criteria for a recommended standard . . . .

OCCUPATIONAL EXPOSURE TO METHYLENE CHLORIDE

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

March 1976

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

HEW Publication No. (NIOSH) 76-138

PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. The National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices, to provide relevant data from which valid criteria for effective standards can be derived. Recommended standards for occupational exposure, which are the result of this work, are based on the health effects of exposure. The Secretary of Labor will weigh these recommendations along with other considerations such as feasibility and means of implementation in developing regulatory standards.

It is intended to present successive reports as research and epidemiologic studies are completed and as sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on methylene chloride by members of my staff and the valuable constructive comments by the Review Consultants on methylene chloride, by the ad hoc committees of the American Industrial Hygiene Association and the American Academy of Occupational Medicine, by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, and by William M. Pierce on respiratory protection and work practices. The NIOSH recommendations for

standards are not necessarily a consensus of all the consultants and professional societies that reviewed this criteria document on methylene chloride. Lists of the NIOSH Review Committee members and of the Review Consultants appear on the following pages.

John F. Finklea, M.D.
Director, National Institute for
Occupational Safety and Health

The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and recommended standard for methylene chloride. Agatha Corporation developed the basic information for consideration by NIOSH staff and consultants under contract No HSM-99-73-20. Jon R. May, Ph.D., had NIOSH program responsibility. Final preparation of the document was accomplished by Robert W. Mason, Ph.D.

REVIEW COMMITTEE
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

Elliott S. Harris, Ph.D.
Director, Division of Biomedical and
Behavioral Sciences

Richard E. Kupel
Division of Physical Sciences
and Engineering

Marshall E. LaNier
Director, Division of Technical Services

Frank L. Mitchell, D.O.
Division of Criteria Documentation and
Standards Development

Department of Labor Liaison:

Robert Manware
Office of Standards

NIOSH REVIEW CONSULTANTS ON METHYLENE CHLORIDE

Jacqueline Messite, M.D.
Assistant Director
Division of Industrial Hygiene
State Department of Labor
New York, New York 10013

David A. Padden
International Union, United Automobile, Aerospace
& Agricultural Implement Workers of America-UAW
Detroit, Michigan 48214

Leonard D. Pagnotto
Division of Occupational Hygiene
Massachusetts Department of Labor and Industries
Boston, Massachusetts 02116

Jack E. Peterson, Ph.D.
Department of Environmental Medicine
Medical College of Wisconsin
Milwaukee, Wisconsin 53226

Robert L. Raleigh, M.D.
Assistant Director
Health and Safety Laboratory
Eastman Kodak Company
Rochester, New York 14650

Lyman K. Skory
DOW Chemical Company
Midland, Michigan 48640

CRITERIA DOCUMENT: RECOMMENDATIONS FOR AN OCCUPATIONAL EXPOSURE STANDARD FOR METHYLENE CHLORIDE

Table of Contents

Table of Contents (continued)

I. RECOMMENDATIONS FOR A METHYLENE CHLORIDE STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that worker exposure to dichloromethane (CH2Cl 2), commonly known as methlylene chloride, be controlled in the workplace by adherence to the following sections. The standard is designed to protect the health and safety of workers for up to a 10-hour workday, 40-hour workweek over a working lifetime; compliance with all sections of the standard should prevent adverse effects of methylene chloride on the health and safety of workers. The standard is measurable by techniques that are valid, reproducible, and available to industry and governmental agencies. Sufficient technology exists to permit compliance with the recommended standard. The standard will be subject to review and revision as necessary.

"Occupational exposure to methylene chloride" is defined as exposure above one-half the daily time-weighted average (TWA) exposure limit, except when there is also exposure to carbon monoxide (CO) at more than 9 ppm.

Because the toxicities of CO and methylene chloride are additive, the appropriate environmental limit and action level of methylene chloride must be reduced in the presence of CO. When CO levels are more than 9 ppm "occupational exposure to methylene chloride" shall be determined from the following formula:

$$\frac{C(CO)}{L(CO)} + \frac{C(CH2Cl\ 2)}{L(CH2Cl\ 2)} \leq 0.5$$

where:

C(CO) = TWA exposure concentration of CO, ppm

L(CO) = the recommended TWA exposure limit of CO = 35 ppm

C(CH2Cl 2) = TWA exposure concentration of methylene chloride, ppm

L(CH2Cl 2) = the recommended TWA exposure limit

of methylene chloride = 75 ppm

Exposure to methylene chloride below the appropriate "occupational exposure" level as defined above will not require adherence to the following sections, except for Section 4(a)(4), Section 6(d), and Sections 7(a) and (b).

Section 1 - Environmental (Workplace Air)

(a) Concentration

(1) In the absence of occupational exposure to CO above a time-weighted average (TWA) of 9 ppm for up to a 10-hour workday, occupational exposure to methylene chloride shall be controlled so that workers are not exposed to methylene chloride in excess of 75 ppm (261 mg/cu m) determined as a TWA for up to a 10-hour workday, 40-hour workweek.

(2) In the presence of exposure to CO in the work environment at more than 9 ppm determined as a TWA exposure for up to a 10-hour workday, exposure limits of CO, or methylene chloride or both shall be reduced to satisfy the relationship:

$$\frac{C(CO)}{L(CO)} + \frac{C(CH2Cl\ 2)}{L(CH2Cl\ 2)} \leq 1$$

where:

C(CO) = TWA exposure concentration of CO, ppm

L(CO) = the recommended TWA exposure limit of CO = 35 ppm

C(CH2Cl 2) = TWA exposure concentration of methylene chloride, ppm

L(CH2Cl 2) = the recommended TWA exposure limit

of methylene chloride = 75 ppm

(3) Occupational exposure shall be controlled so that workers are not exposed to methylene chloride above a peak concentration of 500 ppm (1,740 mg/cu m) as determined by any 15-minute sampling period.

(b) Sampling and analysis

(1) Procedures for sampling and analysis of workroom air for methylene chloride shall be as provided in Appendices I and II, or by any equivalent methods.

(2) Where required, monitoring of workroom air for CO shall be in accord with the sampling requirements of this and the CO standard. Recommended methods for sampling and analysis of workroom air for CO are given in Criteria for a Recommended Standard....Occupational Exposure to Carbon Monoxide.

Section 2 - Medical

(a) Comprehensive preplacement and annual medical examinations shall be made available to all workers subject to exposure to methylene chloride unless a different frequency is indicated by professional medical judgement based on such factors as emergencies, variations in work periods, and preexisting health status of individual workers.

(b) These examinations shall include, but shall not be limited to:

(1) A comprehensive or interim medical and work history to include but not be limited to occurrence of headache, dizziness, fatigue, pain in the limbs, and irritation of the skin and eyes.

(2) A comprehensive medical examination including at least blood counts (hemoglobin or rbc). In addition, clinical impressions of autonomic and pulmonary function shall be noted and follow-up measurements

shall be made where indicated.

(3) An evaluation of the advisability of the workers using respirators.

(4) Such a medical program could also provide the opportunity for advising the worker of the increased hazards of methylene chloride exposure due to CO from tobacco smoking.

(5) It is recommended that COHb values be determined periodically at the end of the workday. It is further recommended that this sampling and analysis be quarterly and coincide with environmental monitoring. If COHb values in excess of 5% are found, an investigation of the source of COHb shall be instituted, and if appropriate from this investigation, periodic environmental monitoring for CO shall be performed.

(c) Medical records shall be maintained for persons employed one or more years in work involving methylene chloride. All medical records with supporting documents shall be maintained at least 5 years after the individual's employment is terminated. The medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employer, and of the employee or former employee shall have access to all medical records.

Section 3 - Labeling (Posting)

The following sign shall be affixed in a readily visible location at or near entrances to areas in which there is occupational exposure to methylene chloride:

METHYLENE CHLORIDE

CAUTION: BREATHING VAPOR MAY BE

HAZARDOUS TO HEALTH.

Use only with adequate ventilation.

Keep containers closed when not in use.

May generate toxic phosgene gas on contact

with flame or very hot metal surface.

AVOID CONTACT WITH SKIN.

Can be absorbed through skin.

This warning sign shall be printed in English and, unless they are otherwise trained and informed of the hazardous conditions, in the predominant language of non-English-speaking workers. Illiterate workers shall be informed.

Section 4 - Personal Protective Equipment and Clothing

(a) Respiratory Protection

(1) Engineering controls shall be used wherever feasible to maintain methylene chloride concentrations at or below the prescribed limits. Compliance with the permissible exposure limits may be achieved by the use of respirators only:

(A) During the time period necessary to install or test the required engineering controls.

(B) For nonroutine operations such as brief exposure at concentrations in excess of the environmental limit for maintenance or repair activities.

(C) During emergencies when air concentrations of methylene chloride may exceed the permissible limit.

(2) When respirators are permitted by paragraph (1) of this Section, a respirator program meeting the requirements of 29 CFR 1910.134 and 30 CFR 11.2-1 shall be established and enforced by the employer.

(3) Only appropriate respirators as described in Table I-1 shall be used pursuant to the following requirements:

(A) For the purpose of determining the type of respirator to be used, the employer shall measure, when possible, the atmospheric concentration of methylene chloride in the workplace initially and thereafter whenever process, worksite, climate, or control changes occur which are likely to increase the methylene chloride concentration; this requirement shall not apply when only supplied-air, positive pressure respirators will be used.

(B) The respirator and canister used shall be of the appropriate class, as determined on the basis of exposure to methylene chloride. The employer shall ensure that no worker is being exposed to methylene chloride in excess of the standard because of improper respirator selection, fit, use, or maintenance.

TABLE I-1

RESPIRATOR SELECTION GUIDE FOR PROTECTION

AGAINST METHYLENE CHLORIDE

Maximum Use Concentrations of Methylene Chloride (Multiples of TWA)	Respirator Type
Less than or equal to 750 ppm (10X)	1) Any supplied air respirator.
Less than or equal to 3,750 ppm (50X)	1) Any supplied air respirator, with full facepiece, helmet or hood. 2) Any self-contained breathing apparatus with full facepiece.
3,750 ppm or more	1) Self-contained breathing apparatus, pressure demand mode (positive pressure), in full facepiece. 2) Combination supplied air respirator, pressure demand mode, with auxiliary self-contained air supply.
Evacuation or escape (no concentration limit)	1) Any escape-type, self-contained breathing apparatus. 2) Any escape-type gas mask providing protection against methylene chloride

(C) The employer shall provide respirators in accordance with Table I-1 and shall ensure that the employee uses the respirator provided.

(D) Respiratory protective devices described in Table I-1 shall be those approved under provisions of 30 CFR 11.

(E) Respirators specified in Table I-1 for use in higher concentrations of methylene chloride are permitted in atmospheres of lower concentrations.

(F) Industrial size and chin-type canisters shall not be used except for escape.

(G) Chemical cartridge respirators shall not be used with methylene chloride.

(H) The employer shall ensure that respirators are adequately cleaned, maintained, and stored and that employees are instructed on the use of respirators and on how to test for leakage.

(4) Where an emergency may develop which could result in employee injury from overexposure to methylene chloride, the employer shall provide respiratory protection as listed in Table I-1.

(b) Protective Clothing

In any operation where the worker may come into direct contact with liquid methylene chloride, protective clothing shall be worn. The clothing shall be both impervious and resistant to methylene chloride. Gloves, boots, overshoes, and bib-type aprons (at least knee length) shall be provided when necessary. Impervious supplied-air hoods or suits shall be worn when entering confined spaces such as pits or tanks. In situations where heat stress is likely to occur, air-supplied suits shall be used.

All protective clothing shall be well aired and inspected for physical defects prior to reuse.

(c) Eye Protection

Eye protection shall be provided for any employee engaged in an operation where methylene chloride liquid or spray may enter the eye. Chemical-type goggles, safety glasses with splash shields, or plastic face shields made completely of methylene chloride-resistant materials shall be used.

Suitable eye protection shall be in accordance with 29 CFR 1910.133.

Section 5 - Informing Employees of Hazards from Methylene Chloride

(a) All new and present employees in a methylene chloride area shall be kept informed of the hazards, relevant symptoms, effects of over-exposure to, and proper precautions concerning safe use and handling of methylene chloride. The increased hazards of methylene chloride exposure from concomitant exposure to CO in the environment and from hard work and smoking shall be included in the information.

(b) The information explaining hazards of working with methylene chloride shall be kept on file and readily accessible to the worker at all places of employment where methylene chloride is manufactured, used, transported or stored.

(c) Information as required shall be recorded on US Department of Labor Form OSHA-20 "Material Safety Data Sheet," or a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Handling and Storage

(1) Containers delivered by truck or rail shall not be unloaded until the vehicle in which they arrived has been ventilated. The vehicle shall not be entered if the odor of methylene chloride is perceptible.

(2) Storage containers, piping, and valves shall be periodically checked for leakage.

(3) Storage facilities shall be designed to:

(A) Contain spills.

(B) Prevent contamination of workroom air.

(b) Contaminant Controls

(1) Suitable engineering controls designed to limit exposure to methylene chloride to that prescribed in subsection (a) of Section 1 shall be utilized. Ventilation systems shall be designed to prevent the accumulation or recirculation of methylene chloride in the workroom and to effectively remove methylene chloride from the breathing zones of workers. Ventilation systems shall be subjected to regular preventive maintenance and cleaning to ensure maximum effectiveness, which shall be verified by periodic airflow measurements.

(2) Portable exhaust ventilation or suitable general ventilation shall be provided for operations that require the application of liquid methylene chloride, such as paint removal or machine degreasing.

(c) Equipment Maintenance and Emergency Procedures

Air saturated with methylene chloride is immediately dangerous to life and creates a limited egress situation.

(1) Exits from methylene chloride hazard areas shall be plainly marked. Emergency exit doors shall be convieniently located and shall open to areas which will remain free of contamination in an emergency.

(2) Confined spaces

(A) Entry into confined spaces or into other areas where there may be limited egress shall be controlled by a permit system. Permits shall be signed by an authorized representative of the employer certifying that preparation of the confined space, precautionary measures, personal protective equipment, and procedures to be used are all adequate.

(B) Tanks, pits, tank cars, process vessels, tunnels, sewers, or other confined spaces which have contained methylene chloride shall be thoroughly ventilated, tested for methylene chloride, oxygen, carbon monoxide, flammable gases, and other suspected noxious gases and inspected prior to entry.

(C) Inadvertent infiltration of methylene chloride into the confined space while work is in progress inside shall be prevented by disconnecting and blanking off methylene chloride supply lines.

(D) Confined spaces shall be ventilated to keep any methylene chloride concentration below the standard and to prevent oxygen deficiency.

(E) Personnel entering confined spaces shall be furnished with adequate personal protective equipment and with a lifeline tended by another worker outside the space. The worker on the outside shall also be equipped with approved respiratory, eye, and skin protection, lifeline, and have contact with a third party.

(F) Written operating instructions and emergency medical procedures shall be formulated and posted in conspicuous locations where accidental exposure to anesthetic concentrations of methylene chloride may occur. These instructions and procedures shall be printed in English and, unless they are otherwise trained and informed of the hazardous areas, in the predominant language of non-English-speaking workers, if any. All illiterate workers shall receive such training.

(d) Showers and Eye Wash Fountains

Showers and eye wash fountains shall be provided and so located as to be readily accessible in all areas where skin or eye splash with methylene chloride is likely. If methylene chloride is splashed on the skin, contaminated clothing shall be promptly removed and the skin washed with soap and water. If liquid methylene chloride contacts the eyes, they shall be thoroughly irrigated with clean water. Medical assistance shall be promptly provided in cases of eye splash. Such incidents shall be reported to the immediate supervisor by the affected employee or by a fellow worker.

Section 7 - Monitoring and Recordkeeping

(a) Where it has been determined that the environmental concentrations do not result in TWA workday exposures above one-half the TWA environmental limit, environmental monitoring is not required. However, records which form the basis for concluding that the exposures are below one-half the limit shall be maintained and exposure surveys shall be made when any process change indicates the need for reevaluation or at the discretion of the compliance officer.

(b) Where exposure concentrations have not been determined, they shall be determined within 6 months of the promulgation of a standard incorporating these recommendations.

(c) Where it has been determined that environmental concentrations result in TWA workday exposures above one-half the limit, employers shall maintain records of environmental exposures to methylene chloride based upon the following sampling and recording schedules:

(1) Samples shall be collected at least every 6 months in accordance with Appendix I for the evaluation of the work environment with respect to the recommended standard.

(2) Environmental samples shall be taken when a new process is installed or when process changes are made which may cause an increase in environmental concentrations. Increased production, relocation of existing operations, and increased overtime also requires resampling.

(3) In all monitoring, samples shall be collected which are representative of breathing-zone exposures characteristic of each job or specific operation in each work area. Sufficient numbers of samples shall be collected to express the variability of exposure for the work situation and to estimate TWA workday exposures and peak exposures for every employee.

(4) The minimum number of representative TWA exposure determinations for an operation or process shall be based on variation in exposures and production schedules, considering the number of workers exposed as suggested in Table I-2, and as indicated by a professional industrial hygienist.

(d) When exposure levels are found to be greater than those prescribed in Section 1(a), environmental concentrations shall be reduced by suitable engineering controls. Exposures shall be monitored at least weekly until the effectiveness of the controls is established.

(e) All records of sampling and of pertinent medical examinations shall be maintained for at least 5 years after the individual's employment is terminated. Records shall indicate the type of personal protective devices, if any, in use at the time of sampling. Each employee shall have access to information on his own environmental exposure.

TABLE I-2

SAMPLING SCHEDULE

Number of Employees Exposed	Number of TWA Determinations
1-20	50% of the number of workers
21-100	10 plus 25% of the excess over 20 workers
more than 100	30 plus 5% of the excess over 100 workers

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing occupational diseases arising from exposure to methylene chloride. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substance which will describe ...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health after a review of data and consultations with others, formalized a system for the development of criteria upon which standards can be established to protect the health of workers from exposure to hazardous chemical and physical agents. It should be pointed out that any criteria and recommended standard should enable management and labor to develop better engineering controls resulting in more healthful work environments and simply complying with the standard should not be the final goal.

These criteria for a standard for methylene chloride are part of a continuing series of criteria developed by NIOSH. The proposed standard applies to the processing, manufacture, and use of methylene chloride as applicable under the Occupational Safety and Health Act of 1970.

These criteria were developed to assure that the standard based thereon would (1) protect against development of acute and chronic

methylene chloride poisoning, (2) be measurable by techniques that are valid, reproducible, and available to industry and governmental agencies, and (3) be attainable with existing technology.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Methylene chloride, (CH2C1 2), also known as methylene dichloride and dichloromethane, is a colorless liquid at room temperature (25 C) with a pleasant odor. [1] Its odor threshold has been determined to be about 200 ppm. [2,3] Some of its physical properties are listed in Table XII-1. [1,4-7]

Commercial production of methylene chloride is by chlorination of methane or methyl chloride which yields a mixture of chloromethanes. Methylene chloride is fractionated from the mixture after washing and alkali scrubbing. Reduction of higher chlorinated methanes, another method of possible manufacture, has no industrial importance. [1,8]

The United States production of methylene chloride increased from 73,963,000 pounds in 1955 to 471,276,000 pounds in 1972. [9-26]

In 1972, manufacture of methylene chloride was reported by 6 companies in the United States. [26] In addition to potential exposures associated with its manufacture, employees of at least 50 companies were potentially exposed to methylene chloride in the manufacture for the retail market of paint and varnish removers, insecticides and fumigants, solvents, cleaners, pressurized spray products, fire extinguishers, and Christmas tree bubble lights. [27]

Persons exposed to methylene chloride in their work could be subjected to additional exposure by home use of commercially available products containing methylene chloride. [27]

Exposure to methylene chloride could occur with each of its many

industrial uses. It is used widely in industry for paint stripping, manufacture of photographic film, and in aerosol propellants. It is used as a solvent in degreasing, in the diphasic treatment of metal surfaces, in the textile and plastic industries, as the carrier in rapid-dry paints, and for extracting heat-sensitive edible fats and essential oils. [1,7,8]

Because of its use as an extractant, it is allowed as a food additive in amounts up to 30 ppm in spice oleoresins, and up to 10 ppm in roasted and instant decaffeinated coffee (21 CFR 121.1039).

