METHYLENE CHLORIDE POISONING: A PARADIGMATIC REVIEW

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Abstract—The incidence of reported cases of toxicity resulting from methylene chloride exposure has increased within the last decade. A vast majority of these reports involve acute episodes, and the prevalence of domestic poisoning is relatively high. Diverse pathologic sequelae attributed to methylene chloride or its metabolites have been reported, although a distinct bias for central nervous system effects is evident. Paradoxically, detoxification of methylene chloride via the mixed-function oxidase pathway is an inherently intoxicating event. Although the anomalous conversion of methylene chloride into carbon monoxide has increased the popularity of methylene chloride poisoning among medical personnel, lack of experience in diagnosis and treatment of methylene chloride poisoning is widespread. This review of 26 cases spanning 50 years reveals that the industrial and domestic use of methylene chloride is equally widespread. A compendium of the clinical experience with methylene chloride poisoning is presented.

Keywords—methylene chloride; dichloromethane; hydrocarbon toxicity; toxicology; neurotoxicology; carbon monoxide; hyperbaric oxygen; halogenated hydrocarbons

INTRODUCTION

Methylene chloride (dichloromethane or DCM) is traditionally regarded as a relatively safe organic agent and is found as an ingredient of domestic and industrial preparations such as paint and varnish removers, aerosol paints, and degreasing solvents. Industrial applications of DCM include acetate film manufacture and various food and beverage extraction processes. The apprehension over fluorocarbon discharge into the atmosphere, together with DCM’s favorable low vapor pressure, has even propelled the solvent into the realm of personal-care aerosol products. Early enthusiasm for its use as an anesthetic disappeared after reports of incomplete narcosis.1 Although it is true that DCM is less toxic than most of the other halogenated hydrocarbons,2,3 the expanding use of this solvent and its characteristic metabolism in the human body justify concern.

DiVincenzo and colleagues11 first observed that absorbed DCM was not completely eliminated by the lungs and further suggested that biotransformation could account for the mole-for-mole discrepancy. Human in vivo metabolism of DCM to carbon monoxide (CO) was first reported by Stewart et al in 1972.13 While participating in a research project designed to assess the effect of air pollution on carboxyhemoglobin (COHb) saturation, one of the authors who had been exposed to paint- and varnish-remover vapors the previous evening manifested an abnormally high COHb level.14 Following this fortuitous discovery, experimental verification in humans15,16 and animals17,18 confirmed that the observed increase in COHb was a result of the metabolism of DCM into CO.

The pathology resulting from DCM exposure arises from the hypoxic effects of CO that include a leftward shift of the oxyhemoglobin desaturation curve and a decrease in the available oxyhemoglobin. Chronic effects of DCM in workers exposed to 300 ppm or greater for an eight-hour workday include a 2 to 4 mm Hg decrease in oxygen half-saturation pressure19 and an apparent compensatory hematopoietic effect among women.20 The extent to which unmetabolized DCM contributes to clinical sequelae is imprecisely known.

The treatment is identical to that for CO poisoning: remove the patient from the source and deliver 100% oxygen (O₂) by tight-fitting mask. Hyperbaric
oxygen (HBO) may be useful in severe or refractory cases, and the nature of endogenous DCM-derived CO may be a further indication for HBO. Specifically, DCM-derived CO has an effective half-life 2.5 times that of exogenously inhaled CO. Continued production of CO represents prolonged cardiovascular stress to cardiovascular disease patients and antagonizes the emancipation of hemoglobin. The distinctive metabolism of DCM to CO and the subsequent formation of COHb affords the emergency physician a quantifiable parameter that is useful in the diagnosis and management of solvent poisoning.

SCOPE OF THIS REVIEW

Dichloromethane literature may be divided into four categories: accidental or abuse-related exposures, occupational or epidemiologic studies of chronically exposed groups, human experimental exposures, and animal or isolated organ studies. This article reviews 26 case reports of DCM exposure reported in the literature from 1936 through October 1986. The full clinical presentation for each case is not presented; instead, the various signs and symptoms are collectively catalogued in Table 1. Human or animal research data are presented when clinically relevant or when otherwise provocative correlations can be made. Detailed discussions of the metabolism and biochemistry of DCM are beyond the purpose of this review; for a concise review of DCM metabolism in the context of saturable metabolism, the interested reader is directed to an excellent and instructive presentation by Anderson. More recent pharmacokinetic analyses of DCM are recommended for a comprehensive interpretation.

