured with an Energetics Science, Inc, 2000 series carbon monoxide ecolyzer. Area oil mist samples were collected at both plants with high-flow Bendix and MSA pumps at flow rates of 2–2.5 l/min for 1 h. The oil mist was collected on Gelman 47-mm (0.08 μ pore size) filter paper and was weighed on an analytical balance.