NIOSH estimates 70,000 people in the US are potentially exposed to methylene chloride in their working environment.

Historical Reports

In 1867, in England, Richardson [28] reported on human and animal experiments with what he thought was methylene chloride. However, his description of its properties included the observation that the material burned readily, indicating that he was not using methylene chloride.

Junker [29] in 1883 summarized 10 deaths in England from "methylene" anesthesia and pointed out that what was used as methylene chloride was in fact a mixture of chloroform and methyl alcohol. Therefore effects of methylene chloride described prior to this report are of doubtful validity.

The following year Regnauld and Villejean [30] reported that the material obtained from England and sold in France as methylene chloride was also a mixture of chloroform and methyl alcohol. Using purified methylene chloride, they found that if anesthesia was prolonged, anesthetized dogs consistently developed clonic movements and epileptiform attacks. In 1922, similar effects were reported by Hellwig [31] to occur in humans, and were

confirmed in 1923 by Bourne and Stehle [32] in dogs and humans. These investigators [31,32] reported a stage of methylene chloride anesthesia, not characteristic of other agents, in which analgesia and unconsciousness could be obtained without loss of muscle tone. With careful administration of methylene chloride, these states could be maintained for hours.

Grasset and Gauthier [33] reported that because of its analgesic properties methylene chloride could be used during labor without concurrent loss of consciousness or muscle tone. All 44 of the women in the study experienced retrograde amnesia.

In 1933, Nuckolls [34] exposed guinea pigs to methylene chloride vapor in concentrations of approximately 10,000, 20,000, and 50,000 ppm for 2 hours. Each group of animals was observed after 5 minutes, 30 minutes, 1 hour, and 2 hours of exposure. At all concentrations, the guinea pigs developed tremors fairly soon after the onset of exposure. Other muscular activity was noticed, for example, twitchings, noticeable movements of the diaphragm, trembling, and loss of coordination. After 1 hour of exposure at 10,000 ppm or 5 minutes of exposure at either 20,000 or 50,000 ppm, most animals became partly anesthetized, and, as the exposure continued, a few were completely anesthetized. Convulsive movements were noted in all animals, even in those that were anesthetized. Autopsy revealed congested and edematous lungs in some animals.

Collier's [35] 1936 report was the first in the English language of adverse effects of occupational exposure to methylene chloride. In this report he quoted a manufacturer of lacquers who discontinued the use of methylene chloride because of its effects on the workers: "...it dopes them, makes them stupid, they suffer from headache, are unreliable at their

work, are awfully apt to stumble around and hurt themselves, are irritable, unhappy and require constant supervision if they are to be kept from making silly mistakes."

The first report of adverse effects in the American literature appeared in 1947. [36] In this report, 4 men had been overcome by methylene chloride exposure in a hops extraction process, and one died. Concentrations were not reported.

Effects on Humans

(a) Central Nervous System Function During Experimental Exposures

Central nervous system (CNS) function was reported to be impaired during methylene chloride exposure by Fodor and Winneke, [37] Winneke, [38] and Stewart et al. [39]

Fodor and Winneke [37] and Winneke [38] used two indicators of behavioral performance: (1) the visual critical flicker frequency (CFF), and (2) an auditory vigilance task.

The CFF is a measure of the frequency of flickering light at which perception of the flickering changes to nonperception, or vice versa. It was determined experimentally by starting with a rapidly flickering light and gradually decreasing the flickering rate until the subject perceived the flickering. The brightness of the flicker light and the on-off ratio were held constant throughout the experiment. During every exposure of each subject, 8 CFF determinations were made at each of the following times: 30, 80, 130, 180, and 230 minutes.

The auditory vigilance task involved detection of faint and frequently occurring auditory signals. The subject listened through

earphones to a series of pulses of white noise, 0.3 seconds in duration and 2 seconds apart. The noise was 30 decibels above the threshold of sound and at random intervals with a probability of 0.033, the intensity was decreased by 4.8 decibels. The subject was required to detect this difference and report it. Each session lasted 3 hours and consisted of 4 observation periods of 45 minutes each. The measurements of performance were the percentages of signals missed within each of the 12 successive 15-minute observation periods.

In the study reported by Fodor and Winneke, [37] female volunteers, 20-30 years of age, were each exposed to methylene chloride at 300 and 800 ppm. For each subject, exposure at the different concentrations occurred 1 week apart. The subjects were tested individually during 4-hour exposure periods. The 18 x 10 x 9-ft exposure chamber was maintained at constant temperature, humidity, and atmospheric pressure. Gas chromatography was used to measure the methylene chloride concentrations.

Fodor and Winneke [37] found that in 6 subjects the CFF decreased to approximately the same end point under exposure at both 300 ppm and 800 ppm, but the response at 800 ppm was much more rapid than at 300 ppm. After 50 minutes of exposure at 800 ppm, a decrease from 36 flashes/second at the beginning to less than 33 flashes/second was observed and reported as statistically significant. At 300 ppm, a decrease approaching this magnitude was not observed until 140 minutes of exposure. In a control experiment with the same 6 subjects, the CFF did not fall below 34 flashes per second.

The ability to detect sound signals in an auditory vigilance study was reduced by exposure to methylene chloride, particularly during the

middle part of the 4-hour exposure. The authors [37] considered that during the last period of testing there was an "end-spurt" performance or extra effort by the subjects. At 800 ppm, the subjects missed up to 30% of the signals, whereas at 300 ppm they missed no more than 20%, compared to around 10% when not exposed to methylene chloride.

Four experiments with human volunteers exposed to methylene chloride at average concentrations of 317, 470, or 751 ppm for 3 or 4 hours were reported by Winneke [38] in 1973. He also reported exposures of volunteers to carbon monoxide (CO) at 50 or 100 ppm for 5 hours. All experiments took place in a 3 x 6 x 3-meter chamber. Methylene chloride or CO were metered into the chamber and mixed with air to the desired atmospheric concentrations. Methylene chloride was monitored by gas chromatography (GC) and CO by infrared (IR) absorption. The auditory vigilance task, CFF, and a battery of psychomotor tasks were studied to ascertain the effects of exposure.

Subjects exposed at concentrations of 317, 470, and 751 ppm of methylene chloride for 3-4 hours showed decreased CFF, auditory vigilance, and decreased performance in most psychomotor tasks, when compared with controls. The performances were less influenced by exposures at 317 and 470 ppm than at 751 ppm.

By contrast, the 18 volunteers exposed at 50 or 100 ppm of CO showed no impairment of CNS function as measured by these tests. [38]

In experiments reported by Stewart et al [39] in 1972, a total of 11 male subjects ranging in age from 23 to 43 years were exposed in a series of experiments to methylene chloride in concentrations from 213 ±10.4 to 986 ±104 ppm. Concentrations in the exposure chamber were continuously

monitored by IR spectrometry and periodically checked by GC.

One subject exposed for 1 hour to methylene chloride at 213 ppm (SD of 10.4 ppm) reported no unusual feelings during the experiment. [39] All 8 subjects exposed to methylene chloride at 514 ppm for 1 hour also reported no unusual feelings. However, 1 of 3 subjects exposed to methylene chloride, first at 514 ppm for 1 hour then at 868 ppm for a second hour, (experiment A) experienced light-headedness 15 minutes after the concentration was increased.

Three subjects exposed to methylene chloride at 986 ppm (SD of 104 ppm) for 2 hours (experiment B) reported its odor to be moderately strong, but experienced no sensory irritation. [39] Two subjects reported light-headedness after 1 hour of exposure. This feeling cleared 5 minutes after the exposure ceased.

CNS function was studied in experiments A and B by means of the Visual Evoked Response (VER), or change in electroencephalograms in response to a flashing light. In experiment A there were decreases in the amplitude of the response, indicating CNS depression, at the end of the first hour of exposure but not at the end of the second hour. In experiment B, 2 of the 3 subjects showed CNS depression at the end of the first hour and all 3 at the end of the second hour.

Studies of 2 groups of 7 men, 20-30 years of age, during 2 sessions, one with exposure to methylene chloride and the other while breathing control air were reported by Gamborale et al [40] in 1975. In each group the 2 study sessions were held one week apart. In one group, the control session occurred first, and in the other group the methylene chloride exposure session occurred first. Each study session was of 2 hours

duration. Except for the presence of methylene chloride, the experiments were conducted in the same way. During the methylene chloride exposure sessions, the concentration was increased at 30-minute intervals. During the first 30 minutes the concentration was 250 ppm, then 500 ppm, then 750 ppm, and during the last 30 minutes of the 2-hour session, the exposure concentration of methylene chloride was 1,000 ppm.

During the last 20 minutes at each exposure concentration 4 performance tests were conducted. These tests included an addition-reaction time test, a short-term memory test, and 2 simple reaction time tests. Responses to these tests were not affected by exposure to methylene chloride. Upon removal from exposure, the subject's evaluation of their own condition indicated that methylene chloride exerted a subjectively favorable change in their experience of calmness, relaxation, disposition, affection, alertness, and activeness.

(b) Impairment of Biological Oxidation

By chance, Stewart and co-workers [39] observed carboxyhemoglobin (COHb) concentrations of 6% and 8% on 2 occasions in a subject after he had used varnish remover containing methylene chloride. Prompted by this observation, they studied COHb and alveolar CO concentrations during and following the above mentioned experimental exposures to methylene chloride described in the previous section.

Prior to exposure, COHb, RBC count, and serum bilirubin were determined and alveolar breath samples were analyzed for CO and methylene chloride by both GC and IR methods. [39]

In a subject exposed to methylene chloride at 213 ppm for 1 hour, the COHb rose from its baseline of 0.4% to 1.5% after 30 minutes of exposure,

1.75% after 60 minutes, and after removal of the subject from exposure, COHb continued to rise to 2.4% at 3 hours after the end of exposure. Twenty hours after exposure, the COHb measurement was 1.5%. In the exposures at the higher methylene chloride concentrations (514 ppm for 1 hour, 514 ppm for 1 hour followed by 869 ppm for 1 hour, and 986 ppm for 2 hours), similar patterns of COHb build-up and disappearance were observed. The peak concentrations of COHb as well as those remaining 17-24 hours later were proportional to the methylene chloride exposure concentrations and times, as were those remaining 17-24 hours after removal from exposure.

This group of investigators have continued their studies of human exposures to methylene chloride. [41,42,43] Male subjects were exposed for 1, 3, and 7.5 hours/day, 5 days/week for 5 weeks as shown in Table III-1. The 3 subjects in group A were exposed 1 hour/day at each concentration, the 3 subjects in group B were exposed for 3 hours/day, and the 4 subjects in group C were exposed for 7.5 hours/day.

The maximum COHb values observed in nonsmokers are shown in the last column of Table III-1. In the 3-hour and 7.5-hour exposures, COHb concentrations generally reached maximum values by the end of exposure, although in a few cases, particularly on Fridays, higher values were observed one hour after exposure than at the end of exposure. In contrast, in the 1-hour exposures most of the COHb values observed 1 hour after exposure were greater than those at the end of exposure. [41]

With 7.5-hour exposures to methylene chloride at 50 ppm, the maximum observed COHb concentrations averaged 2.9% in nonsmokers; at 100 ppm methylene chloride, the maximum observed COHb concentrations in nonsmokers averaged 5.7% on the 5th consecutive day of exposure. [41]

TABLE III-1

SCHEDULE FOR EXPOSURE OF 10 MEN TO METHYLENE CHLORIDE

Exposure Week	Exposure Concentration ppm	Exposure time, daily hours	Number of Subjects	Subject Group	COHb ppm %
1	50	1	3	A	1.3
1	50	3	3	B	1.9
1	50	7.5	4	C	2.9
2	250	1	3	A	3.0
2	250	3	3	B	5.0
2	250	7.5	4	C	10.3
3	250	1	3	A	2.5
3	250	3	3	B	4.3
3	250	7.5	4	C	9.5
4	100	1	3	A	3.2
4	100	3	3	B	3.0
4	100	7.5	4	C	5.7
5	500	1	3	A	4.4
5	500	3	3	B	5.6
5	500	7.5	4	C	11.7

Derived from references 41-43

During the week, COHb values had not returned to normal on Tuesday through Saturday mornings with 7.5-hour exposures at more than 50 ppm methylene chloride. However, by Monday morning, COHb had returned to baseline values. When exposures at 100 ppm or more were of 1 or 3 hours duration, COHb appeared to have returned to baseline values daily, although the data were limited. [41]

In a similar experiment, [42] women were exposed to methylene chloride at 250 ppm on 5 consecutive days. The baseline COHb values were higher in the women (1.3%) than in the men (0.8%). With each exposure time, (1, 3, and 7.5 hours) comparably higher COHb values were found in

nonsmoking women than in nonsmoking men exposed at 250 ppm, as shown in Table III-2.

TABLE III-2

CARBOXYHEMOGLOBIN CONCENTRATIONS IN NONSMOKERS EXPOSED TO METHYLENE CHLORIDE AT 250 ppm

Exposure time, hours	Maximum observed average COHb (%)	
	men [41]	women [42]
0	0.8	1.3
1	3.0	4.0
3	5.0	5.4
7.5	9.6	10.6

COHb formed during and following experimental exposure of human subjects to methylene chloride during rest and exercise was reported by Astrand et al [44] in 1975. These investigators exposed 4 or 5 subjects to methylene chloride in 3 experiments at 250 and 500 ppm at rest and during exercise on a bicycle ergometer. In each experiment, the total exposure time was 2 hours with the 1st 30-60 minutes of exposure occurring during rest. The workloads imposed during the remainder of the exposure were equivalent to 21.7, 43.4 and 65.1 ft-lbs (50, 100, 150 watts). COHb in blood was reported as g/100 ml rather than % COHb. Considering normal Hgb as 15.4 g/100 ml, [44] 1% COHb would be equivalent to 0.154 g COHb/100 ml blood. These investigations also substracted preexposure COHb from the amounts found during exposure.

Because of the design of the experiment, the effects of methylene chloride concentration, exercise level, and exposure time were not clearly seperate. However, it appears from the data that exercise during exposure resulted in lower COHb values at the end of 2 hours of exposure than have been found by others with 2 hours of exposure at rest. COHb continued to rise for up to 3 hours after removal from exposure with exercise, compared to up to 1 hour in experiments previously reported by others. [41,42]

Effects of exposure to a paint remover during rest and exercise were reported by Stewart and Hake [45] in 1976. The volatile components of the paint remover were 80% methylene chloride and 20% methanol by weight. The volume of the exposure chamber was 2,680 cu ft. During a 3-hour experiment, 1 quart of the paint remover was applied to, and scraped from, a baby crib. One subject applied and scraped the paint remover, while another subject sat in the chamber so the results of exposure at work and at rest could be compared. The experiment was conducted 4 times at different ventilation rates and the methylene chloride vapor concentration in the breathing zone of the subjects was continuously monitored by IR. The average breathing zone concentrations of methylene chloride in the 4 experiments were 216, 368, 654, and 788 ppm. Methanol concentrations measured at the end of each hour of exposure averaged 77, 115, and 186 ppm, prespectively in the first 3 experiments, and was not measured in the other.

In these experiments, [45] there were small differences in the COHb values of the active and inactive subjects at the end of exposure, but the differences increased after exposure as the COHb continued rise for up to 4 hours in the active subjects. In all subjects the return of COHb to preexposure values was delayed in comparison to subjects exposed to only

methylene chloride. [41,42] The authors [45] proposed that this prolonged maintenance of elevated COHb was an effect of methanol on methylene chloride uptake and metabolism.

The affinity of 4 subjects' hemoglobin for oxygen was determined during the 5th to 7th hour of exposure on Thursday or Friday of each exposure week. [43] The affinity of Hgb for oxygen was increased. That is, the ability of the red blood cells to give up oxygen to the tissues was decreased. The average oxygen tensions required to saturate 50% of the Hgb are summarized in Table III-3. The data show a progressive decrease in the oxygen tension with increasing methylene chloride exposure concentration, and some recovery toward normal in the week following the last exposure.

The physiological significance of this change in the oxygen binding property of hemoglobin may be minor since arterial blood lactate following exercise was only slightly elevated when the exposure was to methylene chloride at 500 ppm, and not at all elevated when the exposure was at 100 ppm. [43]

TABLE III-3

OXYGEN TENSION FOR 50% HEMOGLOBIN SATURATION
IN SUBJECTS EXPOSED TO METHYLENE CHLORIDE

Exposure week	Exposure concentration ppm	Oxygen tension mm Hg
1st	0	26.7
2nd	50	26.3
5th	100	24.7
3rd	250	24.4
4th	250	24.0
6th	0	25.9

Derived from Forster et al [43]

(c) Absorption

Absorption of inhaled methylene chloride in 2 subjects was reported by Lehmann and Schmidt-Kehl [46] in 1936. The methylene chloride in the room air and in the exhaled air was collected in alcohol and analyzed by alkaline hydrolysis. The percent absorbed was determined from the ratio of the concentration in exhaled air to the concentration in room (inhaled) air. Both subjects absorbed similar amounts; the authors averaged and reported the data as shown in Table III-4.

TABLE III-4

ABSORPTION OF METHYLENE CHLORIDE BY HUMAN SUBJECTS

Experimental day	Inhalation Concentration mg/liter	ppm	Exposure time, min	Abosrbed %
1	2.3	662	20	74
2	2.8	806	30	75
3	4.0	1,152	30	72
4	4.1	1,181	30	70

Derived from Lehmann and Schmidt-Kehl [46]

Other investigators [47,48] reported that lesser amounts of methylene chloride were absorbed. In 1966, Riley et al [47] reported absorption of methylene chloride in 1 subject exposed at 100 ppm for 2 hours as ranging from 70% at the beginning of exposure to 31% at the end. The exposures took place in a specially constructed room where methylene chloride concentrations were measured with a continuously recording hydrocarbon analyzer. The subject was seated and not required to carry out any

physical work.

During exposures at 100 and 200 ppm in the experiments reported by DiVincenzo et al, [48] 50-66% of inhaled methylene chloride was absorbed. (Tables XII-2, XII-3, and XII-4). Astrand et al [44] found that during 30-minute periods of exposure at 250 and 500 ppm at rest about 55% of the inhaled methylene chloride was absorbed. During 30-minute periods of exposure during exercise, the percent absorbed decreased but, because of the greater amount inhaled, the total amount absorbed was increased 2-3 times by exercise.

Stewart and Dodd [49] studied absorption of methylene chloride through the skin of the thumb. Four subjects each immersed 1 thumb in methylene chloride for 30 minutes. Breath concentrations of methylene chloride at 10 and 30 minutes of exposure and at 10, 30, 60, 120, and 300 minutes after exposure are shown in Table III-5.