ABSORPTION, ELIMINATION, AND METABOLISM OF DCM

The dynamics of DCM absorption and elimination were described during a series of experiments conducted by Astrand et al in Sweden. Arterial, venous, and alveolar DCM concentrations were measured simultaneously, in addition to arterial and venous COHb during and after DCM exposure. Absorption was characterized by high arterial DCM concentrations and elimination by high venous DCM and COHb concentrations, the latter of these two continuing to rise well after the cessation of the exposure. This delayed COHb peak phenomenon was first reported by Stewart et al. Based on a specific human exposure regimen, Peterson derived postexposure concentration equations reflecting levels of DCM in the breath and COHb in the blood.

The peak COHb attained is directly proportional to the amount of DCM absorbed, which is in turn linearly related to the exposure concentration. Kim and Carlson note that the COHb half-life in rats is lengthened when DCM concentration is raised; lengthening exposure time has no effect on peak COHb. These results indicate that the metabolic conversion pathway for DCM is easily saturable.

Dichloromethane is converted into other molecules by at least two pathways. The first follows oxidation by the microsomal cytochrome P-450 mixed-function oxidase (MFO) system to generate CO, reduced nicotinamide adenine dinucleotide phosphate (NADPH), and carbon dioxide (CO2). Radiolabeling studies confirm that CO2 is also a major metabolite of DCM and that molecular oxygen, as opposed to oxygen from water, contributes the oxygen that appears in CO. The second metabolic conversion pathway utilizes glutathione S-transferase (GST) and ultimately liberates formaldehyde and inorganic halide. The latter is a minor pathway, although it is implicated as qualitatively important in the brain. Recent work from Anderson and colleagues finds a correlation between tumor incidence in mice and the amount of DCM metabolized by the GST pathway. No analogous correlation to the MFO pathway was found. Gargas et al recently characterized the kinetics of the two pathways in a comparative study. DiVincenzo and Hamilton find no evidence that DCM is dehalogenated to methyl chloride or dimethyl ether, and Ugazio et al report that DCM is not a strong reactive inducer of free radical formation. Interestingly, trihalomethanes (including chloroform) are also metabolized to CO, yet chloroform (methyl chloride) does not appear to succumb to the same fate. A loosely coupled continuum of circulatory, respiratory, and nervous system effects is observed across the chlorinated methane series.
et al, in earlier work, presented convincing evidence that DCM in concentrations up to 1% by volume does not change the relative binding of O₂ and CO to hemoglobin. Similar results under anoxic conditions showed that DCM fails to alter the absolute affinity of hemoglobin for CO. The second possible explanation for elevated COHb after DCM exposure is that the solvent accelerates the breakdown of heme proteins or otherwise increases purely endogenous CO formation. Urinalyses and hemotologic studies of DCM-exposed human volunteers failed to demonstrate increased red blood cell (RBC) destruction. Collateral in vitro studies from another laboratory came to the same conclusion.

The extent to which DCM is stored in body tissues is an issue of considerable debate. Based on a relatively simple physiologic model, Riley and co-workers estimated that it would take several days to saturate fatty tissue with DCM. DiVincenzo and Hamilton confirmed that the overall uptake of radiolabeled DCM after intraperitoneal administration in the rat is small and that there is no significant accumulation of radioactivity in fat. Opposite results were obtained by Carlsson and Hultengren in a similar inhalation study with rats. They found the concentration of radioactive carbon per gram of tissue to be the highest in white adipose tissue, although the omission of total tissue weight makes a full comparison with DiVincenzo's findings difficult. Angelo et al recently characterized the pharmacokinetics and disposition of radioactive DCM in mice and rats. In mice, the highest concentrations of DCM were found in the liver, kidney, and lung. Sovaolainen found DCM present in brain, liver, lungs, and perirenal fat during a series of high-concentration inhalation studies with rats. Chiuchta et al found DCM absorption to be proportional to body weight in rats and attributed this in part to greater fat deposition. Radiolabeling experiments conducted by Yesair et al found primarily liver and blood compartmentalization of DCM.