TABLE III-5

ALVEOLAR AIR CONCENTRATIONS OF METHYLENE CHLORIDE FROM THUMB IMMERSION

Time, min	Concentration, ppm
After beginning of exposure	
10	1.4-2.4
30	2.3-3.6
After end of exposure	
10	2.1-4.1
30	1.1-6.6
60	0.6-4.1
120	0.26-1.7
300	<0.1

Derived from Stewart and Dodd [49]

(d) Excretion and Blood Concentrations

In the experiments reported by DiVincenzo et al, [48] concentrations of methylene chloride in the blood and its excretion in the breath and urine were studied in 11 healthy human volunteers, 28-60 years of age. Exposures were either at 100 or 200 ppm for 2 hours, or at 100 ppm for 4 hours. To establish exposure room concentrations, liquid methylene chloride was delivered at constant flow over a heated surface. The resulting vapor was carried in a continuous flow of nitrogen into the intake mixture throughout the chamber where day to day variations in methylene chloride concentrations were ±5-10% of the intended concentration. During exposure, the subjects were usually seated in a 5 x 6.5 x 11-ft chamber. In some experiments conducted in the same chamber, the subjects exercised intermittently during the exposure.

Exhaled breath samples, not alveolar air samples, were collected in plastic bags and 25-ml aliquots were injected into the gas chromatograph. Two-milliliter samples of venous blood were transferred to 25-ml heparinized Erlenmeyer flasks, and urine was collected in amber bottles from which 2-ml aliquots were transferred to 25-ml Erlenmeyer flasks for analysis. The Erlenmeyer flasks containing the urine and the blood samples were heated at 75-80 C for 5 minutes, and head space vapor was drawn off directly into the chromatograph for methylene chloride analysis.

DiVincenzo et al [48] in 1972 graphically summarized the data on excretion of methylene chloride in the breath. The tabular data, subsequently supplied to NIOSH by the authors, are presented in Tables XII-2 to XII-6. The subjects, while at rest, were exposed either at 100 or 200 ppm of methylene chloride for 2 hours (Tables XII-2 and XII-4). The

magnitude of exhaled breath concentrations was directly proportional to the magnitude of exposure. After the exposure ceased, the concentration of methylene chloride in the breath decreased rapidly and by 5 hours the concentration was less than 1 ppm.

With a given concentration, DiVincenzo et al [48] found that increasing the exposure time from 2 hours to 4 hours did not double the concentrations of methylene chloride in exhaled breath after exposure, but doubling the exposure concentration did. The postexposure breath concentrations for the 2-hour and 4-hour exposures at 100 ppm of methylene chloride are shown in Tables XII-2 and XII-3.

Individuals who exercised during exposure at 100 ppm absorbed more methylene chloride than those who did not exercise, as evidenced by elevated postexposure excretion (Table XII-6). [48]

The concentrations of methylene chloride in blood during and after the 2-hour exposure at 200 ppm, and after the 2-hour exposure at 100 ppm, are presented in Tables XII-7 and XII-8. [48] The concentrations in blood at the end of exposure were proportional to the initial exposure concentration. Upon cessation of exposure, blood methylene chloride decreased rapidly at first, then more slowly.

The urinary excretion of methylene chloride by 4 individuals exposed at 100 ppm for 2 hours and by 7 individuals exposed at 200 ppm for 2 hours was studied. [48] An average of 22.6 μg of methylene chloride was excreted in 24 hours by the group exposed at 100 ppm (Table XII-9) and an average of 81.6 μg by the group exposed at 200 ppm (Table XII-10). Fluid consumption was not regulated.

Venous blood concentrations found by Astrand et al [44] in subjects exposed at 250 ppm for 2 hours who had exercised for 1.5 hours averaged 3.6 mg/kg compared to a maximum of 2.2 mg/liter reported by Divincenzo et al [48] for their subjects who had been exposed at rest. Four hours after removal from exposure the concentration of methylene chloride in the subjects reported by Astrand et al [44] was 0.8 mg/kg compared to a maximum of 0.155 mg/liter in the subjects reported by Divincenzo et al. [48]

Based on data from a series of exposure concentrations (44-680 ppm) and exposure times (2-150 minutes), Riley et al [47] developed a model for estimating exposure concentrations from methylene chloride concentrations in the breath after exposure. They had an opportunity to test the model when a workman was accidently anesthetized by a 4-hour exposure to methylene chloride. Breath samples collected 3.5, 19, and 44 hours after the workman was removed from the exposure area contained approximately 500, 30, and 3 ppm methylene chloride, respectively. Using the model, they estimated that the man had been exposed at 8,000-10,000 ppm of methylene chloride.

(e) Occupational Exposures

One of the earliest reports of methylene chloride intoxication in industry was by Collier [35] in 1936. Four painters had been removing paint from the walls of a large room with closed windows. A paint remover which contained approximately 96% methylene chloride was used to soften the paint which was then scraped off by hand. Concentrations of methylene chloride to which the men were exposed were not determined. All 4 men complained that while using the paint remover they became faint, giddy, and "stupid." They also stated that "the stupor passed off after a few hours,"

that they "felt better when not at work," that the "stuff upset their appetites," and that they "did not care for food." Two of the 4 men were sufficiently ill to have to leave work.

One of them was 42 years old and had been a painter for 13 years. He complained of irregular but severe pains in the legs and arms, "hot flushes," headache, vertigo, "stupidity" while working with paint remover, poor eyesight at night, anorexia, precordial pain, rapid pulse, shortness of breath, great fatigue on exertion, and attacks of rapid heart beat.

The second painter examined by Collier [35] was 45 years of age, had been a painter for 20 years, and had been using the paint remover indoors extensively for the last 2 years. He claimed to be drowsy at work and disinclined to do anything in the evenings. He was irritable and had pains in his head and tingling in his hands and feet. In this case, the blood picture was essentially normal and showed no punctate basophilia. Collier [35] found that the patient had a peptic ulcer and had suffered intermittently for 2 years from methylene chloride intoxication. No specific laboratory studies to confirm methylene chloride poisoning were reported.

A report of 4 cases of acute exposure to methylene chloride was made by Moskowitz and Shapiro [50] in 1952. The exposures occurred in a factory in which methylene chloride was used to extract an oleoresin from plant material. The operations in the plant were mainly in closed systems, but there was some opportunity for methylene chloride vapor to escape into the workroom. Workers were instructed to leave the plant as soon as they could detect the odor of the solvent. The exposure took place during the night shift in the winter. The exposure times were known to have been from less

than 1 hour to about 3 hours, but the concentrations of methylene chloride in the work atmosphere were not known. The 4 men were found unconscious, either on the first floor or in the basement. Two of the 4 workers had contusions and lacerations of the head. They were all removed to a hospital where 1 worker was found to be dead on arrival and the others recovered. The 3 survivors remained unconscious for about 2.5 hours after they were removed from the plant. [50]

Two of the men were hospitalized for 4 days, and the other for 8 days. None of them remembered smelling methylene chloride. They exhibited signs of either eye, lung, or respiratory tract irritation. They had low hemoglobin values (76-79%) and low RBC counts (3,550,000-3,950,000). All other findings appeared normal. The individual who died had been employed in the plant for 7 months prior to the accident. On necropsy the dura mater was found adherent to the skull and the veins of the pia-arachnoid were conspicuously engorged. The authors reported that there was no evidence of skull fracture. The lung tissue contained 0.1 ml of methylene chloride per 500 g of tissue. [50]

A 19-year-old laborer was the subject of a report by Hughes [51] in 1954. The man was exposed to methylene chloride for 4 hours while degreasing copper gaskets in a small, poorly ventilated room. Concentrations of methylene chloride were not measured. He reported that he noticed an oppressive odor and that his eyes were irritated. During the latter part of the shift he complained of excessive fatigue, weakness, sleepiness, lightheadedness, chilly sensations, and nausea. He was admitted to the hospital with shortness of breath, substernal pain of 8 hours duration, weakness, a dry nonproductive cough, temperature of 100 F,

pulse of 100, and respiratory rate of 42. Rales were heard at the base of his right lung and occasionally elsewhere over the chest. A chest x-ray showed diffuse spongy infiltration of both lung fields, characteristic of pulmonary edema. The patient was treated with penicillin, and all symptoms subsided 18 hours after exposure to methylene chloride. Chest x-rays made after intervals of 3 and 5 days were reported as normal.

Christensen and Huizinga [52] reported on the case of a 17-year-old male who was found dead in a turret where he had been using a mixture of 80% methylene chloride and 14.9% methanol to remove paint. The autopsy showed slight enlargement of the liver and heart and voluminous lungs. The alveoli contained enlarged nodules of bloody fluid. Barbiturate derivatives were found by thin-layer chromatography in the blood, urine, brain, and stomach contents. Death was ascribed to the combination of barbiturates and methylene chloride.

Stewart and Hake [45] reported on a fatality following exposure to a paint stripping formulation that contained 80% methylene chloride. Other components of the formulation were not reported. Although this was not an occupational exposure, it was the result of an application of methylene chloride that does occur occupationally. The 66-year-old man used the paint stripper in his basement on 3 occasions for 2-3 hours each time. On each occasion he developed severe radiating retrosternal pain. On the 1st 2 occasions he was hospitalized. The patient's 1st hospital course was uncomplicated, but during hospitalization for the next acute myocardial infarction that occurred with the 2nd exposure 2 weeks later, cardiogenic shock, dysrhythmia, and heart failure occurred. The fatal exposure occurred 6 months after discharge from this hospitalization. On this final

occasion, the man developed chest pain, collasped, and died 2 hours after working slowly with the paint stripper.

(f) Phosgene Hazards from Methylene Chloride

Phosgene is a combustion product of methylene chloride, [34,53] and two cases resembling phosgene poisoning in persons using methylene chloride paint remover in the presence of kerosene flames were reported by Gerritsen and Buschmann [53] in 1960. A 52-year-old painter, working in a small room with the windows closed and a kerosene stove in use, experienced a burning sensation in his throat. He continued working and after a few hours had feelings of tightness in his chest. Later that day, he was admitted to the hospital after having been found extremely dyspneic and cyanotic. He died a few hours after arrival at the hospital. The diagnosis was influenzal pneumonia with pulmonary edema and cardiac decompensation. Extensive degenerative changes were found in the epithelium of the trachea, bronchi, and bronchioli together with hemorrhagic edematous focal pneumonia. Confirmatory microbiolgial studies were not performed. While there is no basis to question the physician's diagnosis, it seems that an equally tenable diagnosis, from the data presented, was phosgene poisoning.

In the second case [53], a 38-year-old woman in the 7th month of pregnancy used a paint remover containing methylene chloride in a cellar heated by a portable kerosene stove. The exposure occurred during a 3-hour period in the afternoon. In the evening, she had a feeling of tightness in her chest. She expectorated some blood-stained sputum. The next morning she felt much worse with symptoms of dyspnea and cyanosis. Her pulse was 120 and her temperature was 101 F. A chest x-ray revealed opacities similar to those seen in cases of pulmonary edema. The patient was treated

and discharged 8 days later. Two months later, she gave birth to a healthy child. [53]

Another case resembling phosgene poisoning was reported in 1964 by English. [54] A 67-year-old interior decorator used methylene chloride in the presence of a kerosene stove in a small, unventilated room. After 8 hours he experienced breathlessness, headache, giddiness, and a tight feeling across the chest. On admission to the hospital the next morning, the breathlessness had increased. The patient was cyanotic, sweating, and tachypneic, with extensive coarse rales in both lungs. He had extreme right hypochondrial tenderness. He had nausea with vomiting, dyspnea, hypotension, and a history of chronic bronchitis and a quiescent duodenal ulcer. Anorexia and intractable retrosternal and epigastric pain persisted for 4 weeks after admission. After 5 weeks of hospitalization the patient was discharged, but he experienced lassitude, weakness, and hypochondriasis for 3 additional months. Since the man had previously used paint strippers containing methylene chloride without such effects, the diagnosis was phosgene poisoning from methylene chloride decomposition in the presence of heat from the kerosene stove. [54]

Epidimiologic Studies

A study of 33 workers, 17 women and 16 men, who used methylene chloride in the production of cellulose acetate film foils, was reported by Kuzelova and Vlasak [55] in 1966. The film foils were produced from a solution of 13% cellulose triacetate, 78% of which was methylene chloride, and the remainder a mixture of methanol, triphenylphosphate, and dibutylphthalate. The methylene chloride also contained impurities of

0.25% methyl chloride, 0.25% chloroform, and 1% ethyl alcohol. The concentrations of methylene chloride in the air of the workplace were determined for 13 locations within the plant, but the method of analysis was not stated. The concentrations ranged from 30 to 5,000 ppm (0.1-14 mg/liter) (Table XII-11). [55]

Most of the workers had been exposed for an average of 2 years. Many of the exposed workers reported experiencing a sweet taste, mild intoxication, and heart palpitations. The authors [55] reported that 72% of the workers complained of headache and 50% of increased fatigue, that 49% had irritation of the upper respiratory tract and conjunctiva, that 30% had digestive disorders and that neurasthenic disorders were found in 50% of the exposed persons. Clinical and laboratory examinations revealed no abnormalities. On the assumption that methylene chloride was metabolized to formaldehyde and formic acid, the investigators [55] studied formic acid in the urine. Although formic acid was found in the urine of most exposed persons, there was no correlation between the intensity of exposure to methylene chloride and the concentration of formic acid in the urine. [55]

Fifty-nine workers chronically exposed in Russian chemical plants to mixtures of chlorinated methanes including methylene chloride were studied by Fokina [56] and reported in 1965. The maximum permissible concentrations (MAC) of individual components were exceeded at times, but detailed exposure data were not presented. The Russian MAC for the chlorinated methanes were: methyl chloride, 2.42 ppm; carbon tetrachloride, 3.2 ppm, methylene chloride, 14.4 ppm; chloroform, not established at that time. [57] Thirty-three of the workers showed signs of autonomic dysfunction, including deterioration or disappearance of the

corneal reflexes, dissociation between the deep (exaggerated) and superficial (sluggish) reflexes, marked persistent dermographism, general hyperhydrosis, acrohyperhydrosis, blotchiness of the skin on hands and forearms, tenderness when pressure was applied to specific cervical points, and arterial hypotension. In 18 workers there were signs of "diencephalic" disturbances including 13 with "narcoleptic-like" attacks of "irresistible somnolence," 4 with "autonomic vascular crises," and one with "cataleptic" type numbness. Signs of autonomic-sensory neuritis were found in 8 additional workers. Autonomic dysfunction was mainly found in workers employed for less than 3 years. Workers employed for more than 5 years showed autonomic polyneuritis and diencephalic disturbances. [56] The meaning of this study is difficult to interpret or apply because the exposure concentrations were not reported in sufficient detail and the terminology used to describe the worker responses was not clear.

A 39-year-old chemist in a pharmaceutical factory was judged by Weiss [58] in 1967 to have developed toxic encephalosis from chronic exposure to methylene chloride by inhalation and skin absorption. The chemist had worked several hours a day for 5 years in an unventilated 100-cubic meter room where sodium chloride was rinsed in methylene chloride and recrystallized. Methylene chloride in the workroom air arose from the distillation of the salt solution into 2 open containers, from opening the distillation apparatus several times each day to remove the salt, and by evaporation from the salt which was spread on filters to dry. Measurements of methylene chloride in the workroom air were 660 ppm above the container, 900 ppm in the breathing zone above the open distillation equipment, and 3,600 ppm at 20 cm above the ground. The method of analysis was not given.

[58] The hands and arms of the chemist were also exposed to liquid methylene chloride when the salt was removed from the distillation apparatus.

After 3 years of exposure the chemist complained of a burning pain around the heart, a feeling of pressure, palpitations, and restlessness. He also complained of forgetfulness, insomnia, and a feeling of drunkenness. At first these disturbances disappeared after he left the workplace, but later he claimed that he needed a few days away from the job to recover. During the last few months of the 5 years during which the worker had been exposed to methylene chloride, he developed auditory and visual hallucinations. Examination of the man did not show any organic disorder, especially no sign of liver trouble. The ECG showed no circulatory problems and there were no changes in hemoglobin or RBC count. There was slight erythema on the skin of the hands and underarms. Several days after removal from exposure the man felt better and eventually recovered. [58]

Ratney et al [59] studied concentrations of CO in their own alveolar air and that of 4 workers engaged in manufacturing plastic film. A commercial instrument that utilized a 3-electrode electrochemical cell was used to measure CO concentration. The workmen were 20, 21, 26, and 33 years of age, and the 3 members of the investigative team were 33, 33, and 41 years of age. Two of the workers were smokers who agreed not to smoke from 12 hours before the first alveolar air samples were taken and until the final samples were collected. The employees had worked in the plant 8 hours/day, 6 days/week for several years. The investigators and the workers were exposed to methylene chloride in the factory air on the day

prior to and on the day of the alveolar breath sampling.

In the manufacturing process, methylene chloride was the main component of the solvent mixture which also contained chloroform and toluene. Workroom air concentrations of methylene chloride were measured periodically for 42 hours, beginning 18 hours prior to alveolar breath sampling. [59] The environmental concentrations of methylene chloride are summarized in Table XII-12. (LD Pagnotto, written communication, December 1973) On the first day, the concentrations at the location where workers spent most of their time ranged from 210-471 ppm. During the day on which alveolar air samples were taken, methylene chloride concentrations at the same location, determined by collection on charcoal and analysis by gas chromatography, ranged from 159 to 219 ppm with a mean of 183 ppm. The authors [59] reported that there was no measurable CO in the workroom air.

Alveolar air samples were taken from the 7 subjects at regular intervals during a 24-hour period beginning 18 hours after environmental sampling had started. All of the breath samples were analyzed for CO and some for methylene chloride. Methylene chloride was detected qualitatively in the breath of the subjects. The authors [599] estimated COHb percentages from alveolar CO concentrations from the formula:

%COHb = 230 (PCO2) x (%O2Hb/PO2), where:

PO2 is assumed to be 98 mmHg, and

% O2Hb is assumed to be (99-%COHb).

The alveolar CO concentrations and the estimated COHb percentages derived from them for the 7 subjects are presented in Table XII-13. COHb, estimated from the breath sample CO measurements at the time the employees arrived at work on the day of the alveolar air sampling, averaged 4.9% with

a range of 3.3-5.3%. Eight hours after the onset of exposure, the mean estimated COHb was 8.3% with a range of 5.7-12.0%; at the beginning of the next workday, COHb ranged from 3.6 to 4.9%.

Animal Toxicity

(a) Acute Inhalation Exposures

In 1931, Flury and Zernik [60] reported their previously unpublished experiments in which they exposed animals to methylene chloride. Mice exposed for 2 hours developed narcosis at 10,000 ppm and died at 14,500 ppm. Dogs and rabbits exposed at 4,000 ppm for 6 hours developed light narcosis after 2.5 and 6 hours, respectively. After removal from exposure, recovery was "soon." During exposure to methylene chloride at 6,000 ppm for 6 hours, light narcosis was reached in 3/4 hour in rabbits and cats, 2 hours in dogs, and 2 to 2.5 hours in guinea pigs. All the experimental animals recovered from narcosis in 15-60 minutes after removal from exposure. The rabbits died 24 hours later, but no deaths were reported in the other species. The number of animals used in these experiments was not given.

Muller [61] in 1925 gave "fatal" concentrations for mice as 17,000 ppm (63 mg/liter) and Lazarew [62] in 1929 determined them at 14,500 ppm (50 mg/liter). Svirbely et al [63] exposed groups of 20 mice each to a series of methylene chloride concentrations (13,000-17,000 ppm) for 7 hours and estimated the LC50 to be 16,188 ±98 ppm within 8 hours after exposure. The mice exposed by Svirbely et al [63] were restless and had muscular twitchings, uncoordinated movements, labored respiration, and narcosis.