### Table 1. Signs, Symptoms, and Complications of DMC Poisoning

<table>
<thead>
<tr>
<th>Sign, Symptom, or Complication</th>
<th>Symptomatic Cases as a Fraction of Total Number of Cases: Reference Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorized by System</td>
<td>Acute</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
</tr>
<tr>
<td>Cognitive</td>
<td>2/21:80,108</td>
</tr>
<tr>
<td>Sensory</td>
<td>2/21:108(2)</td>
</tr>
<tr>
<td>Motor</td>
<td>1/21:69</td>
</tr>
<tr>
<td>Behavioral</td>
<td>5/21:71,75,92,104,108</td>
</tr>
<tr>
<td>Headache</td>
<td>5/21:79,75,92,104,108(2)</td>
</tr>
<tr>
<td>Unconsciousness</td>
<td>7/21:69,71,92,104(3),110</td>
</tr>
<tr>
<td>Respiratory</td>
<td>6/21:81,104,109(3),114</td>
</tr>
<tr>
<td>Pulmonary edema/dyspnea</td>
<td>6/21:80,81,100(2),108,114</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5/21:69,71,78,92,114</td>
</tr>
<tr>
<td>Hepatic/renal</td>
<td>2/21:78,78</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>8/21:69,80,92,100,104,108,109,110</td>
</tr>
<tr>
<td>Hematologic</td>
<td>3/21:69,75,78</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1/21:27</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>3/21:71,78,114</td>
</tr>
<tr>
<td>Shock</td>
<td>2/21:27,110</td>
</tr>
<tr>
<td>Death</td>
<td>4/21:27,100,109,113</td>
</tr>
</tbody>
</table>

### ABUSE-RELATED EXPOSURES

The literature through 1986 contains three reports of abuse-related DCM exposure. The first, a suicide attempt, was contributed by Roberts and Marshall in 1976. A 38-year-old man ingested 1 to 2 pints of a paint-remover preparation containing DCM, methanol, and detergent. The patient was unconscious and unresponsive to painful stimuli. The oral mode of ingestion in this case resulted in erythematos, blistered skin associated with contact areas and ulceration of the duodenojejunal junction, which developed into diverticula at six months. Gross hemoglobinuria was present and was probably related to the other constituents in the ingested mixture. The conversion of oral doses of DCM to CO has been demonstrated. Unfortunately, COHb levels were not
obtained in this case. The prolonged unconsciousness of this patient (14 h), when viewed in light of the gastrointestinal damage, may well represent the direct toxicity of DCM on the central nervous system (CNS).

Dichloromethane does not appear to be the inhalant of preference among recreational sniffers. Sturmann et al. present a case of an adolescent boy seen in the emergency department after inhaling an artificial flower-cleaning preparation containing 60% DCM. A sock saturated with the solvent served as the vehicle of delivery. The patient was lethargic and presented with nausea and chills. Although the exact duration and time course of the exposure were not known, an appraisal of the approximate time of onset was given by the boy’s mother.

A COHb value of 13% was obtained in the emergency department almost ten hours after the estimated onset of exposure. The patient had received 100% oxygen (delivery unspecified) both during transport and before COHb percent determination in the emergency department. An additional COHb measurement of 7.5% was made five hours after the original, during which time the patient was on 100% normobaric oxygen. By our calculations based on these two COHb percent values, an elimination half-life of 5.8 h is obtained. The elimination half-life for exogenously inhaled CO under conditions of 100% normobaric oxygen is 1.5 h. These results parallel the experimental data of Ratnay and colleagues, who found the air elimination half-life of DCM-derived CO to be greater than that for inhaled CO. Table 2 compares the results from several investigators with respect to CO elimination half-life. The explanation for this prolonged off-gassing is the sequestration of DCM in tissue stores and hence the continued presence of the chemical precursor to CO.

An interesting case report from Horowitz describes the course of a 35-year-old man with a chronic paint-sniffing habit. The patient exhibited stuporous and then violent behavior in public. Perinasal and oral areas were painted bronze, and the aerosol paint in question was found to contain 25% DCM by weight in addition to copper powder and other constituents. A 6.7% COHb was demonstrated, and additional hypoxic potential was present in the form of 2.4% methemoglobin (Fe3+, nonoxygen binding). Dichloromethane is not implicated in the formation of methemoglobin; the authors attribute the altered erythrocyte metabolism to elemental copper, which was positive in a toxicologic screen of this patient. Thirty minutes after the initial determination, COHb was 9.6%, despite the fact that the man received 3 L of O2 via nasal prongs in the interim. The elevation of COHb as a result of exposure to aerosol paint fumes containing DCM was experimentally demonstrated in a controlled trial by Stevenson et al.

### Table 2. Carbon Monoxide Elimination Half-Lives (T1/2)

<table>
<thead>
<tr>
<th>Patient Breathing</th>
<th>Exogenous CO T1/2</th>
<th>Endogenous CO T1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room air</td>
<td>5.3 h</td>
<td>13 h</td>
</tr>
<tr>
<td>Normobaric O2</td>
<td>1.5 h</td>
<td>5.8 h</td>
</tr>
<tr>
<td>2.5 ATA HBO</td>
<td>0.31 h</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

ATA HBO, atmosphere absolute of hyperbaric oxygen. Estimated from reference 52.

**ACUTE EXPOSURES**

Several acute exposure case reports exemplify the potential severity of complications associated with exposure to DCM. Keogh et al. present evidence for an association between chlorinated hydrocarbons and Goodpasture’s syndrome. In this case, a 16-year-old girl was subjected to DCM and 1,1,1-trichloroethane vapors while an office machine was being cleaned. The role of DCM in the etiology of the disease is unclear, yet the implications of such a connection are worthy of attention.

Miller et al. relate a case of a 19-year-old man using a tile remover in a poorly ventilated room. This patient presented with a challenging array of signs and symptoms ranging from liver enzyme elevations to poorly localized abdominal pain. Renal studies and biopsy confirmed the diagnosis of acute tubular necrosis. Histologic studies demonstrated plasma membrane changes in addition to mitochondrial effects suggestive of anoxic damage. Serum enzyme changes noted during the patient’s hospital course suggested that hepatocellular injury accompanied the nephrotoxic sequelae. In addition to DCM, the solvent mixture contained mineral spirits and methanol. Unfortunately, neither COHb nor DCM concentrations were measured. Further evidence for hepatic effects of DCM were reported by Puurunen and Sotaniemi. One week after a brief but extensive body exposure to DCM, serum alanine aminotransferase was elevated threefold in a 24-year-old male chemical factory worker.

Another multisystem disorder was reported by Meimon and Davidson. Coincidentally, the causative paint stripper in this case (Nitromors) was the same preparation used in the suicide attempt described earlier. A 25 year old accountant used the preparation in a confined space for three to four hours. Swollen stiff
joints and a profuse pink rash developed within 72 h of the exposure. The origin of the rash was unexplained and the possibility of an immune complex-mediated Arthus reaction was not speculated upon. Poor immediate recall and the inability to concentrate suggested CNS involvement. Carboxhemoglobin levels were not reported.

Exposure to paint remover fumes was reportedly pathogenic in a serious case of pulmonary edema with bilateral exudative pleural effusions. In this case, a 34-year-old man presented with respiratory distress after stripping furniture with a DCM-containing preparation. Work-area ventilation was poor on the fourth and final day of the project. The authors speculate that hydrochloric acid, a product of DCM under warm, moist conditions, may have played a role in this patient's parenchymal abnormalities. Treatment with respiratory smooth-muscle relaxants, methylprednisolone, and oxygen effected complete recovery excepting neuropsychiatric abnormalities that may have been related to the solvent exposure.

Considerable controversy exists over the potential for DCM or its metabolites to induce pathologic changes in the liver, kidney, and lung. Since the early work of Heppel et al in 1944,82,83 it has been known that many species can tolerate high concentrations of DCM. Nevertheless, subsequent animal studies confirm the potential for morphologic and functional deficit resulting from DCM exposure. Table 3 briefly reviews the collective conclusions from these studies. Noteworthy findings include hepatic triglyceride elevation, minimal evidence of organ necrosis, and increased peroxidation of lung lipids.84-89 In these studies the exposure concentrations precipitating pathologic changes are generally much higher than the recommended National Institute of Occupational Safety and Health (NIOSH) human exposure limits of 100 ppm for an eight-hour work day exposure with a 500-ppm ceiling value. Olson et al,90 however, noted that these levels are readily exceeded under home-use conditions of chemical paint removers.