Von Oettingen et al [64] studied the effects of methylene chloride on dogs breathing through a tracheal cannula. At 15,000 and 20,000 ppm, pupillary and corneal reflexes disappeared after 10-20 minutes when methylene chloride concentrations in the blood were 33 mg%. Complete muscular relaxation developed after 25-35 minutes at which time methylene chloride concentrations in the blood were 42 mg %. At 40,000 ppm, corneal and pupillary reflexes also disappeared after 10-20 minutes, but complete muscular relaxation developed after 16 minutes when the methylene chloride concentrations in the blood were 46-50 mg %. Of the 5 dogs exposed at 40,000 ppm, 1 died after 2.5 hours, 1 after 4.5 hours, and 1 after 5 hours. No deaths occurred in the dogs exposed at either 15,000 or 20,000 ppm.

Other effects of methylene chloride on the central nervous system were studied by Berger and Fodor [65] who exposed rats to methylene chloride at concentrations ranging from 2,800 to 28,000 ppm. Electrodes were implanted on albino rats in order to study electroencephalograms (EEG) and electromyograms (EMG). In these exposures, an initial excitement period was followed by a deep narcosis, a decrease in muscular tonus detected by EMG and a reduction of EEG activity. This was followed by breathing difficulties, tremors, and a continued, gradual decrease in electrical amplitudes. At concentrations between 25,000 and 28,000 ppm, electrical activity stopped after 1.5 hours, and after 6 hours at concentrations between 16,000 and 18,000 ppm. Wheather the decreases in electrical amplitudes and the later cessation of electrical activity were due to EEG or EMG was not explained.

At concentrations ranging from 5,000 to 9,000 ppm, long sleeping periods occurred without desynchronization phases which usually appear every few moments with normal sleep. [65] Measurable changes in EMG and EEG patterns were not found with concentrations below 5,000 ppm, but when rapid eye movements (REM) were then examined as a criterion of sleep pattern, changes were found. A 14-hour inhalation of 2,800 ppm methylene chloride decreased the proportion of REM sleep in relation to the entire sleeping time. During the subsequent 24-hour period, the investigators [65] found an increase in wake periods and a normalization in the proportion of REM phases.

Sleeping patterns as indicators of CNS function were also studied by Fodor and Winneke [37] in albino rats exposed to methylene chloride. Sleep-wakefulness behavior was assessed by EEG and EMG activity on 3 consecutive days in 20 female albino rats weighing 180-220 g. On the first and third days, the animals inhaled air in a 16 x 16 x 25-inch test chamber. On the second day, the rats were exposed to methylene chloride at either 500, 1,000, or 3,000 ppm. Under nonexposure conditions the animals slept approximately 56% of the time, of which 16% was REM sleep. During exposure, total sleep time and the time between 2 successive REM periods increased in proportion to the methylene chloride concentration. At 500 ppm, the effect on total sleep time was small and REM sleep was almost identical to that in controls.

Running activity of male rats in activity cages was studied by Heppel and Neal. [66] Data for all the animals are shown in Table XII-14. Five young adult male rats were selected for this experiment on the basis of running activity. They were housed in regular stock colony cages and were

fed dry dog food and cabbage. The rats were put in activity cages in the evenings and allowed to adjust to their environment for 30 minutes. Then the number of revolutions of the drum was recorded for 1 hour. The rats were then removed from the chamber to feed for 90 minutes. Twenty preexposure determinations were made for each rat. The rats were then exposed to methylene chloride on 5 alternate days as follows: the exposure chamber was charged with 5,000 ppm methylene chloride, the rats were placed in the exposure chamber for 30 minutes to adjust to the environment, the running activity was measured for 1 hour, the vapor flow was turned off and 30 minutes were allowed to pass, then the activity was measured for another hour. On the intervening days, activity was measured as during the preexposure period. [66]

The average numbers of revolutions for the 5 rats during the preexposure period were 186, 482, 518, 725, and 928. These running scores were generally greater than those during the exposure period. For example, the rat which had a score of 725 during preexposure conditions had scores of 1, 136, 0, 276, and 232, respectively, during exposures to methylene chloride. During the exposure period, the rats ran more on the days when there was no exposure. On the exposure days they ran more during the postexposure hour than during the exposure hour. [66]

Excretion of methylene chloride in fasted male beagle dogs, 6 years of age, was studied by DiVincenzo et al. [48] In a 1-cubic meter inhalation chamber, dogs were exposed at 100, 200, 500, or 1,000 ppm for 2 or 4 hours. Methylene chloride was introduced into the chamber by means of a dual action syringe pump. Postexposure breath samples were collected with a tracheal tube or with a latex mask equipped with a 2-way valve. Venous

blood was withdrawn from the femoral vein. Samples were analyzed by gas chromatography. [48]

As with their human subjects, the serial breath excretion curves in the dogs were proportional to the initial concentration. [48] Methylene chloride was more concentrated in the breath of dogs than in that of humans exposed at the same concentrations for the same time, but humans eliminated methylene chloride at a faster rate. The concentrations of methylene chloride in the blood were parallel to those in the breath. The half-life of methylene chloride in the blood was found to be 1.5 hours. As in humans, only a slight increase in methylene chloride concentration in the breath occurred when the exposure time was doubled.

Carbon monoxide concentrations in the blood of a large number of rats exposed to methylene chloride, CO, and combinations of the two were reported by Fodor et al [67] in 1973. Carbon monoxide was determined by gas analysis methods and COHb percentages were estimated from the blood CO concentrations. The control air contained 0.5-2 ppm CO, and its inhalation by the rats for 3 hours gave control CO concentrations in the blood of 1.0 10.2 μg/ml of blood, and an estimated 0.4% COHb. Carbon monoxide in the blood following exposure at 100 ppm of CO for 3 hours was 27.4 μg/ml and the estimated COHb was 10.9%. Measurements of CO in the blood of rats exposed to methylene chloride for 3 hours were elevated as shown in Table III-6.

TABLE III-6

CARBON MONOXIDE IN RAT BLOOD AFTER METHYLENE CHLORIDE EXPOSURE

CH_2Cl_2 Concentration, ppm	μg CO/ml blood	Estimated COHb, %
50	7.6 ±1.3	3.2
100	15.3 ±2.4	6.2
500	26.1 ±3.3	10.5
1,000	31.1 ±3.7	12.5

Derived from Fodor et al [67]

With exposure for 3 hours to a mixture of 100 ppm CO and 100 ppm methylene chloride, CO in the blood measured 40.8 ±2.5 μg/ml, and the estimated COHb percentage was 16.4. When the exposure concentration of CO was 100 ppm and methylene chloride was 1,000 ppm, the measured CO in the blood was 47.3 ±5.5 μg/ml and the estimated COHb percentage was 19.0. [67]

Concentrations of COHb in the blood of rabbits exposed for 20 minutes at 2,000-12,000 ppm methylene chloride were found by Roth et al [68] to be a linear function of methylene chloride exposure concentration, approximately 5.5% at 2,000 ppm methylene chloride and 13% at 12,000 ppm. The rabbits were exposed individually by face mask. In 4-hour exposures at about 7,000 ppm methylene chloride (6,850-7,320 ppm) steady state COHb concentrations of 14% were reported. These reported COHb concentrations were the determined values minus the preexposure values, which averaged 0.75%. COHb was determined spectrophotometrically from absorbance at 3 wave lengths on a double beam spectrophotometer. [68]

wave lengths on a double beam spectrophotometer. [68]

(b) Chronic Intermittent Inhalation Exposures

Effects of daily inhalation of methylene chloride on several species of animals were reported by Heppel et al [69] in 1944. In a preliminary experiment, 2 monkeys, 2 dogs, 2 pups, 4 rabbits, 16 guinea pigs, and 16 young rats were exposed to methylene chloride at 500 ppm for 8 hours/day, 5 days/week for 15 weeks. Three of the 16 experimental rats died within the first 6 weeks; none of the 16 controls died. One exposed, and 2 of the 16 control guinea pigs died. All other exposed animals appeared to remain in excellent condition. Rabbits showed a slight increase in eosinophils after the 8th week of exposure; other hematologic measurements were not changed.

In a second preliminary experiment reported by Heppel et al, [69] 4 cats, 4 rabbits, 16 young rats, and 16 young guinea pigs were exposed to methylene chloride at 1,100 ppm for 8 hours/day, 5 days/week for 15 weeks. One experimental and 2 control guinea pigs died and 2 rabbits died postpartum. Cats "did not seem to thrive," but young rats and guinea pigs made good weight gains and the rats gave birth to many litters during the experiment.

Heppel et al [69] then exposed dogs, rabbits, guinea pigs, and rats in a 4 x 4 x 6-ft chamber at 5,000 ppm for 7 hours/day, 5 days/week for up to 6 months. Three of the 14 guinea pigs and one of the 20 rats died. The 2 female rabbits had litters during the experiment, but did not raise them. All 6 dogs, 2 puppies born in the exposure chambers, and 4 rabbits survived. The 2 pups gained weight normally. The exposed guinea pigs ate less than the controls and, at the end of the experiment, weighed 820 g compared to the control weight of 1,025 g.

There were no hematologic changes in rabbits, but RBC counts rose slightly in 3 of 5 dogs. Many other observations were made on the dogs without any abnormal findings. These observations included: the appearance of the cornea, sclera, eye grounds, eye movements, and mucous membranes; the states of deep reflexes and sensory perception; arterial blood pressure; bromosulfonephthalein (BSP) excretion, and icteric index; plasma proteins; and studies of the urine including pH, specific gravity, albumin, sugar, acetone, urobilin, urobilinogen, and cellular constituents.

Four dogs, 2 monkeys, 5 rabbits, 12 guinea pigs, and 16 rats were exposed to methylene chloride at an average of 10,000 ppm for 4 hours/day, 5 days/week for 8 weeks. [69] All animals became inactive during each exposure, but some underwent an initial excitement stage. Because of the severity of the excitement stage, dogs were not exposed more than 6 times. Three rabbits died, 1 each after 1, 12, and 22 exposures; 1 rat died after 33 exposures and another after 38.

All experimental animals exposed at 5,000 and 10,000 ppm and some of the controls were necropsied. Only pulmonary changes such as congestion and edema were found on gross examination. At 5,000 ppm, no microscopic lesions were found which appeared to be related to exposure. [69] At 10,000 ppm, moderate centrilobular congestion with narrowing of liver cell cords and slight to moderate fatty degeneration were found in 2 of the 4 dogs. No other organs were examined in the dogs. Slight to moderate fatty degeneration of the liver was found in 4 of the 6 exposed, and one of the 4 control guinea pigs. No microscopic lesions attributable to the exposure were found in the monkeys, rats, or rabbits. [69]

(c) Continuous Inhalation Exposures

Interest in possible exposure of astronauts to methylene chloride evaporated from construction materials in space cabins prompted research on continuous 90-day exposures of animals. Several reports of this research have been published by members of the investigative team. [70-74]

The effects on the livers of female mice exposed continuously at 5,000 ppm of methylene chloride for 7 days (168 hours) were studied by Weinstein et al. [71] Two "Thomas type" exposure domes were used as exposure chambers, one serving as a control chamber. For all experiments, mice were randomly separated into groups consisting of 13-20 mice. The groups of animals were maintained in the exposure chambers for the desired times, and then were killed by cervical dislocation within 5 minutes after removal from the chamber. The concentration of methylene chloride was maintained by a pressure-activated induction system and was continuously monitored with an automatic hydrocarbon analyzer. The atmospheric concentration of methylene chloride was 5,000 ±170 ppm. [71]

After the "first few hours" of exposure, physical activity and food and water intake decreased. Beginning at 24 hours of exposure, the mice became lethargic, assumed a hunched posture, and developed yellow, greasy, rough appearing hair coats. After 96 hours of exposure, normal activity resumed, eating and drinking increased and improvement was seen in postures and hair coats. At the end of the 168 hours of exposure, the abnormal signs had disappeared except for the appearance of emaciation and dehydration. [71] The body weights of the control mice remained fairly constant throughout the experiment, but the body weights of the exposed mice decreased from approximately 24 g to a mean of 18.0 g during the 7

days of exposure. The ratios of liver weight to body weight were significantly higher in animals from the exposed group throughout the experiment (Table XII-15). [71] Although the liver weights were not reported, the average weights calculated from the body weights and the liver/body weight ratios (Table XII-15) indicate an increased weight in the first days of the experiment, with a return to control values. This is in accord with the information on fat content. The concentrations of liver triglycerides were significantly greater in the experimental animals than in the controls on all days of exposure. In controls, the concentrations were about 10 mg/g wet weight throughout the experimental period. In the exposed animals, peak concentrations between 90 and 100 mg/g wet weight were reached after 72 hours of exposure. The concentrations then decreased to an average of 20 mg/g wet weight on the 6th and 7th days of exposure. [71]

With these exposures at 5,000 ppm, the earliest lesion in the liver dectected by the electron microscope was observed after 12 hours of exposure and consisted of dissociation of polyribosomes and swelling of the rough endoplasmic reticulum. Fatty infiltration was first noticed after 24 hours and involved the entire lobule. Hepatocytes in the central half of each lobule contained one or more large lipid droplets, while periportal hepatocytes contained many small droplets. On the 2nd day, centrilobular cells showed severe hydropic degeneration. On the 4th day, a few necrotic hepatocytes were observed as well as mild accumulations of lipid in Kupffer cells. On the 7th day, centrilobular fatty infiltration was found in the livers of the exposed mice. [71]

Incorporation of tritium labeled leucine into liver proteins was studied in 8 exposed and 8 control mice by Weinstein et al. [71] At exposure intervals of 4, 12, 24, and 48 hours, mice of both groups were given 20 μci/g body weight of the labeled L-leucine via the tail veil and killed 45 minutes later. Uniform labeling of hepatocytes was shown for all controls and mice exposed for 4 and 12 hours. Reduced labeling was observed after 24 hours of exposure and a further reduction was noted at 48 hours.

Fatty changes were found in the renal tubules of exposed mice on days 5 through 7. [71]

Continuous, 24-hour a day exposures of animals at either 1,000 or 5,000 ppm of methylene chloride for 14 weeks were studied by MacEwen et al [73] and reported in 1972. Concentrations of methylene chloride were continuously monitored with a flame-ionization hydrocarbon analyzer. Three exposure chambers [75] were used, 1 for control and 2 for exposure. Four female rhesus monkeys, 8 female beagle dogs, 20 male Sprague-Dawley rats, and 400 female ICR mice were placed in each. The chambers were operated at 50% relative humidity (±10%), 72 F (±5%), and 275 torr, or a little over 1/3 of an atmosphere.

At 5,000 ppm, animals of all species became relatively inactive in the first 2 days. Mice began to die on the 2nd day of exposure and 23 had died by the end of the 3rd day. The total number of mice that died during the first 35 days (as approximated from a graph) was 118. A monkey died after 10 days of exposure and 4 dogs died, 1 each on days 16 and 21, and 2 on day 22. Because of the severity of the responses, the exposures were discontinued after 35 days, except for 10 rats.

At 1,000 ppm, 6 of the 8 dogs died, 1 each on days 34, 38, 41, and 46, and 2 on day 48. Ten mice died; the monkeys and rats all survived the exposure.

The average concentration of methylene chloride in the blood of dogs exposed at 5,000 ppm for 16 days was 183 mg/liter, compared to 36 mg/liter in dogs exposed at 1,000 ppm. Methylene chloride found in the urine of 2 dogs exposed at 5,000 ppm was 51 mg/liter after 6 hours of exposure and 33 mg/liter after 48 hours.

Hematocrit, hemoglobin concentrations, RBC counts, and the activities of serum glutamic-pyruvic transaminase (SGPT) and isocitric dehydrogenase (ICDH) were all elevated and BSP retention was increased in dogs exposed to methylene chloride at 1,000 ppm for 4 weeks (Table XII-16). Changes in these items were not as great nor as consistent in monkeys exposed to methylene chloride at 1,000 ppm as they were in dogs. [73]

Dogs that died during exposure showed fatty livers, icterus, pneumonia, and splenic atrophy and in the 4 dogs that died from exposure at 5,000 ppm, edema of the brain or meninges was also present. In addition to fatty changes in the liver, vacuolar changes in the renal tubules were found by histological examination.

Monkeys exposed at 1,000 ppm showed no gross lesions, but microscopically some abnormal fat accumulation around the hepatic veins was observed in 3 of 4 monkeys. After 4 weeks of exposure at 5,000 ppm mild-to-moderate fatty changes, mild atrophy, and swelling of the livers were found. Bifrontal encephalomalacia was found in the monkey that died. [73]

The livers of mice that survived exposure at 1,000 ppm for 14 weeks were soft, atrophied, slightly pale in color, and had irregular surfaces.

Microscopic findings in the liver included concentration of pigment including hemosiderin around portal areas, ductal proliferation into portal area with focal collapse involving a few cells, occasional pyknotic cells, and some cytoplasmic and nuclear degeneration. Some hemosiderin was also found in some renal tubules of half the mice examined. [73]

Hepatic changes similar to those noted in mice were found in tissues from rats exposed at both 1,000 and 5,000 ppm of methylene chloride. Iron pigmentation and cell degeneration were noted in renal cortical tubular cells of rats exposed at either concentration for 14 weeks.

The studies with lower concentrations, 25 and 100 ppm of methylene chloride, were reported by Haun et al [70] in 1972. Two hundred mice were exposed continuously at 100 ppm of methylene chloride and 200 were exposed continuously at 25 ppm for up to 2 weeks. Mice were periodically added to, and removed from, the exposure chamber in groups of twenty to get different exposure times. Concentrations of triglycerides in the liver were determined and the livers were examined by electron microscopy. Then 2 groups of 100 mice each were exposed continuously at either 25 or 100 ppm for various exposure times up to 2 months. Following this, 3 groups of 170 mice, 20 rats, 4 monkeys, and 16 dogs each were exposed to methylene chloride at 0, 25, or 100 ppm. Most of the animals in the final experiment were used for special tests, but 20 rats, 20 mice, 4 monkeys, and 4 dogs in each group were exposed continuously for 100 days.

Haun et al [70] reported that no animals showed any overt signs of toxic stress during exposure. Body weight gains were not affected by the exposures at these concentrations. No significant differences were found between groups of mice in hexobarbital sleep-time determinations.

Cytochrome P-450 was reduced in the livers of mice by exposure at 100 ppm methylene chloride. Cytochromes b5 and P-420 were also reduced at 30 days, but were elevated at 90 days of exposure. Mice exposed at 25 ppm did not show significant differences from controls in any of the cytochromes. The data are presented in Table XII-17. [70]

Positive fat stains and cytoplasmic vacuolization were found in livers of mice exposed at 100 ppm of methylene chloride, and positive Oil-Red-O stains were found in livers of mice exposed at both concentrations. Only nonspecific tubular degenerative and regenerative changes were found in the kidneys of rats exposed at 25 and 100 ppm of methylene chloride. The authors [70] reported no significant differences in organ weights between the exposed and the control rats and no significant findings in hematologic, chemical, or microscopic examinations of dogs and monkeys exposed to methylene chloride.

Monkeys had less methylene chloride in the blood than dogs exposed to the same concentrations as shown in Table III-7.