Two reports in the literature illustrate the likelihood of severe CO intoxication secondary to DCM use under conditions of low ventilation or vapor stratification. The first case, reported by Fagin et al,92 is that of a 20-year-old art student using a paint remover in a poorly ventilated room. A one-hour exposure resulted in unconsciousness. Upon admission the patient had cherry-red skin and mucosa, a throbbing headache, and a COHb level of 50%. The authors note that symptoms were mild in contrast to the magnitude of COHb elevation. Response to a curious therapy of 60% oxygen at 4 L/min was good, but COHb was still 20% after 12 hours of oxygen therapy.

In the second report, two physicians, who were ambitious furniture strippers, worked with a DCM-containing paint remover in a large enclosed basement for six hours. Upon arriving at work the next morning they discovered that their avocation raised their COHb values to 26% and 40%, respectively. Despite these high values, the two remained asymptomatic. Multiple sessions demonstrated incremental contributions to COHb. Ratney found residual morning COHb in nonsmoking workers exposed to DCM daily to be on the order of 4.5%.15 DiVincenzo and Kaplan observed that COHb values returned to preexposure control levels nearly 16 hours after eight hours of exposure to DCM at concentrations of 50, 100, 150, and 200 ppm.91 The additive effect of exogenous CO has been quantitated, and exercise is known to increase the absorption of DCM.92,93 Concomitant exposure to smoking and exercise drastically reduces the occupational safety factor of DCM-exposed workers.97

To date, the only reported domestic-setting death attributed to DCM was reported by Stewart and Hake.27 A 66-year-old man experienced the signs and symptoms of myocardial infarction on three separate occasions while using a liquid gel paint- and varnish-remover in his basement workshop. Shortly after the third incident, he died before the arrival of the ambulance. The authors postulate that he experienced cardiovascular stress secondary to COHb-mediated hypoxia. In connection with an extensive occupational study conducted by Ott et al,98 24-hour ECG monitoring of a DCM-exposed population failed to demonstrate increases in ventricular or supraventricular ectopic activity or episodic ST-segment depression.99 The companion case report to the fatality presented above supports the literature documenting elevated COHb levels subsequent to DCM exposure. In short, a 36-year-old, nonsmoking male cardiologist manifested 6% and 8% COHb levels on successive mornings following evening exposures to paint- and varnish-remover vapors.

An unusual acute domestic case occurred when a 38-year-old pregnant woman developed tightness in the chest and expectorated blood-stained sputum following an afternoon of cupboard renovation that in volved the use of a paint remover containing DCM.100 Radiography suggested pulmonary edema. Ultimately she recovered and delivered a healthy infant. Although animal studies fail to establish overt embryotoxic or teratogenic effects of DCM,101,102 Hardin and Manson report increases in maternal liver weight and decreased fetal body weight in rats subjected to high DCM concentrations during gestation.103 The
Table 3. Animal Experiments Investigating DCM or Metabolite Effect on Liver, Kidney, and Lung

<table>
<thead>
<tr>
<th>Effect or Observation</th>
<th>Animal(s):</th>
<th>Reference number(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Mouse:</td>
<td>2</td>
</tr>
<tr>
<td>Inflammatory changes</td>
<td>Dog:</td>
<td>3</td>
</tr>
<tr>
<td>Neutrophil infiltrates</td>
<td>Guinea pig:</td>
<td>21, 84</td>
</tr>
<tr>
<td>Histologic changes, increased hepatic triglyceride</td>
<td>Rat, guinea pig, mouse:</td>
<td>36, 43, 84, 85, 86, 87</td>
</tr>
<tr>
<td>Biochemical changes, increase in liver weight, fatty infiltration</td>
<td>Dog:</td>
<td>3</td>
</tr>
<tr>
<td>Kidney</td>
<td>Mouse, dog:</td>
<td>3, 8</td>
</tr>
<tr>
<td>Slight calcification of renal tubules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of necrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal necrosis of convoluted tubule</td>
<td>Mouse:</td>
<td>3</td>
</tr>
<tr>
<td>Lung</td>
<td>Rat:</td>
<td>88, 89, 90</td>
</tr>
<tr>
<td>Increased secretion of enzymatic and nonenzymatic macromolecules</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

overriding consideration in this case was a small portable kerosene stove that heated the cellar workroom. Retrospective experiments conducted by the authors under conditions simulating the woman's exposure conclusively demonstrated the production of toxic concentrations of phosgene gas purportedly formed by the reaction between chlorine from DCM decomposition and CO from the combustion of fuel.