TABLE III-7

METHYLENE CHLORIDE IN BLOOD OF DOGS AND MONKEYS

Exposure Time wks	Exposure Concentration ppm	Monkeys CH_2Cl_2 µg/ml	Dogs CH_2Cl_2 µg/ml
6	25	0.6	1.1
	100	3.1	5.1
13	25	1.0	1.8
	100	2.7	4.0

Derived from Haun et al [70]

Significantly elevated COHb was found in exposed dogs and monkeys. The 100-ppm monkeys showed the highest COHb percentages, followed by the 100-ppm dogs, then the 25-ppm exposed monkeys. Dogs exposed to methylene chloride at 25 ppm did not have significantly elevated COHb. [70]

Exploratory studies of spontaneous activity of mice continuously exposed to methylene chloride at 25 and 100 ppm were reported by Thomas et al. [72] Baseline measurements of spontaneous activity were made daily during 2-hour recording sessions for 2 weeks before exposure to methylene chloride. During the 14 weeks of exposure to methylene chloride, the activity of the mice exposed at 100 ppm did not differ from that of controls, but the activity of the mice exposed at 25 ppm was always greater than either the controls or those exposed at 100 ppm.

The light and electron microscopic studies of the livers of exposed ICR strain female mice exposed continuously to methylene chloride at 100 ppm for up to 10 weeks were reported by Weinstein and Diamond [74] in 1972. Liver triglyceride concentrations and liver and body weights were also reported, as noted below.

Twelve groups of 16 mice each were maintained in the exposure chambers for 3 days or for 1, 2, 3, 4, or 10 weeks. The body and liver weights of the exposed mice were consistently less than the controls during the experiment. The fat content of the livers of the exposed group increased for 3 weeks and then decreased. The maximum concentration was 27.88 mg/g liver after 3 weeks of exposure; it declined to 11.80 mg/g liver after 10 weeks of continuous exposure. The fat content of control livers varied between 6.10 and 8.23 mg/g. [74]

All livers from exposed mice which were examined by light microscopy after 7 days of exposure showed a decrease in hepatocyte glycogen and an infiltration of many small fat droplets in centrilobular hepatocytes. At 3, 4, and 10 weeks many hepatocyte nuclei appeared enlarged, but hydropic degeneration and hepatocyte necrosis were not observed. With electron microscopy, small autophagic vacuoles containing clumped membranous debris were found at 3, 4, and 10 weeks of exposure. At 10 weeks of exposure, large autophagic vacuoles were also found in a few centrilobular hepatocytes. Other organelles, including both the smooth and rough endoplasmic reticulum, appeared normal. [74]

(d) Skin Exposure

In 1960, Schutz [76,77] reported studies of absorption of methylene chloride through skin of rats. The hair was shaved from the stomach in a 4.5 x 5.5-cm rectangular patch, to a length of 0.5 mm, 3 days before the experiment. At the beginning of the experiment, each rat was intubated with 40 ml/kg of tap water, then the shaved area was covered with an inverted beaker containing 2 ml of liquid methylene chloride. After exposures of 2, 5, 10, 15, or 20 minutes, the skin was blotted dry and the rats were placed in separate cages for urine collection during the following 3 hours.

The volume of urine voided during 3 hours decreased as exposure time increased; controls voided slightly more than 8 ml, those exposed for 2 minutes voided 8 ml, and those exposed for 20 minutes voided less than 1 ml. There was no hemoglobin in the urine of control animals. Hemoglobin was found in the urine of 34 of the 50 exposed rats; in half of those exposed for 2 and 20 minutes and in 8, 9, and 7, respectively of the 10

rats in each of the groups exposed for 5, 10, or 15 minutes. [76,77]

(e) Teratogenicity

Schwetz et al [78] exposed 19 pregnant rats and 9 pregnant mice for 7 hours daily to methylene chloride at 1,250 ppm on days 5 through 15 of gestation. There was some evidence of both maternal and fetal toxicity in both species. Maternal liver weights were significantly increased in both species. In mice both the absolute and relative maternal liver weights were increased. Extra sternebrae were found in 6 (50%) of the litters of mice from exposed dams and in 3 or 14% of control litters. Cleft pellets and rotated kidneys were each found in 2 experimental litters and no control litters. 'In fetal rats there were increased incidences of dilated renal pelvis and delayed ossification of the sternebra. Other measurements were normal.

(f) Metabolism and Mechanism of Action

The chloromethanes have similarities in their metabolism and mechanism of action. [79,80] Chloroform can be formed from carbon tetrachloride and methylene chloride can be formed from chloroform. [80] Carbon dioxide is a metabolic product of both carbon tetrachloride, [80] chloroform, [80] and methylene chloride. [81]

Reynolds and Yee [82] administered carbon-14 labeled chloromethanes (methyl chloride, methylene chloride, chloroform, and carbon tetrachloride) to rats in oral doses of 8.3 and 26 mM/g body weight. (It is noted that in this paper [82] the legends to Figures 10 and 11 are reversed.) Labeled carbon from carbon tetrachloride and chloroform appeared in the amino acid fraction corresponding to methionine, whereas the labeled carbon from methylene chloride and methyl chloride appeared in the amino acid fraction

corresponding to serine. In electrophoretic lipid analysis, the label from carbon tetrachloride was generally distributed over all lipid fractions, the label from chloroform was limited to phospholipids, and the labels from methylene chloride and methyl chloride were limited to only the slower moving phospholipids.

Heppel and Porterfield [83] found that protein fractions from liver catalyzed the hydrolysis of methylene chloride to hydrogen ion, halide ion and formaldehyde. Kuzelova and Vlasak [55] found formic acid in the urine of workers exposed to methylene chloride, indicating that formaldehyde would be in the pathway of methylene chloride metabolism by man. DeVincenzo and Hamilton [81] did not find labeled formaldehyde in rat serum 2 hours following ip injection (1 ml/kg) of carbon-14 labeled methylene chloride. However, when labeled formaldehyde was fed to rats by Reynolds and Yee, [82] the labeling pattern of proteins and fats was similar to the labeling patterns of ingested methylene chloride and methyl chloride. According to the authors, [82] the similarity of methylene chloride and formaldehyde label patterns into serine suggested that methylene chloride was heterolytically cleaved into 2 ions.

By contrast to the evidence for heterolytic cleavage of methylene chloride, evidence exists that carbon tetrachloride and chloroform undergo homolytic cleavage to 2 free radicals each. [84,85] Carbon tetrachloride [86] and, to a lesser extent, chloroform [87] cause lipoperoxidation and necrosis of the liver. This action was related to metabolism o, these compounds, and gave evidence of their homolytic cleavage. [88,89] Methylene chloride has not been shown to cause either lipoperoxidation or liver necrosis, [90] lending support to the evidence of heterolytic cleavage of

Methylene chloride combined with reduced cytochrome P-450 to cause a spectral shift similar to that caused by carbon tetrachloride. [91,92] These shifts were also similar to, but clearly at longer wavelengths than, the shift caused by CO. The reaction of carbon tetrachloride with cytochrome P-450 was associated with a reduced ability of the enzyme systems to oxidatively demethylate ethylmorphine and aminopyrine, and to hydroxylate hexobarbital. Methylene chloride did not inhibit these enzyme reactions. [93,94]

With methylene chloride, cytochrome P-450 was not decreased 3 hours after a single oral dose of 1.25 ml/kg as it was with carbon tetrachloride. [94] However, upon continuous exposure at 100 ppm methylene chloride, but not at 25 ppm, cytochrome P-450 was decreased when measured after 30, 60, and 90 days of exposure. [70]

Chloroform was shown to combine with equine, rabbit, bovine, and human ferrihemoglobin, and similar combination of carbon tetrachloride and methylene chloride was confirmed with equine ferrihemoglobin. [95,96] In the case of equine ferrihemoglobin, all 3 compounds caused similar spectral shifts with significant absorption in the range of 390 to 430 nm. Chloroform did not give a spectral change with reduced equine hemoglobin or rabbit oxyhemoglobin; these studies were not carried out with methylene chloride. Further evidence of the interaction of methylene chloride with equine methemoglobin was given by a shift in the specific rotation trough minimum from 232.5 to 220 nm, indicative of structural changes in the protein. [95,96]

Crystals of sperm whale metmyoglobin were found to bind methylene chloride at a binding site in the interior of the myoglobin molecule,

approximately equidistant from one of the pyrrole rings of the heme group and the ring of heme-linked histidine. [97] The binding site corresponded to that of xenon and cyclopropane which increase the affinity of myoglobin for CO. [97]

In 1972, Stewart et al [39] reported finding elevated COHb concentrations in the blood and CO in the breath of subjects exposed to methylene chloride. Breath samples were analyzed for methylene chloride and CO by GC and IR. Blood samples were routinely analyzed for COHb with an automated spectrophotometer, and the authors reported that the readings were cross-checked by the gas chromatographic method of Porter and Volman. [98]

Following the report by Stewart et al, [39] other reports of CO in the blood or breath of man and animals during and after methylene chloride exposure appeared. [59,67,68,70,81,99,100] In some of these studies the analytical methods were not given in sufficient detail for evaluation. [70,59]

Fassett [99] described an experiment where 1 ml/kg labeled methylene chloride was administered ip to rats. The animals were killed serially at 30-minute intervals, and COHb was determined by the procedure of Van Slyke et al. [101] Radioactivity was present in the liberated gas. Fassett [99] stated that the CO apparently came from methylene chloride. DiVincenzo and Hamilton [81] found that within 24 hours after ip administration of carbon-14 labeled methylene chloride most of it was eliminated unchanged in the breath, and that about 3% was exhaled as carbon dioxide, 2% as CO, and 1% as an unidentified metabolite.

Carlsson and Hultengren [102] exposed 10 rats at 550 ppm of radioactive methylene chloride for 1 hour and determined the COHb and radioactive CO formed. A correlation coefficient of about 0.9 was found between COHb and radioactive CO.

Kubic et al [100] studied COHb concentrations in blood of rats following administration of dihalomethanes. In all cases they found elevated COHb during 1 to 6 hours following ip injections of 3 mM/kg. With methylene chloride doses of 1.5, 3.0, and 6 mM/kg, maximum COHb measurements of about 5%, 8%, and 9%, respectively, were found. The COHb was measured by GC. [103]

Kubic et al [100] found that pretreatment with either phenobarbital or 3-methylcholanthrene did not alter the amount of COHb after ip administration of methylene chloride and Roth et al [68] found that this was the case when rabbits were exposed to methylene chloride by inhalation. These experiments [68,100] indicate that microsomal hydroxylating enzymes are not involved in metabolism of methylene chloride to CO. However, repeated administration of methylene chloride may stimulate activity of the enzymes involved in the transformation. Kubic et al [100] reported that when methylene chloride was administered to rats ip daily for 5 days, more COHb was found after administration of the 5th dose than after administration of the first dose, [100] but the data were not adjusted for baseline values. Evidence that repeated inhalation of methylene chloride by rabbits led to increased amounts of COHb was not found by Roth et al, [68] when their data were adjusted for baseline values.

Using carbon-13 labeled methylene chloride, Kubic et al [100] found that the IR spectrum of the labeled hemoglobin resembled the spectrum of

COHb obtained from exposure to similarly labeled CO.

These studies provide information that methylene chloride is metabolized to CO in man and several animal species, and some information that formaldehyde and formic acid are other metabolites. Kassebart and Angerer [104] proposed a mechanism by which both formic acid and CO could form from methylene chloride. They proposed formaldehyde formation from hydrolytic dehydrochlorination and oxidation of the formaldehyde to formic acid which would be oxidized to carbon dioxide and water and dehydrated to CO and water. Such a mechanism would be compatible with most of the data presented in this section.

Correlation of Exposure and Effect

(a) CNS and Behavioral Effects

Methylene chloride was initially used as an anesthetic and was found to have a number of side effects; not all were undesirable. A number of investigators [31-33] reported that with methylene chloride an anesthetic stage of analgesia and unconsciousness could be obtained without the loss of muscle tone. As recently as 1950, Grasset and Gauthier [33] reported that when methylene chloride was administered to women during labor, muscle tone was maintained, and the patients experienced retrograde amnesia afterward. Exposure of humans and experimental animals [31,32] at concentrations of methylene chloride capable of producing narcosis often resulted in epileptiform attacks while subjects were anesthetized.

Moskowitz and Shapiro [50] reported that in a plant where methylene chloride was used as an extractant, the 4 workers on the night shift all became unconscious. One of them died. The workers were exposed for 1-3

hours, but no concentration measurements were obtained. None of the men remembered detecting the odor of methylene chloride. The individual who died had been working in the plant for 7 months. Autopsy revealed that the dura mater was adherent to the skull and the veins of the pia-arachnoid were conspicuously engorged. The methylene chloride content of the brain was 0.1 ml/500 g tissue. Two of the 4 workers had contusions and lacerations of the head suggesting that this was either the result of falling when unconscious or of muscular movements while unconscious.

Weiss [58] described the effects of methylene chloride on a 39-year old chemist who worked 5 years in a pharmaceutical factory where sodium chloride was dissolved in methylene chloride then recrystallized after evaporation of methylene chloride. The man was exposed at vapor concentrations of methylene chloride ranging from 660 to 3,600 ppm for several hours a day, and his hands and arms were often exposed to liquid methylene chloride. After 3 years, the man complained of forgetfulness, insomnia, and a feeling of drunkenness. During the last few months of his 5th year of exposure, he complained of auditory and visual hallucinations.

In 1966, Kuzelova and Vlasak [55] studied workers in a factory where cellulose acetate films were manufactured using methylene chloride as the principal solvent. Other components of the solvent mixture were methanol, triphenyl phosphate, and dibutyl phtalate. The concentrations of methylene chloride in the air ranged from approximately 25 to 5,000 ppm in 14 locations (Table XII-11). Of the 33 workers who had been exposed for 1.5 to 2 years, slightly more than 72% complained of headaches, about half complained of increased fatigue, and approximately 50% of nervous disorders.

In experimental exposures of humans to methylene chloride, Stewart et al [39] reported that 2 of 3 subjects exposed at 986 ppm for 2 hours became lightheaded after 1 hour. This feeling cleared 5 minutes after the exposure ceased. Similar results occurred in subjects exposed at 868 ppm. Subjects exposed at 986 showed alterations in VER indicative of the initial phases of CNS depression at both 1 hour and 2 hours of exposure. The subjects showed the same response when exposed at 514 ppm for 1 hour, but in this experiment the response was not maintained during a 2nd hour of exposure at 868 ppm.

Fodor and Winneke [37] and Winneke [38] reported that human subjects showed decreased behavioral performance on certain controlled tests. In 12 female subjects exposed at 317 ppm methylene chloride by Fodor and Winneke, [37] the CFF was decreased by a statistically significant amount after 100 minutes of exposure. At 751 ppm the effect occurred after 50 minutes of exposure. In exposures at 317 and 470 ppm, auditory vigilance was decreased by similar amounts. At 751 ppm, auditory vigilance was decreased much more. [38] Winneke [38] reported significant impairment on a battery of psychometer tests during exposure at 751 ppm for 4 hours.

Gamborale et al [40] found no decrement in performance on the 4 psychomotor tests they used during 2 hours of exposure in which the concentration of methylene chloride increased at 30-minute intervals from 250 to 1,000 ppm. The tests used were addition-reaction time, memory, and two simple reaction time tests.

No CNS or behavioral effects of methylene chloride were reported by the Massachusetts Department of Labor and Industries among workmen exposed to methylene chloride. (LD Pagnotto, written communication, December 1973)

Atmospheric concentrations in the casting room, where most of the workers spent their time were between 100 and 280 ppm.

(b) Effects on Internal Organs

At lower concentrations, eg 25 ppm for 90 days continuous exposure, no effects were evident on liver and kidneys of mice, rats, monkeys or dogs. The magnitude of the liver and kidney effects increase in such a way that extremely high doses of methylene chloride, taking concentrations and duration of exposure into account, can produce toxic effects. [69,70-72]

A variety of animals were exposed at 10,000 ppm by Heppel et al [69] for 4 hours/day, 5 days/week for 8 weeks. Necropsies were performed on all of the exposed animals. Gross examination revealed pulmonary congestion and edema with focal necrosis and focal extravasation of blood in rabbits and rats. Microscopic examination of liver tissue revealed moderate centrilobular congestion and fatty degeneration of the liver in dogs and guinea pigs. In a similar experiment at 5,000 ppm, no gross or microscopic abnormalities were found. [69]

Weinstein et al [71] exposed mice to methylene chloride continuously at 5,000 ppm for 7 days. Throughout the experiment the ratio of liver weight to body weight was significantly higher for the exposed animals. The concentrations of liver triglyceride were also significantly greater in the experimental animals. All animals were killed. Microscopic examination of the tissues showed fatty changes in the renal tubules; in the livers, centrilobular fatty infiltration and hydropic degeneration of hepatocytes were found.

Fourteen-week continuous exposures at 5,000 ppm resulted in more severe toxic effects to mice, rats, dogs, and monkeys in the experiments

reported by MacEwen et al. [73] There was high mortality in all species. Fatty livers, icterus, pneumonia, splenic atrophy, and vacuolar changes in the renal tubules were found. With an exposure concentration of 1,000 ppm for the same period of time, MacEwen et al [73] reported elevated liver enzymes and bilirubin levels, centrilobular fat accumulation, and elevated BSP retention time.

Weinstein and Diamond [74] exposed mice at 100 ppm continuously for 10 weeks to determine the hepatotoxicity of methylene chloride as determined by tissue triglyceride concentrations, liver and body weights, and microscopic examination of the liver. The liver and body weights were essentially the same for exposed and control animals, but liver triglyceride levels were elevated after 2 weeks of exposure to methylene chloride. There was centrilobular fatty infiltration, vacuolization in liver cells, and a decrease in hepatocyte glycogen of the exposed mice.

The results of experiments by Haun et al [70] showed similar findings. Mice exposed continuously at 100 ppm for periods of 2 weeks to 2 months had altered levels of the cytochromes P-450, P-420, and b5, fatty infiltration of the liver, and vacuolization in liver cells. Only nonspecific tubular degenerative and regenerative changes were found in the kidneys. Animals exposed at 25 ppm continuously showed no overt signs of toxicity, and only nonspecific degenerative and regenerative changes were found in the renal tubules.

(c) Effects on the Skin and Mucous Membranes

Stewart and Dodd [49] studied effects of methylene chloride in 4 subjects each of whom immersed one thumb in methylene chloride for 30 minutes. All subjects experienced an intense burning sensation within 2

minutes following immersion of the thumbs in methylene chloride. After 10 minutes the burning sensation was mixed with a numb or cold feeling. The slightest movement of the thumb triggered intense pain. A slight degree of white scale was noted on the thumb as well as a mild secretion. The erythema and paresthesia subsided within 1 hour. In these experiments, it was shown by breath analysis that methylene chloride was absorbed through the skin.

Effects of methylene chloride applied to shaved skin of rats were reported by Schutz. [76,77] Fifty rats were each subjected to 2 ml methylene chloride applied to the skin for 2, 5, 10, 15, or 20 minutes. As application time increased, the urine voided in 3 hours decreased from approximately 8.0 ml to 1.0 ml. Thirty-five of the 50 exposed rats, but none of the controls, had hemoglobin in the urine.

In a number of occupational studies where workers have been exposed to methylene chloride there have been reports of irritation of the eyes and respiratory tract. [50,51,55] Kuzelova and Vlasak [55] reported that 16 of 33 workers exposed at a range of 25-5,000 ppm for an average of 2 years experienced irritation of the respiratory tract and conjunctiva.

A laborer degreasing copper gaskets in a small and poorly ventilated room experienced nausea and eye irritation. [51] The exposed man had been working for 4 hours; the concentrations of methylene chloride were not measured.