An accompanying case report from the same authors implicates DCM in an occupational fatality. In this instance a 52-year-old painter used a chemical paint remover in a small room heated by a kerosene stove. Subsequently, the man noted a burning sensation in his throat and tightness in his chest. Upon examination, rales and pulmonary edema were noted. He died within 12 h of the exposure and necropsy showed extensive degenerative changes in respiratory epithelium and hemorrhagic edematous focal pneumonia. As with the case of the pregnant woman, the direct role of DCM itself was probably insignificant in comparison to the proposed contribution of phosgene. A third and nonfatal case of DCM-associated phosgene poisoning describes pulmonary pathology consistent with these two cases.104 Undoubtedly, the expected COHb elevation in these cases would worsen the hypoxic potential posed by injury to the absorptive epithelium of the lung. The diagnosis of solvent poisoning must consider the likelihood of constituent decomposition as a result of contact between the solvent and open flames or hot surfaces.105,106

It is noteworthy that the cases discussed thus far involve multiconstituent paint removers, solvent mixtures, and, in one case, a paint preparation. This is in contrast to the cases in both categories of occupation-al exposure that almost exclusively involve only DCM. Several laboratories addressed the effects of hydrocarbon additives and alcohols in particular on DCM kinetics. Balzer et al21 found that ethyl alcohol given in concert with DCM actually reduced the COIIB response in guinea pigs and attributed the favorable effect on competition for a common enzyme system. The same mixture also reduced mortality compared with similar high concentrations of DCM alone. Ciuchta et al23 reported similar results with isopropyl alcohol but found that methanol, when given with DCM, failed to change the peak COHb values from control monkeys and rats. Stewart and Hake24 exposed volunteers to DCM and a paint-remover preparation containing 80% DCM and 20% methanol. Based on their COHb time-course values and the half-life presented in Table 2, the methanol increased the half-life of DCM on order of 15% to 20%. They also noted that peak COHb with DCM alone usually occurred at one hour postexposure, whereas exposure to paint-remover vapor containing methanol resulted in rising COHb that peaked as late as four hours postexposure. Roth et al25 showed that COHb levels after DCM inhalation are reduced when the potent hepatotoxin carbon tetrachloride (CCl₄) is present. Thus, a variety of agents can alter DCM metabolism. Reciprocally, Tufgard and his colleagues present evidence that DCM modifies the metabolism, and hence toxicity, of certain environmental contaminants.107

The first clinical presentations of acute occupational exposure to DCM date back to 1935,108 when four painters using a DCM-containing agent attempted to remove the paint from a large wall in an
enclosed room. Subsequently they registered various complaints, including faintness, stupidity, stupor, and loss of appetite. Detailed histories of two individuals were presented. Chronic lead intoxication complicated the clinical picture in at least one case. Collier described the observed nervous system effects as "largely subjective" and posed attendant chronic anemia. In light of DCM's biotransformation, Collier's interpretations were prophetic without intent.

Moskowitz and Shapiro describe the exposure of four men to one to three hours of DCM vapor resulting in three to six hours of unconsciousness and one death. The three surviving men presented with irritation of the eyes and upper respiratory passages, irritation of bronchi and lungs, and unexplained adverse effects on the hemopoietic system as evidenced by reduced hemoglobin and red cell count values. The three survivors all regained consciousness about 2½ hours after they were removed from the plant. This report emphasizes the effects of local environment on the magnitude of exposure. All of the internal structures of the oleoresin extraction plant had been removed and replaced with metal grillwork that facilitated the free diffusion of solvent. Dichloromethane vapor is more dense than air, which might have played a role in this industrial accident, since the unconscious men were all found at the lower areas of the production complex.