Three of 4 workers rendered unconscious by unknown concentrations of methylene chloride were studied by Moskowitz and Shapiro [50] and all three exhibited some signs of either eye, lung, or respiratory tract irritation.

(d) Blood CO and COHb Measurements

Several investigators [39,41,43,59,67,68,70,100] reported COHb in blood and CO in exhaled breath with exposure to methylene chloride. The response was proportional to both exposure time and concentration of methylene chloride in the exposure atmosphere.

These data need to be evaluated cautiously because it has not been unequivocally proven that either CO or COHb was totally responsible for all the measured responses. Methylene chloride was shown by Bucher [95] in 1968 to combine with methemoglobin. The combination absorbs light in the analytical range for COHb (390-430 nm) and may interfere with COHb measurements determined spectrophotometrically. Other investigators [39,58,67,68,70,100] have apparently not been aware of this phenomenon which was first reported in 1971. [96] In several studies [39,41-43] COHb was estimated from analysis of CO in exhaled breath samples, and the reports did not give details about the conversion factor for CO to COHb. In one report, the authors [39] indicated that both CO and methylene chloride in the breath samples were analyzed by GC and IR but the data to compare the 2 methods were not presented.

Haun et al [70] found elevated measurements of COHb in dogs when exposed continuously to methylene chloride at 100 ppm, but not when exposed at 25 ppm. In the same experiment, monkeys showed elevated COHb measurements which were proportional to the exposure concentration. The authors noted that the dogs had higher methylene chloride concentrations in the blood than the monkeys, but the monkeys had the higher COHb percentage measurements, suggesting that the monkeys' metabolic processes were more effective in converting methylene chloride to CO.

Fodor et al [67] measured CO content of the blood during 3-hour exposures of rats to methylene chloride at 40, 100, 500, and 1,000 ppm. They also exposed groups of rats for 3 hours to CO at 100 ppm and to combinations of 100 ppm CO with 100 and 1,000 ppm methylene chloride. At 1,000 ppm of methylene chloride, the rats developed 12.5% COHb, at 100 ppm they developed 10.9% COHb, and with the combination exposure at 1,000 ppm of methylene chloride and 100 ppm CO, they developed 19.0% COHb. Fodor et al [67] gave no data on how they determined CO or COHb, except to say "the blood CO concentration was determined by gas analysis methods." Since exposures to the combination of CO and methylene chloride, each at 100 ppm, resulted in COHb values that could not be attained by exposure at 100 ppm CO, it would appear that the affinity of hemoglobin for CO was increased by exposure to methylene chloride.

Carlsson and Hultengren [102] found a high correlation (r=0.9) between COHb and radioactive CO of rats exposed to labeled methylene chloride at 550 ppm for 1 hour.

Kubic et al [100] studied COHb in rats injected with methylene chloride ip. Their method of determining blood CO was by GC, [103] similar to the method of Porter and Volman [98] that was used by Stewart et al. [39] The COHb was estimated by dividing blood CO content by the product of 1.39 and the total hemoglobin concentration determined by the cyanomethemoglobin method. [101] When rats were given 0.125, 0.25, and 0.5 g/kg of methylene chloride, maximum COHb percentages were 5, 8, and 9, respectively. These data were derived from single animals because, as the authors stated, "although multiple experiments were conducted in virtually all cases, animal-to-animal variation made averaging and statistical processing of curves difficult."

On the assumption that metabolism of methylene chloride to CO was mediated through hydroxylating enzyme systems, Kubic et al [100] pretreated rats with the enzyme inducers, phenobarbital and 3-methylcholanthrene, and with the enzyme inhibitor 2-diethylaminoethyl 2,2-diphenylvalerate HCl. Pretreated rats did not produce measurably different amounts of CO when subsequently given methylene chloride than did the controls when given methylene chloride without the enzyme modifiers, indicating that hydroxylating enzymes were not involved. Roth et al [68] obtained similar results by inhalation exposure to methylene chloride in rabbits. Rats injected with methylene chloride on 5 consecutive days had higher COHb measurements on the 5th day than controls, [100] but a similar response was not found in rabbits from repeated inhalation exposures. [68] Kubic et al [100] did not measure COHb on the 5th day before injection of methylene chloride.

Finally, Kubic et al [100] studied the IR spectrum of rat blood equilibrated with CO labeled with carbon-13, and compared this with the absorption spectrum of rat blood taken 2.5 hours after injection of similarly labeled methylene chloride. The absorption spectra appeared identical, but the absorption of rat blood treated in vitro with labeled methylene chloride was not determined. Also, no quantitative analysis was made of the amount of CO that might have been formed.

Extensive studies of COHb in human subjects experimentally exposed to methylene chloride have been conducted. [39,41-43] Exposure concentrations of 50, 100, 250, and 500 ppm each with exposure times of 1, 3, and 7.5 hours were employed. Each combination was repeated on 5 consecutive days. In addition, effects of single 2-hour exposures at

approximately 700 and 1,000 ppm were studied. [39] In some cases, COHb percentages (measured spectrophotometrically) were greater 1 hour after the end of exposure than at the end of exposure. This occurred more often with the shorter exposure times, higher exposure concentrations, and on Fridays. [39,41] Maximum COHb percentages determined sprectophotometrically in nonsmokers are presented in Table III-8.

TABLE III-8

MAXIMUM COHb PERCENTAGES OBSERVED IN NONSMOKERS EXPOSED TO METHYLENE CHLORIDE

Exposure Concentration, ppm	Exposure Time, Hours			
	1	2	3	7.5
50	1.3		1.6*	2.9
100	3.2*		3.0*	5.7
200	2.4			
250	3.0		4.3	9.6
500	4.4		5.6	11.4
700		8.0		
1,000		15.0		

* End exposure values, all others are 1-hour after exposure
Derived from Stewart et al [41]

The studies reported by Astrand et al [44] in 1975, and by Stewart and Hake [45] in 1976 indicate that the COHb values encountered in employees exposed to methylene chloride would be related to the work load. These studies also indicate that the maximum COHb values of exposed workers

might occur 3-4 hours after leaving work.

With 3- and 7.5-hour daily exposures at 100, 250, and 500 ppm, COHb percentages remained elevated above baseline values on the mornings following exposure. However, after 5 consecutive 7.5-hour days of exposure at either 100 or 250 ppm, they returned to normal by Monday morning. [41]

In the subjects exposed for 7.5 hours daily, the oxygen dissociation curves were distorted in proportion to exposure concentration. Following exercise the blood lactate in the subjects exposed at 500 ppm, but not those exposed at 100 ppm, became slightly elevated above control values. [43]

Concentrations of CO in the breath of 7 individuals exposed to methylene chloride in a working environment were studied by Ratney et al. [59] The CO was determined by an electrochemical method not equilibrated with air mixtures of CO and methylene chloride. The workroom concentrations of methylene chloride were measured periodically during the workday. They were greater in the afternoon (219-610 ppm) than in the morning (159-172 ppm). All individuals had been exposed to higher concentrations of methylene chloride on the previous day (300-966 ppm). Four of the 7 subjects were employees who had been exposed to methylene chloride for years. The measured concentrations of CO in exhaled air of the subjects ranged between 24 and 32 ppm at the beginning of the workday. The concentrations, measured hourly, gradually increased during the day, and at the end of the workday they ranged from 36 to 77 ppm. The COHb percentages derived from these breath data ranged from 3.3 to 5.3 at the beginning of the day and from 5.7 to 12.0 at the end of the day. The following morning, the measured CO concentrations in the exhaled breath

ranged from 17-29 ppm and the derived COHb percentages ranged from 3.6 to 4.9. Measurements of methylene chloride exhaled by the subjects were not reported. [59]

(e) Summary

Data to correlate exposure and effect are summarized in Table XII-18.

IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION OF EXPOSURE

Environmental Concentrations

Concentrations of methylene chloride in a plant manufacturing plastic film were supplied by the Department of Labor and Industries, State of Massachusetts. (LD Pagnotto, written communication, December 1973) These data are discussed in detail below.

The solvent mixture used in the operation contained 75% methylene chloride, 22% chloroform, and the remaining 3% consisted of toluene, methyl glycol, and methanol. The plant operated 24 hours a day and used 240,000 pounds of methylene chloride a year. Four men were employed for each of 3 shifts. The employees spent most of their time in the room where the film was cast and most of the samples were taken in this environment. Besides the casting room, other general locations surveyed were the filter room, winding room, office, and laboratory.

For collection of samples, workroom air was drawn through a U-tube filled with 7 g of silica gel at a rate of 0.5 liters/min for 90-120 minutes. The collected vapors were desorbed from the silica gel by soaking in isopropyl alcohol for 2 hours. Aliquots of this solution were hydrolyzed by potassium hydroxide for 17 hours for cholroform estimates, and for 65 hours for methylene chloride estimates. The hydrolyzed solutions were neutralized with acetic acid and the chloride was titrated with silver nitrate, using potassium dichromate as the indicator.

To differentiate between the amounts of chloride recovered from methylene chloride and chloroform, it was necessary to use empirical chloride recovery factors determined from control samples analyzed in parallel. [59] During the first 17 hours of hydrolysis, averages of about

4% of the methylene chloride and about 80% of the chloroform were hydrolyzed. During 65 hours of hydrolysis, an average of about 20% of the methylene chloride, but virtually no additional chloroform, was hydrolyzed. Methylene chloride and chloroform controls were analyzed for each determination.

During 5 years of surveillance, 13 samples were taken near one of the desks in the casting room (Table XII-19). The concentrations varied from 55 to 310 ppm with an average of 169 ppm. At other locations in the casting room, 45 samples were collected with methylene chloride concentrations ranging from 70 to 495 ppm. The overall average methylene chloride concentration in the casting room was 203 ppm. Concentrations in the filter room varied from 155 to 590 ppm of methylene chloride, with an average of 294 ppm. In the winding room, office, and laboratory, the samples ranged from 35 to 215 ppm of methylene chloride. [59]

In 1973, another study (LD Pagnotto, written communication, December 1973) was conducted using charcoal as a collection medium with GC as the analytical method, in addition to the previously used method. In collecting the samples on charcoal, workroom air was drawn through a glass tube with an inside diameter of 6 mm. This tube was packed with 1 g of 6 x 16 mesh charcoal. The sample was collected at 1 liter/min for 10 minutes. Vapors adsorbed onto the charcoal were eluted with carbon disulfide by shaking on a mechanical shaker for 30 minutes. Aliquots of the resulting solution were injected into a GC in which the column consisted of a free fatty acid stationary phase on a solid support of coral shell treated with dimethyldichlorosilane. This method was modified from that of White et al. [105]

Two surveys were made on successive days. The data are presented in Table XII-12. During the first day, two 90- to 130-minute samples collected on silica gel near a desk in the casting room and analyzed by alkaline hydrolysis contained 210 and 250 ppm of methylene chloride. A 10-minute sample taken by the desk, collected on charcoal and analyzed by GC, indicated 471 ppm. The average concentration of these 3 samples was 282 ppm. The rest of the samples in the casting room varied between 30 and 594 ppm with an average of 457 ppm.

On the second sampling day, 3 samples were taken near the desk at intervals of 2 hours during the morning shift. The average methylene chloride concentration at this location, determined by GC, was 183 ppm. The overall average for all samples taken in the casting room on the second day was 312 ppm. The average of the 5 measured concentrations for the 2 days of sampling in the casting room was 391 ppm. [59]

The concentrations of methylene chloride found using the silica gel method appear to be lower than the ones collected with the charcoal and analyzed by gas chromatography (Table XII-20). The averages for the casting room differ by almost 100 ppm; the differences in the filter room and the office are even greater, while in the winding room the averages are essentially the same. Even though the samples for the 2 methods were not collected simultaneously, the possibility of error attributable to analytical method exists. The old method was not specific for methylene chloride, and the presence of chloroform could have interfered. Other sources of error, which may account for the lower methylene chloride concentrations in the old method than in the new one, are: (1) competition of water vapor with methylene chloride when silica gel is used as the

collecting medium; and (2) an elaborate hydrolysis procedure using empirical fractional chloride recovery factors derived from two hydrolyses. The problem of interference from water vapor in collection on charcoal is not as pronounced as with silica gel, [106] and with gas chromotography, methylene chloride and chloroform can be easily differentiated. [105]

During 1973 and 1974, 7 studies of methylene chloride exposure concentrations in a variety of jobs were reported. [107-113] The data are summarized in Table IV-1.

TABLE IV-1

METHYLENE CHLORIDE EXPOSURE CONCENTRATIONS

Type of Operation	Samples Type	Samples No.	CH_2Cl_2 ppm	Reference
Servicing diesel engines	GA*	1	11	107
Spray painting booths	BZ**	8	1-74	108
Chemical plant	BZ	14	0-5,520	109
8 hr TWA exposure			875	109
Plastic tank construction	BZ	124	a few ppm	110
Ski manufacture	BZ	51	0-36	111
Cleaning foam heads	BZ	7	4-29	112
	GA	6	3-17	112
Cleaning nozzles in plastics manufacture	BZ	10	5-37	113
	GA	3	19-31	113

* General air
** Breathing zone

Another environmental study involving continuous use of methylene chloride was reported by Kuzelova and Vlasak. [55] The location was a plastic film factory in which cellulose triacetate was dissolved in organic solvents. Methylene chloride represented 78% of the mixture when charged. Trace impurities in methylene chloride were reported as 0.15% methyl chloride, 0.25% chloroform, and 1% methyl alcohol. A 3-year survey was

conducted in which environmental concentrations were reported within a range from 30 to 5,000 ppm. A total of 318 samples were taken in 13 working locations. The list of the sites and the concentrations found are presented in Table XII-11. The average concentration was 627 ppm. Unfortunately, the authors did not report the monitoring and analytical methods used to determine the reported environmental concentrations.

Environmental Sampling and Analytical Method

(a) Collection Methods

Most of the analytical methods are dependent on effective and reproducible uptake of methylene chloride by different collection media. Air samples are usually collected and transported to a laboratory, then desorbed or chemically treated, and finally analyzed quantitatively.

Silica gel has been used as a collection medium. [59,114] Silica gel is a polar adsorbent and shows pronounced selectivity in adsorbing polar molecules, particularly water. Hence, when sampling large volumes, atmospheric moisture may compete for the adsorption sites and displace methylene chloride. [106] When sampling more than 3 liters of air through 1-inch silica gel tubes, the silica gel could become saturated with water and this would impair its retentive properties. [106]

Activated charcoal has been used as a collection medium in conjunction with GC. [105] It is nonpolar and will generally adsorb organic vapors in preference to water vapor resulting in less interference from atmospheric moisture than silica gel. [106]

Williams and Umstead [115] reported the use of porous polymer beads as a collection medium. With this method, the same column was used for sample collection and GC analysis. The advantage of this method is that it consolidates collection and analysis into one operation. However, only one analysis can be performed on each sample. This method has not been developed for field use.

Liquids have been used to collect methylene chloride from contaminated atmospheres. Midget impingers containing m-xylene have been used for collection in conjunction with GC analysis, [116] and "bubble bottles" containing a pyridine solution have been used for collection in conjunction with the Fujiwara colorimetric analysis. [117] The successful use of impingers and bubble bottles for collection of breathing zone samples requires careful handling of glassware during collection and shipment of samples to the laboratory.

Other investigators have collected grab samples of contaminated atmospheres in a variety of containers ranging from plastic bags to hypodermic syringes. [118]

(b) Desorption Methods

When solid collection media are used, it is necessary to desorb the methylene chloride from the medium. Isopropyl alcohol and heat were used by the Massachusetts Department of Labor and Industries to desorb methylene chloride from silica gel. Otterson and Guy [118] recommended the use of different desorbing agents for charcoal depending upon the comparative gas chromatograph retention times of the desorber and the contaminant. They found that carbon disulfide was the best desorbent of those studied for methylene chloride.

(c) Analysis

Several methods have been used to quantify methylene chloride contained in air samples. The analytical methods can be divided into 2 broad categories: (1) methods based on chemical reactions, and (2) methods based on physicochemical characteristics.

(1) Chemical Methods

The 3 chemical methods that have been used extensively are: (1) dechlorination with strong alkali followed by titration of the chloride (alkaline hydrolysis); (2) colorimetric measurement of the reaction products of methylene chloride and pyridine heated in alkali solution (Fujiwara reaction) [117]; and (3) direct reading colorimetric indicators. [119]

For the alkaline hydrolysis method, methylene chloride collected with a suitable collection medium is hydrolyzed during about 20 hours by KOH in isopropyl alcohol. After neutralization and precipitation with silver nitrate, the liberated chloride is titrated with potassium cyanide. The hydrolyzed methylene chloride is determined by comparison between samples and known standards. Disadvantages of this method are that the amount of chloride liberated depends on the duration of the dechlorination step, and that, with a mixture of chlorinated hydrocarbons, it is difficult to differentiate the chloride liberated from the different components.

In the colorimetric analytical method based on the Fujiwara reaction, a stream of air containing methylene chloride is passed through a wash bottle containing pyridine. [117] After collection in pyridine, methyl-ethyl ketone (MEK) and NaOH are added to an aliquot of the sample, and this mixture together with an aliquot of the MEK and NaOH solution are heated in

a boiling water bath and cooled over a fixed time period. The absorption coefficients are then determined with a suitable spectrophotometer. This method requires less time than the dechlorination method, but the problem of specificity with mixtures of chlorinated hydrocarbons remains.

The third chemical method utilizes direct reading detector tubes. [119] These are glass tubes packed with solid chemicals that change color when a measured and controlled flow of air containing methylene chloride is passed through the packed material. The test vapor may be drawn directly through the tube followed by comparison with a calibration chart, or it may be drawn into a pyrolyzer, then through the packed tube. [119] Either way, the method is not specific for methylene chloride since the stain to be read is produced by the liberated halogen ion, and any halogen or halogenated compound will interfere. Colorimetric indicator tubes should be correct within ± 25% of the values read, as specified in 42 CFR 84.20(e).

(2) Physicochemical Methods

The category of analytical methods based on the physicochemical properties of methylene chloride includes gas chromatography, [118] infrared spectrometry, [120] and photodetector analyzers. [121] Gas chromatography provides a specific quantitative analytical method when appropriate column conditions are specified. [105] However, the possibility exists that several compounds found in an occupational environment may have similar column retention times. Resolution of interferences can be overcome by altering the stationary phase of the GC column, or by changing the column temperature or other analytical parameters. Altering conditions will usually change the retention times and separate the components. Two

chromatographic columns with different stationary phases can also be used for more positive identification of compounds.

A mass spectrometer can be used with gas chromatography to identify the substances present more positively. A capillary charcoal tube can be employed to trap and transfer the material associated with a gas chromatogram peak to a mass spectrometer for qualitative identification as described by Cooper et al. [122]

Otterson and Guy [118] combined charcoal collection, carbon disulfide desorption, and gas chromatography and considered the combination to be the best available for industrial hygiene studies of substances for which it was applicable. Fraust and Hermann [123] determined optimal charcoal granule size, sampling rate, and total sample volume for charcoal sampling tubes. White et al [105] applied the findings of Fraust and Hermann [123] and, in addition, determined the optimal cross section of the charcoal tubes and the optimal number of charcoal sections. The tubes were further modified for use with personal air sampling pumps to determine exposure to chlorinated hydrocarbons. [124]

An IR spectrophotometer in conjunction with a suitable recorder can be used to indicate instantaneous concentrations. With this method, concentrations are measured directly and it is not necessary to collect individual samples and transport them to a laboratory for analysis. IR has been used for continous monitoring of industrial operations for chlorinated hydrocarbons. [120] However, complicated instrumentation is necessary to draw samples and to continuously record the data. There is also the need to assure that the atmosphere of relevant working stations is sampled, and that such samples correspond to the breathing zone of the workers at the

working stations. [120] IR analysis is subject to interferences from other air contaminants and these interferences are not easily detected or resolved without substantial knowledge of IR spectrophotometry.

Halide meters are based on the detection of the increased brightness of an a-c arc (metal electrode) when enveloped by an atmosphere contaminated with halogenated hydrocarbons. [121] These instruments are sensitive to all halogens and halogenated compounds and consequently are not specific for methylene chloride. Halide meters seem suitable for continuous monitoring if there is only methylene chloride present as the air contaminant.

(d) Conclusions and Recommendations

(1) Compliance Method

On the basis of the review of analytical methods, it is recommended that GC be chosen as the method of sample analysis with sample collection in tubes containing activated charcoal. Carbon disulfide is the preferred desorbent.

The selection of this sampling and analytical method is based on the following attributes:

(A) Charcoal tubes are easy to ship and store.

(B) Estimation of exposure with personal samplers is easy.

(C) Desorption with carbon disulfide is efficient and reproducible.

(D) Methylene chloride can be identified in combination with many other compounds.

(E) At the sample volumes recommended, interference by moisture is minimal.

(F) The sampling tubes and personal pumps are commercially available.

A disadvantage of the method is the indirect system of measurement requiring collection and desorption prior to analysis.

(2) Monitoring Methods

It is also recommended that direct reading colorimetric tubes (gas detection tubes) be used as an inexpensive way to estimate methylene chloride concentrations. The tubes must be used as instructed by the manufacturer. The indicators must be accurate to ±25%.

For situations in which there is a continuous and constant methylene chloride use, it is recommended that a continuous system of monitoring the working location be established. The workroom air should be monitored by a multiprobe continuous air sampler/analyzer in different locations representative of the exposures of workers. An appropriate time-location study of the workmen at the different probe locations can be used to estimate the TWA exposures.

The analytical apparatus for continuous monitoring should be a calibrated IR spectrophotometer or, if the only halogenated hydrocarbon present is methylene chloride, a halide meter may be used. If various other hydrocarbons are present, a GC or IR should be used. [120] The continuous monitoring findings should be corroborated with the recommended personal sampling method (Appendix I).

Biologic Evaluation of Exposure

Methylene chloride exposure may be monitored by its determination in blood, breath, or urine of exposed persons. [39,44,45,47,48,52]

Methylene chloride and formic acid were found in measurable amounts in the urine of persons exposed to methylene chloride. [48,55] The amount of methylene chloride found during a 24-hour period after 24-hour exposure at 100 and 200 ppm was proportional to the exposure concentrations. [48] Formic acid was found in the urine of most persons exposed to methylene chloride in a particular occupational study, but no correlation between the intensity of exposure and the concentration of formic acid could be determined. [55]

Methylene chloride has also been measured in the blood and breath of persons exposed to it. [44,47,48] The concentrations of methylene chloride in the blood and breath have been representative of the exposure. In one study, a model was developed for the determination of exposure concentrations from breath data. [47]

Measurements of COHb in persons exposed to methylene chloride at rest are related to the exposure concentrations and exposure times, as well as CO exposure. [39,41,42] However these relationships are disrupted by work, and where work is involved, maximum COHb values may not be attained until 3-4 hours after the end of the exposure. [45,44] COHb can and should be monitored in workers exposed to methylene chloride, but the time that the measurements should be made in relation to the end of exposure is not well established; consequently, a series of measurements is suggested. Until relationships between alveolar CO and COHb have been established for methylene chloride workers, it is not recommended that breath analysis for CO be used to estimate COHb.

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

A list of maximum allowable concentrations (MAC) of atmospheric contaminants compiled by Cook, [125] in 1945, included one state standard for methylene chloride (California, 200 ppm), one unofficial state guide (New York State Department of Labor, Division of Industrial Hygiene, 500 ppm), and his own recommendation of 500 ppm based on the report of Heppel et al. [69] The concentrations tabulated by Cook [125] were accepted as MAC for prolonged exposures, ie, a 40-hour week.

The recommendation of Cook [125] was adopted by the American Conference of Governmental Industrial Hygienists (ACGIH) in 1946. [126]

The methylene chloride TWA occupational exposure limit of 500 ppm for an 8-hour day, 40-hour week was supported in edition 2 (1966) of Documentation of Threshold Limit Values [127] by 2 published reports. [35,69]

The American Industrial Hygiene Association in a hygienic guide for dichloromethane published in 1965 suggested a TWA of 500 ppm and a short exposure tolerance of "approximately 1,000 ppm" for 30 minutes. [128] This recommendation was based in part on the report by Nuckolls, [34] the monograph by von Oettingen et al, [64] and unpublished data.

In 1969, the American National Standards Institute Inc (ANSI) recommended, for methylene chloride, an 8-hour day TWA of 500 ppm. It also established an acceptable ceiling concentration of 1,000 ppm and an acceptable maximum peak above the acceptable ceiling concentration of 2000 ppm for no more than 5 minutes in any 2 hours. [5] These recommendations

were based on the review by Irish, [129] the animal experiments of Heppel et al, [69] and the experiments of Stewart et al. [39]

The 1971 Documentation of Threshold Limit Values for Substances in Workroom Air [130] recommended 500 ppm for methylene chloride and cited references 35,50,55,58,63,64,69, and 131. In 1972, the Committee on Threshold Limit Values of the ACGIH included methylene chloride in the list of intended changes [132] and proposed a TLV of 250 ppm. The basis for this recommendation included the studies of Stewart et al [39] in addition to the information used in the 1971 documentation. [126]

In 1970 the International Labour Office in Geneva published tables of permissible levels of toxic substances for many countries. [57] The methylene chloride standards for 8 countries are given in Table V-1.

TABLE V-1

PERMISSIBLE LEVELS OF TOXIC SUBSTANCES FOR 8 COUNTRIES

Country	Standard, ppm	Type
Czechoslovakia	141	MAC normal
Czechoslovakia	707	MAC peak exposure
Finland	500	MAC 8-hour
Germany (Federal Republic)	500	MAC
Japan	500	Not specified
Poland *	141**	Not specified
Poland *	14**	Not specified
Rumania	57	MAC
USSR	14**	MAC
Yugoslavia	500	MAC

** Original tabulation in mg/cu m
* Dichloromethane and methylene chloride were both listed
Derived from reference 57

The Czechoslovak Committee of MAC listed standards for Hungary (6 ppm), Great Britain (500 ppm) and GDR (141 ppm). [133] The Czechoslovak Committee considered that contamination of methylene chloride with methyl chloride was the reason for the low USSR standard.

The 1969 ANSI Z-37 standard [5] was adopted as the federal standard, 29 CFR 1910.1000, Table G2. This standard is a TWA of 500 ppm for an 8 hour/day, a ceiling concentration of 1,000 ppm, and a maximum peak of 2,000 ppm for no more than 5 minutes in any 2 hours.

Basis for Recommended Environmental Standard

From the review of the literature in Chapter III on the biologic effects of methylene chloride, the most salient parts of which are summarized below, the basis for the recommended standard is prevention of significant interferences with delivery of oxygen to tissues and terminal oxidation phenomena, and abnormalities in CNS function. Complaints commonly reported by workers using methylene chloride indicative of these effects include chest pains, heart palpitations, rapid pulse, shortness of breath, dyspnea, tingling in the hands and feet, muscular pains in the arms and legs, headache, and increased fatigue. [35,51,54,55,58]

Methylene chloride has been shown through studies with labeled carbon to be metabolized to CO, [82,100,102] and CO and COHb have been studied extensively in animals and man in connection with methylene chloride exposures. [39,41,43-45, 59,67,68,70,82,100,102] These studies have shown that COHb concentrations are a function of the methylene chloride absorbed and depend on methylene chloride exposure concentration and time and amount of air inhaled.

Human male subjects (nonsmokers) exposed experimentally to methylene chloride for 7.5 hours daily on 5 consecutive days attained average peak COHb percentages of 2.9% at 50 ppm methylene chloride, 5.7% at 100 ppm methylene chloride, and 9.6% at 250 ppm methylene chloride. In each case, the peaks were attained on the 5th day of exposure. [41] Higher values would be expected if subjects exercised during exposure.

Undesirable COHb values ranging up to 12% at the end of the workday were reported in workers exposed daily to methylene chloride (see Tables XII-12 and XII-13). [59] These data need to be evaluated cautiously because of the high values observed at the beginning of the workdays (Table XII-13) and the uncertainty of the total exposure. However, the limited experimental data on subjects exposed to methylene chloride during exercise indicate that the COHb values observed in these workers might be consistent with the reported exposure concentrations.

In subjects experimentally exposed at rest to methylene chloride at 50 ppm COHb percentages returned to baseline values by the following morning after each 7.5-hour day of exposure. The maximum COHb (2.9%) observed with 50 ppm methylene chloride together with the ability to recover normal values overnight suggests that it is not necessary to restrict occupational exposures to this level to prevent undesirable COHb concentrations. [41] However further research is needed with subjects exposed during exercise to substantiate this suggestion.

With 7.5-hour daily experimental exposures during rest to methylene chloride at 100 or 250 ppm, baseline values were not recovered the following mornings. [41,42] However, baseline values were recovered by the following Monday morning after daily exposures for 7.5 hours on Monday

through Friday at either 100 or 250 ppm methylene chloride. [41] COHb percentages in nonsmokers exposed at rest at 100 ppm reached 5.7% on Friday, the 5th consecutive day of 7.5-hour exposures. If the subjects had exercised during the exposure, this level may have been reached earlier in the week. COHb concentrations of workers engaged in light work and exposed at this level of methylene chloride would probably not be acceptable.

In addition to forming CO, methylene chloride has been shown to combine with the respiratory pigments ferrihemoglobin, cytochrome P-450, cytochrome B5, and metmyoglobin. [91,92,95-97] Since CO is an inhibitor of cytochrome P-450 reactions, when formed in the tissues from methylene chloride, the same degree of CO inhibition could occur with less COHb than when the CO source is environmental air. [68] It has been suggested from comparative biochemical studies that methylene chloride may increase the affinity of hemoglobin for CO. [97] This has not been confirmed by studying the relationship between COHb and alveolar CO in humans during and after experimental or occupational exposures to methylene chloride and CO. However, the additive effects on COHb concentrations in rats simultaneously exposed to methylene chloride and CO (see Table V-2) tend to confirm that the affinity of hemoglobin for CO is increased. [67]

Some information exists that if these effects occur in man they would not be of significant magnitude with TWA daily exposures at 50-100 ppm. [43] The affinity of Hb for oxygen was slightly increased in experimental subjects by 7.5-hour/day exposures at 100 ppm methylene chloride, but not at 50 ppm, [43] In the subject's exposure at 100 ppm, arterial blood lactate levels attained during exercise were not increased over their control values, indicating that occupational exposures of this magnitude

would not cause significant interference with oxygen transport or cellular oxidation. [43]

TABLE V-2

CARBOXYHEMOGLOBIN CONCENTRATIONS IN RATS EXPOSED TO CO AND METHYLENE CHLORIDE

Exposure Concentrations, ppm		
CH_2Cl_2	CO	COHb
100	0.5-2	6.2
1000	0.5-2	12.5
0	100	10.9
100	100	16.4
1000	100	19.0

Derived from Fodor et al [67]

On the basis of COHb values attained by repeated 7.5 hour exposures at rest at 50 ppm methylene chloride, [41] it appears that daily TWA exposures of workers at 75 ppm methylene chloride would be a safe level of exposure for most work situations and it is concluded that the environmental exposure limit to recommend, in the absence of occupational exposure to CO, is 75 ppm as a time-weighted average.

There are several reasons for not recommending higher daily TWA exposures to methylene chloride. The experimental basis for determining the safe level was data obtained from nonsmoking males exposed at rest. [41] Exposure during rest to methylene chloride at 100 ppm for 7.5 hours [41,42] has resulted in COHb values that are similar to those resulting from exposure to CO at the recommended occupational exposure limit of 35

ppm as a workday TWA. [134] Subjects who exercised during exposure absorbed greater amounts of methylene chloride then when they were exposed at rest. [44] Other subjects who exercised during exposure developed higher COHb levels then their companions who did not exercise. [45] The maximum COHb levels in subjects exposed during exercise were attained 3-4 hours after removal from exposure. [45,44] In an experimental exposure of females at 250 ppm, somewhat higher COHb values were obtained than in males similarly exposed. [42] During exposures of males at 500 ppm, blood lactate during exercise became slightly more elevated during exercise than in the same subjects when not exposed to methylene chloride. [43] COHb values in excess of 9% were obtained by exposures at 250 ppm for 7.5 hours. [41,42] Finally, the affinity of Hb for oxygen was increased in proportion to methylene chloride exposure concentrations in the 50-500 ppm range. [43]

Experimental studies of humans exposed to combinations of methylene chloride and CO have not been reported. However, with 3-hour exposures of rats to combinations of methylene chloride and CO, Foder et al [67] found that the effects of COHb concentrations were additive as shown by their data presented in Table V-2. Therefore, if there is exposure to both methylene chloride and CO in the work environment, it is recommended that the exposure limits of both compounds be reduced. This indicates the need for monitoring CO where there is work with methylene chloride. Procedures for monitoring CO are included in the Criteria for a Recommended Standard....Occupational Exposure to Carbon Monoxide. [134]

For substances with an additive effect, the limits of exposure to combinations of these two substances can be determined from equation (a) (29 CFR 1910.1000):

$$\frac{C(CO)}{L\ (CO)} + \frac{C(CH2Cl\ 2)}{L\ (CH2Cl\ 2)} \leq 1$$

where:

C(CO) = the TWA exposure concentration of CO

L(CO) = the recommended TWA exposure limit of CO = 35 ppm [135]

C(CH2Cl 2) = the TWA exposure concentration of methylene chloride

L(CH2Cl 2) = the recommended TWA exposure limit of methylene chloride = 75 ppm

Concentrations of CO in the air of US cities are usually less than 10 ppm but frequently greater than 5 ppm. [135] The federal air quality standard for CO is 9 ppm for an 8-hour average not to be exceeded more than once a year (40 CFR 50.8). It is recommended that no adjustment in the recommended environmental limit for methylene chloride be made unless TWA CO exposure concentrations in the workplace are more than 9 ppm. When CO exposures are more than this, it is recommended that either CO or methylene chloride exposures or both be reduced in accordance with equation (a). The solution of equation (a) for CO concentrations of 10-35 ppm is shown graphically in Figure XII-1. Examples of TWA exposure limits derived from equation (a) and selected from Figure XII-1 are shown in Table V-3.

Restrictions on the magnitude of exposure to methylene chloride for shorter time periods are necessary to prevent undesirable CNS effects. Stupor, headache, irritability, giddiness, drowsiness, and forgetfulness have all been experienced with occupational exposures to methylene chloride. [35,50,51]

Table V-3

TWA EXPOSURE LIMITS FOR METHYLENE CHLORIDE WHEN CO IS JOINTLY PRESENT IN THE OCCUPATIONAL ENVIRONMENT.

CO TWA	CH_2Cl_2, ppm	
	TWA	Action
0-9	75	37.5
10	54	27
15	43	21.5
20	32	16
25	21	10.5
30	11	5.5
35	0	0

Responses of the central nervous system to acute methylene chloride exposure also have been studied experimentally in humans. [37,38,39,40] Stewart et al [39] found that some subjects exposed at either 868 or 986 ppm for 1 hour became light-headed. A response of this nature was not reported by subjects exposed at concentrations of 750 ppm or less for up to 5 hours. [37] Some objective measurements have shown that central nervous system function was depressed by exposure at concentrations of 317-986 ppm. [37,38,39] Other measurements of psychomotor function were not affected by 2 hours of exposure at concentrations of 250, 500, 750, and 1,000 ppm during consecutive 30-minute periods. [40]

After 1 hour of exposure at either 514 or 986 ppm methylene chloride, Stewart et al [39] found alterations in the VER resembling those of the initial phases of CNS depression. Motor speed, speed of reaction, and control precision (especially left-hand control precision) were impaired during exposures at 750 ppm, in an experiment reported by Winneke. [38]

These functions were not studied at lower concentrations.

Another visual function, CFF, was impaired by exposure to methylene chloride at 317 ppm or more. The decrease in CFF attained similar magnitudes at 317 and 470 ppm, but developed more rapidly at 470 ppm. The magnitude of the decrease attained at 750 ppm was double that found at the lower concentrations. [38] More than 77 minutes of exposure were required to significantly reduce CFF at the lower concentrations whereas, at 750 ppm, the decrease was significant at this time. CFF was not studied in exposures at less than 317 ppm methylene chloride.

In auditory vigilance tests, the subjects exposed to methylene chloride at 317 ppm began to miss more signals after about 1 hour of exposure than they did in a similar experiment when they were not being exposed to methylene chloride. When the same subjects were exposed at 750 ppm in a similar experiment they began to miss signals sooner and missed more as the exposure progressed than they did at 317 ppm. [38]

The data indicate that neither undesirable CNS responses nor COHb values are likely to occur with exposures to methylene chloride at 300 ppm for up to 1 hour. [38-42] It was reported [39] that a CNS response was obtained within 15 minutes of exposure at about 900 ppm methylene chloride following exposure at 500 ppm for 1 hour, indicating that exposures of this magnitude should not be allowed. Exposures at 750 ppm have affected CNS function in less than 1 hour indicating that this concentration is also excessive. [38] Exposures at 500 ppm for less than 1 hour have been without CNS effect. However at this level, exposure for 1 hour would likely produce excessive COHb levels. In addition, it seems unsound industrial hygiene practice to allow excursions up to nearly 7

times TWA limit for as long as an hour. Therefore, a ceiling of 500 ppm, as determined by a sampling time of 15 minutes, is recommended.

It is recognized that many workers handle small amounts of methylene chloride or work in situations where, regardless of the amounts used, there is only negligible contact with the substance. Under these conditions, it should not be necessary to comply with all of the provisions of this recommended standard. However, concern for worker health requires that protective measures be instituted below the enforceable limit to ensure that exposures stay below that limit. For these reasons, "occupational exposure to methylene chloride" has been defined as exposure above half the environmental limit that is appropriate for the concomitant CO exposure level. This action level delineates those work situations that do not require the expenditure of health resources for environmental and medical monitoring and associated recordkeeping. One-half the environmental limit has been chosen on the basis of professional judgment rather than on quantitative data that delineate nonhazardous areas from areas in which a hazard definitely exists.

Regardless of environmental concentrations, many work practices are necessary for protection of the worker. These are discussed in Chapter VI and it is recommended that all sections of the standard not specifically exempted apply to all work with methylene chloride.

VI. WORK PRACTICES

The principal method for the manufacture of methylene chloride is the chlorination of methane, [1] and suitable controls for safe use of methane and chlorine should be used. Engineering controls required for the safe handling of chlorine are discussed in the Manufacturing Chemists Association's Safety Data Sheet SD-80. The major hazards from methane are its flammability and explosive characteristics. Caution must be taken to avoid exposure to other chloromethanes that may be co-products of methylene chloride manufacture and caustion must bb.