It is of interest that in many of the domestic exposures presented in this review, the paint stripping or solvent use occurred in a poorly ventilated basement, the worst-case scenario with regard to vapor stratification. Similarly, the spatial and temporal distribution of DCM in commercial settings may vary considerably. In the context of a study of an occupationally exposed group, Ratney et al measured the concentration of ambient DCM in a plastic film production plant. Over a two-day period, DCM concentrations ranged from 159 to 471 ppm, with a mean of 286 ppm on the first day and 183 ppm on a second. A 300-ppm reading was obtained near a film stretcher and a 845-ppm reading in a solvent/resin mixing and filtering area. Vapor concentrations under conditions of domestic use also depend upon the specific product or preparation used. In a well-controlled study, Otson et al found that DCM concentration levels ranged from 177 to 776 ppm for six different paint removers applied to a sheet of plywood in an enclosed room. When the doors of the test room remained open for the trials, the eight hour time-weighted average concentration was reduced almost sevenfold for the paint remover responsible for the highest value under nonventilated conditions. This study also assessed the stratification patterns of DCM, and as expected, DCM concentrations were generally greater at the lower levels of the test room.

A brief report from Wells and Waldron in England documents second- and third-degree burns on the legs of a man overcome by DCM fumes in a small open vessel. He had overturned a bucket of the solvent and was burned on areas of his legs bearing the weight of his body. After an exposure of approximately 30 min, the man was rescued from the vessel and oxygen (delivery unspecified) was administered. After one hour, COHb was 12%.

Stewart's laboratory conducted a short series of experiments in 1964 to determine whether or not toxic quantities of DCM could be absorbed through the skin. Although DCM was relatively permeant to skin, a 30-min thumb immersion resulted in a peak mean breath concentration of only 3.1 ppm in four subjects. The effects of immersion included intense burning sensations, numbness, coldness, and excruciating thumb pain upon movement during the exposure. Using a physiologically based pharmacokinetic model, McDougal et al recently characterized the dermal absorption of DCM. Analyses such as these may ultimately be applicable to risk-assessment strategies for workers dermally exposed to extremely high concentrations of DCM.

Two additional acute occupational cases involve dip-tank operators, the first of whom was found slumped over his tank with his forehead immersed in DCM. He had been exposed for no more than an hour. Autopsy revealed bilateral pulmonary congestion with focal hemorrhage, moderate edema of the brain, 29.8 mg/dL blood DCM, and chemical burns of the forehead. The basement in which this 20-year-old man worked was poorly ventilated and the description of the degreasing equipment and operation suggests that very high solvent concentrations were generated. The second report concerns a 29-year-old man admitted to the hospital with shortness of breath, cough, and substernal pain after working over an open drum of DCM. Consistent with Stewart's results, the solvent "felt like ice water" on this man's bare hands. X-ray examination indicated pulmonary edema, and rales were heard at the base of the right lung. Complete relief of symptoms occurred after 18 h, and the patient was discharged from the hospital following resolution of pulmonary sequelae.

A recent review of "industrial gassings" in the British literature reveals an additional 33 cases of acute DCM exposure. Although detailed case histories are not reported, summary data indicate that the CNS symptoms were prominent.
CHRONIC OCCUPATIONAL EXPOSURES

Epidemiologic studies identify and characterize populations of workers who are likely to be at greatest risk for DCM poisoning by virtue of their chronic exposure. Controlled human trials report attention deficits and trends toward impaired reaction time among DCM-exposed workers. Cherry et al noted a higher incidence of self-reported neurologic symptoms in workers in a film factory, although further data collection and analysis deemed this statistically insignificant. In a controlled comparative study of 5% COHb toxicity, Putz et al found similar impairment of visual-manual and auditory vigilance tasks in human volunteers exposed to either DCM or CO. Alexeeff and Kilgore demonstrated a significant learning deficit in young mice following long-term exposures to high concentrations of DCM. Dichloromethane was shown to decrease nerve conduction velocity and to reduce the peak inward current in voltage-clamped axons.

More recently, investigations have turned toward two important questions: the cellular and biochemical events of DCM-induced CNS effects and the carcinogenic potential of the solvent. Recent work, conducted by Braving and colleagues, documents changes in amino acid and phosphoethanolamine levels localized to distinct regions within the gerbil brain following a three-month exposure to 210 ppm DCM. In a related study simulating chronic DCM exposure, Rosengren et al found increased concentrations of cortical astroglial proteins and decreased concentrations of DNA, indicating cell loss, in the hippocampus. Whether these changes are responsible for the memory deficit observed with DCM exposure is not certain.

Studies considering the potential carcinogenicity of DCM generally utilize bacterial mutagen assays and the most basic mammalian test systems. Concerted studies carried out by a consortium of investigators evaluated the toxicity and carcinogenicity of DCM administered in the drinking water of rodents. Treatment-related toxic effects were noted in all animals. Increased tumor incidence was demonstrated in some groups, although the authors are quick to point out that these are within range of historic controls. Another 2-year study designed to answer the cancer question used an inhalation exposure regimen. Although the total number of benign tumors in some male and female treatment groups was increased, the total number of rats with benign tumors remained the same. Hamsters exposed to the same experimental conditions were not affected similarly. While these studies generally employ concentra-

tions beyond the range of idealized human extrapolation, they provide insight into potential effects of chronic human occupational exposures.

Clinical case reports of chronically exposed persons are rare. The first of two cases to be reported here documents delirium attributed to a long-term occupational exposure to DCM. Tariot describes the neuropsychiatric course of a 52-year-old strip-tanks operator who arrived at the hospital presenting with confusion and headache. The patient's exposure to a machine-part degreaser containing 78% DCM was of four year's duration, the last 12 months of which were marked by intermittent headaches, blurred vision, and short-term memory deficits that worsened near the end of the work day. Forty-eight hours postadmission the patient reported auditory hallucinations, and during the course of his hospital stay he exhibited violent behavior toward the staff, becoming delusional. Mental status improved, but on the seventh day the patient exhibited focal seizures in his left arm followed by a generalized seizure. A right hemispheric focus was confirmed.

Barrowcliff and Knell attribute the cerebral deterioration of a 60-year-old male patient to persistent elevated CO levels due to chronic DCM exposure. There was no direct measurement of the ambient DCM levels of the work environment, but retrospective calculations by the authors suggest that atmospheric DCM was between 500 and 1,000 ppm in the poorly ventilated work area. The man was exposed to the solvent routinely for three years. He found the smell objectionable, suffered throat and eye irritation, and complained of memory loss and difficulty with word enunciation. Degenerative vascular disease was not evident.

SUMMARY

The 26 cases of DCM poisoning reviewed in this manuscript can be categorized by the nature of the exposure. Of the 24 acute exposures, 13 occurred in a domestic setting, and 11 were occupationally linked. Three of the acute domestic poisonings were abuse-related. Three additional cases were remarkable in that the exposed individuals were asymptomatic despite elevated COHb values. One death occurred in the acute domestic category and three deaths were attributed to occupational exposure. Only two of the 26 case reports could be described as chronic (occupational) exposure.

The pathogenesis of DCM poisoning is intimately associated with its biotransformation into CO via the MFO pathway. Since this enzyme system is appar-
ently saturable, some of the observed effects of DCM poisoning may be due to the solvent itself. A satisfactory model to investigate the differential effects of CO, COHb, and DCM has not yet been developed. Central nervous system abnormalities constitute a majority of the DCM exposure-related effects, although respiratory and gastrointestinal sequelae are not common. Hepatic and renal effects resulting from DCM poisoning are rare, and yet the severity of nephrotoxic injury in one case was extreme. Dichloromethane irritates eyes and skin and prolonged dermal contact will result in chemical burns.

Based on the elevation of COHb subsequent to DCM exposure, administration of 100% oxygen by tight-fitting mask is recommended. Hyperbaric oxygen may be indicated for serious or refractory cases. The precise role of oxygen in the management of DCM poisoning is an area for future basic research. The effect of oxygen on the conversion of DCM into CO is of particular clinical relevance. Only four of the 21 acute symptomatic cases discussed here report the use of oxygen in the treatment of DCM poisoning. Of the 17 cases not treated with oxygen, three were dead-on-arrival fatalities and six were published before the knowledge of DCM's conversion to CO. The difficulty in the diagnosis of DCM poisoning is further evidenced by the low number of cases (seven) reporting COHb values. Although a thorough patient history should cue the possibility of DCM exposure, such a history may not always be available. In the future, COHb determination may become a routine addition to the laboratory tests used in the differential diagnosis of suspected solvent poisoning.

REFERENCES


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