Further information concerning specific work practices for methylene chloride can be found in the Manufacturing Chemists Association's Safety Data Sheet SD-86. [137]

(a) Transport, Handling, and Use

Containers for storage or transportation of methylene chloride should be made of plain, galvanized, or lead lined, mild steel because it may be corrosive to iron, some stainless steels, copper, nickel, and other metals, especially at elevated temperatures and when in contact with water. [1,138,139] It also reacts with alkali metals (alloys of sodium are potentially explosive), aluminum, and magnesium. Aluminum, rubber, and polyvinyl chloride also are not resistant to methylene chloride.

All piping and valves at the loading or unloading station should be of material that is resistant to methylene chloride and should be carefully inspected prior to connection to the transport vehicle and periodically during the operation. Personal protection must be provided during both inspection and connection. Eye wash and safety shower installations should

be readily available in the immediate area. Unloading areas must be posted "Caution: loading or unloading methylene chloride."

Broken drums or other storage or transporting containers should not be welded until thoroughly purged. [140] Although methylene chloride is oxidized only under rigorous conditions, it forms explosive mixture when combined with oxygen under pressure and phosgene, hydrochloric acid, and carbon dixoide in the presence of open flames or high intensity ultraviolet light (Table XII-21). [34,53,140]

Processes in which methylene chloride is used in large quantities should be carried out in closed systems. Well designed hoods and ventilation systems should be used to maintain exposures at or below concentrations specified by this standard. Further protective measures include the use of personal protective equipment and clothing and purging of equipment prior to and during servicing and maintenance.

Methylene chloride is a common solvent in paints and paint strippers and is therefore used in confined spaces or areas in which there are no hoods or specially constructed ventilation systems. For these uses, care must be taken to assure sufficient general room air ventilation to maintain exposures below the standard. This may require engineering controls, such as installation of fans, as well as leaving all doors and windows open. Portable heating units should not be used in confined areas where methylene chloride is used.

Safety showers and eye wash facilities are necessary in areas where methylene chloride is handled. In temporary locations where such facilities are not available, such as in painting or paint stripping operations, a container of water for emergency use must be kept with the first-aid supplies.

Special handling and disposal procedures are required because of the ability of methylene chloride to chemically react with other materials. Reactions of methylene chloride with alloys of sodium are potentially explosive. Mixtures of methylene chloride with acetone may become flammable upon evaporation in air. Cleaning rags should not be burned.

Because of its corrosive properties and its high vapor pressure, methylene chloride should be stored in cool, dry, well-ventilated areas, away from direct sunlight.

(b) Equipment Maintenance

All equipment used for handling methylene chloride must be emptied and purged prior to entry or disassembly. Pipe lines should be disconnected and capped. Under conditions where it is necessary to enter or otherwise work with methylene chloride contaminated equipment, maintenance personnel must use either a self-contained breathing apparatus, pressure demand type, with an impervious protective suit, or a combination supplied air suit with auxiliary self-contained air supply. Ventilation should still be continued during this time by blowing or drawing fresh air through the system. Safety precautions for emergency rescue require that all maintenance personnel be informed of the toxic properties of methylene chloride and be instructed on the necessity of wearing personal protective equipment. [137] Constant observation of anyone entering a tank should be maintained in case rescue work is necessary.

(c) Emergencies

Spills must be anticipated. Storage tanks should be diked to contain the contents of the tank. Drum storage areas must also be diked to contain the volume of methylene chloride present in the drums to prevent release to

other areas. Areas where major spills are likely to occur should be constructed so that they may be closed until properly protected personnel can enter, clear, and ventilate the area. Normal work should not be continued until the concentration of methylene chloride has been reduced to that prescribed by this standard. Any combustion operations must be stopped until the spill is cleared. Sewering of methylene chloride should be done in compliance with local, state, and federal waste disposal regulations. Consideration should be given to pumping the diked spill to another tank. In addition, it is advisable to have facilities for transfer of the contents of a leaking tank to another suitable tank.

Areas in which small spills have occurred must be evacuated and well ventilated. Small portable fans may be used in confined areas where local exhaust ventilation is not feasible. Workers should not return to any work area until the odor of methylene chloride is no longer perceptible.

(d) Respiratory Protection

For adequate respiratory protection against the multiplicity of conditions which may be encountered in individual operations, many types of respirators have been developed and approved. Each has a particular field of application and limitations from the viewpoint of protection, as well as advantages and disadvantages from the viewpoint of operational procedures and maintenance. Detailed information on the selection and use of respirators can be obtained from the Respiratory Protective Devices Manual [141] published by the AIHA and the ACGIH in 1963. The American National Standard: Practices for Respiratory Protection, ANSI Z88.2-1969, [142] also classifies, describes, and gives the limitations of respirators.

There are 3 categories of respirators: atmosphere-supplying respirators, air-purifying respirators, and combination atmosphere-supplying and air-purifying respirators.

One factor that affects the overall performance of demand type (negative pressure) respirators is the variability of the face seal. Facepiece leakage is the major limitation of half-mask and quarter-mask facepieces operated with a negative pressure.

For purposes of uniform regulations covering the many face sizes and shapes of the US population, NIOSH recommends that the half-mask or quarter-mask facepieces operated with a negative pressure be used only for protection at or below 10 times the TWA limit, although the majority of wearers can obtain protection in atmospheres of higher methylene chloride concentrations. On the same basis, NIOSH recommends that the full facepiece, operated with negative pressure, may be used up to 50 times the TWA limit.

These maximum use concentration guides do not take into account the service life of the filters and absorbent canisters which also affect the performance of air-purifying respirators. The approval tests (under 30 CFR 11) for these 2 devices specify only carbon tetrachloride for the service life test. Based on recent tests by Nelson and Harder [143] who tested standard respirator cartridges against many types of industrial organic solvents, it is now possible to estimate the service life of approved organic vapor canisters or cartridges against methylene chloride. With a test concentration of 1,000 ppm of methylene chloride, they reported that the standard organic vapor cartridge has a service life of 15.8 minutes before a breakthrough of 100 ppm of methylene chloride. Under the same

test conditions, a service life of 90 minutes for carbon tetrachloride was obtained. The standard industrial size gas mask canister is tested against 20,000 ppm of carbon tetrachloride and it must have a service life of 12 minutes before a breakthrough of 5 ppm. Since it has been shown that charcoal can absorb 6 times as much carbon tetrachloride as methylene chloride, it can be estimated that the service life for an industrial size canister is estimated at 40 minutes in an atmosphere of 1,000 ppm, methylene chloride. The chin-type canister and the chemical cartridge respirator with much smaller volumes of sorbent are not recommended for use in methylene chloride contaminated atmospheres because of the very short breakthrough time of methylene chloride.

NIOSH periodically issues a list of approved or certified respiratory protective devices. All devices approved by the Bureau of Mines are listed in Information Circular 8559 and supplements. All types of devices certified by the Testing and Certification Laboratory of NIOSH are listed in a separate publication. These are available from the Testing and Certification Laboratory, NIOSH, Morgantown, West Virginia 26505.

VII. Research Needs

The finding that carbon monoxide is a major metabolite of methylene chloride opened up an entirely new field in methylene chloride toxicity. That this metabolic conversion occurs is well established. However, the biochemical mechanism by which it is accomplished is only speculation. There is evidence that other methylene chloride metabolites include formaldehyde and formic acid. It is important to study the metabolism of methylene chloride to determine the enzyme systems involved in these transformations in order to establish the significance of the intake, both in and out of the work environment, of other substances. For example, the effects on methylene chloride toxicity of alcohols, barbiturates and other enzyme-inducing substances has received little attention.

Whether similar COHb values obtained from inhaling CO and from metabolizing methylene chloride have the same significance has not been the subject of a specific study. It could be assumed that a level of COHb obtained from metabolism of methylene chloride would be more significant than the same level acquired from inhaling CO. The reasoning for such an assumption would be the premise that the ratio of tissue concentrations of CO to blood concentration should be greater when the CO is moving from the tissues to the blood. Information relative to this point is needed in order to adequately evaluate methylene chloride exposures. The affinity of hemoglobin for CO may be alerted when methylene chloride is present. This is of concern because there is some evidence that methylene chloride combines in some way with hemoglobin, and similar substances, to alter the CO, and oxygen, dissociation curves. There was some indication in the data

reviewed that the ratio of % COHb to alveolar CO concentration was different following methylene chloride exposure than had been determined following CO exposure. Information is needed on these relationships in order to use alveolar breath samples to monitor COHb values of workers.

In the realm of cellular oxidation, there are potential problems that need investigation. Among these are indications that methylene chloride could interfere by direct combination with heme pigments, making them unavailable for transport purposes, and that oxygen dissociation curves may be altered. An important need for evaluating methylene chloride toxicity is knowledge of the shape of these curves at low tension.

Additional information is also needed on the chronic effects of methylene chloride, both animal experimentation, studies of exposed workers, and experimental human exposures at 25-75 ppm.

VIII. REFERENCES

1. Hardie DWF: Methylene chloride, in Kirk RE, Othmer DT (eds): Encyclopedia of Chemical Technology, ed 2. New York, Interscience Publishers, 1969, vol 5, pp 111-19

2. May J: Odor thresholds of solvents for assessment of solvent odors in the air. Staub-Reinhalt Luft 26:34-38, 1966

3. Leonardos G, Kendall D, Barnard N: Odor threshold determinations of 53 odorant chemicals. J Air Pollut Control Assoc 19:91-95, 1969

4. Weast RC (ed): Handbook of Chemistry and Physics--A Ready-Reference Book of Chemical and Physical Data, ed 50. Cleveland, The Chemical Rubber Publishing Co, 1969, pp C-367, D-148

5. American National Standard Acceptable Concentrations of Methylene Chloride (Dichloromethane), ANSI Z37.23-1969, Revision of Z37.23-1962. New York, American National Standards Institute Inc, 1970, 8 pp

6. Christensen HE, Luginbyhl TT (eds): The Toxic Substances List 1974 Edition, HSM-99-73-45. US Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 1974, p 477

7. Dow Methylene Chloride--The Versatile Solvent to Help You Create Better Products. Midland, Mich, The Dow Chemical Co., 1972, 15 pp

8. Faith WL, Keyes DB, Clark RL: Industrial Chemicals, ed 3. New York, John Wiley & Sons Inc, 1965, pp 507-13

9. Synthetic Organic Chemicals, United States Production and Sales, 1955, Report No. 198, Second Series. US Tariff Commission, 1956, p 57

10. Synthetic Organic Chemicals, United States Production and Sales, 1956, Report No. 200, Second Series. US Tariff Commission, 1957, p 56

11. Synthetic Organic Chemicals, United States Production and Sales, 1957, Report No. 203, Second Series. US Tariff Commission, 1958, p 55

12. Synthetic Organic Chemicals, United States Production and Sales, 1958, Report No. 205, Second Series. US Tariff Commission, 1959, p 51

13. Synthetic Organic Chemicals, United States Production and Sales, 1959, Report No. 206, Second Series. US Tariff Commission, 1960, p 55

14. Synthetic Organic Chemicals, United States Production and Sales, 1960, TC Publication 34. US Tariff Commission, 1961, p 54

15. Synthetic Organic Chemicals, United States Production and Sales, 1961, TC Publication 72. US Tariff Comission, 1962, p 55

16. Synthetic Organic Chemicals, United States Production and Sales, 1962, TC Publication 114. US Tariff Commission, 1963, p 58

17. Synthetic Organic Chemicals, United States Production and Sales, 1963, TC Publication 143. US Tariff Commission, 1964, p 57

18. Synthetic Organic Chemicals, United States Production and Sales, 1964, TC Publication 167. US Tariff Commission, 1965, p 57

19. Synthetic Organic Chemicals, United States Production and Sales, 1965, TC Publication 206. US Tariff Commission, 1967, p 58

20. Synthetic Organic Chemicals, United States Production and Sales, 1966, TC Publication 248. US Tariff Commission, 1968, p 60

21. Synthetic Organic Chemicals, United States Production and Sales, 1967, TC Publication 295. US Tariff Commission, 1969, p 59

22. Synthetic Organic Chemicals, United States Production and Sales, 1968, TC Publication 327. US Tariff Commission, 1970, p 216

23. Synthetic Organic Chemicals, United States Production and Sales, 1969, TC Publication 412. US Tariff Commission, 1971, p 206

24. Synthetic Organic Chemicals, United States Production and Sales, 1970, TC Publication 479. US Tariff Commission, 1972, p 215

25. Synthetic Organic Chemicals, United States Production and Sales, 1971, TC Publication 614. US Tariff Commission, 1973, p 207

26. Synthetic Organic Chemicals, United States Production and Sales, 1972, TC Publication 681. US Tariff Commission, 1974, pp 206-07, 233-34, 238-40

27. Gleason MN, Gosselin RE, Hodge HC, Smith RP: Clinical Toxicology of Commercial Products--Acute Poisoning, ed 3. Baltimore, Williams & Wilkins Co, 1969, 1427 pp

28. Richardson BW: Lectures on experimental and practical medicine--on bichloride of methylene as a general anaesthetic. Med Times Gaz II: 423-24, 479-83, 1867

29. Junker F: Remarks on death from methylene and on the use of other anaesthetics. Br Med J 2:104-07, 1883

30. Regnauld J, Villejean: [Comparative physiologic characteristics of chloroform and methylene chloride. (CH2Cl 2)] Comp. Rend Soc Biol 1:158-62, 1884 (Fr)

31. Hellwig A: [Clinical narcosis with Solaesthin.] Klin Wochenschr 1:215-17, 1922 (Ger)

32. Bourne W, Stehle RL: Methylene chloride in anaesthesia. Can Med Assoc J 13:432-33, 1923

33. Grasset J, Gauthier R: [Clinical and graphic study of the analgesic action of methyl chloride in obstetrics.] Sem Hop Paris 26:1280-83, 1950 (Fr)

34. Nuckolls AH: Underwriters' Laboratories' Report on the Comparative Life, Fire, and Explosion Hazards of Common Refrigerants, Miscellaneous Hazard No. 2375. Chicago, Underwriters' Laboratories, 1933, pp 24-26, 53-57, 76-77, 85, 87-88, 92-93, Tables XIX, XXI, XXV

35. Collier H: Methylene dichloride intoxication in industry--A report of two cases. Lancet 1:594-95, 1936

36. Methylene Chloride. Ind Hyg Newsletter 7:15, September 1947

37. Fodor GG, Winneke G: Nervous system disturbances in men and animals experimentally exposed to industrial solvent vapors, in England HM (ed): Proceedings of the 2nd International Clean Air Congress. New York, Academic Press, 1971, pp 238-43

38. Winneke G: Behavioral effects of methylene chloride and carbon monoxide as assessed by sensory and psychomotor performance, in Xintaras C, Johnson BL, deGroot I (eds): Behavioral Toxicology--Early Detection of Occupational Hazards, Publication HEW No. (NIOSH) 74-126. US Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 1974, pp 130-44

39. Stewart RD, Fisher TN, Hosko MJ, Peterson JE, Baretta ED, Dodd HC: Experimental human exposure to methylene chloride. Arch Environ Health 25:342-48, 1972

40. Gamborale F, Annwall BA, Hultengren M: Exposure to Methylene chloride--II. Psychological functions. Scand J Work Environ Health 1:95-103, 1975

41. Stewart RD, Forster HV, Hake CL, Lebrun AJ, Peterson JE: Human Responses to Controlled Exposures of Methylene Chloride Vapor. Report No. NIOSH-MCOW-ENVM-MC-73-7. Milwaukee, Wis, The Medical College of Wisconsin, Department of Environmental Medicine, December, 1973, 82 pp

42. Hake CL, Stewart RD, Forster HV, Lebrun AJ, Peterson JE, Wu A: Results of the Controlled Exposure of Human Females to the Vapor of Methylene Chloride. Report No. NIOSH-MCOW-ENVM-MC-74-3. Milwaukee, Wis, The Medical College of Wisconsin, Department of Environmental Medicine, March 1974, 22 pp

43. Forster HV, Graff S, Hake CL, Soto R, Stewart RD: Pulmonary-Hematologic Studies on Humans During Exposure to Methylene Chloride, Report No. NIOSH-MCOW-ENVM-MC-74-4. The Medical College of Wisconsin, Department of Environmental Medicine, Milwaukee Wis, April 1974, 17 pp

44. Astrand I, Ovrum P, Carlsson A: Exposure to methylene chloride--I. Its concentration in alveolar air and blood during rest and exercise and its metabolism. Scand J Work Environ Health 1:78-94, 1975

45. Stewart RD, Hake CL: Paint-remover hazard. JAMA 235:398-401, 1976

46. Lehmann KB, Schmidt-Kehl L: [The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene.] Arch Hyg 116:131-268, 1936 (Ger)

47. Riley EC, Fassett DW, Sutton WL: Methylene chloride vapor in expired air of human subjects. Am Ind Hyg Assoc J 27:341-48, 1966

48. DiVincenzo GD, Yanno FJ, Astill BD: Human and canine exposures to methylene chloride vapor. Am Ind Hyg Assoc J 33:125-35, 1972

49. Stewart RD, Dodd HC: Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride, and 1,1,1-trichloroethane through the human skin. Am Ind Hyg Assoc J 25: 439-46, 1964

50. Moskowitz S, Shapiro H: Fatal exposure to methylene chloride vapor. Arch Ind Hyg Occup Med 6:116-23, 1952

51. Hughes JP: Hazardous exposure to some so-called safe solvents. JAMA 156:234-37, 1954

52. Christensen EKJ, Huizinga T: [A fatal case of methylene chloride intoxication.] Pharm Weekblad 106:301-05, 1971 (Dut)

53. Gerritsen WB, Buschmann CH: Phosgene poisoning caused by the use of chemical paint removers containing methylene chloride in ill-ventilated rooms heated by kerosene stoves. Br J Ind Med 17: 187-89, 1960

54. English JM: A case of probable phosgene poisoning. Br Med J 1:38, 1964

55. Kuzelova M, Vlasak R: [The effect of methylene-dichloride on the health of workers in production of film-foils and investigation of

formic acid as a methylene-dichloride metabolite.] Pracovni Lekarstvi 18:167-70, 1966 (Cze)

56. Fokina KV: The functional state of the olfactory and vestibular analyzers on exposure to chlorine derivitives of methane. Hyg Sanit 30:182-86, 1965

57. Permissible Levels of Toxic Substances in the Working Environment--6th Session of the Joint ILO/WHO Committee on Occupational Health, Geneva, June 4-10, 1968, Occupational Safety and Health Series No. 20. Geneva, International Labour Office, 1970, pp 182-87, 194, 196, 198-99, 202, 209-11, 217-18, 222, 224, 226, 229, 237, 276, 286, 289, 329, 335, 345, 347

58. Weiss G: [Toxic encephalosis as an occupational hazard with methylene chloride.] Zentralbl Arbeitsmed 17:282-85, 1967 (Ger)

59. Ratney RS, Wegman DH, Elkins HB: In vivo conversion of methylene chloride to carbon monoxide. Arch Environ Health 28:223-26, 1974

60. Flury F, Zernik F: [Harmful Gases, Vapors, Fogs, Smoke, and Dust.] Berlin, Julius Springer, 1931, pp 311-12 (Ger)

61. Muller J: [Comparative investigations on the anesthetic and toxic effect of some halogenated hydrocarbons.] Arch Exp Pathol Pharmakol 109:276-94, 1925 (Ger)

62. Lazarew NW: [Narcotic effect of the vapors of the chlorine derivatives of methane, ethane and ethylene.] Naunyn-Schmiedeb Arch Exp Pathol Pharmakol 141:19-24, 1929 (Ger)

63. Svirbely JL, Highman B, Alford WC, Von Oettingen WF: The toxicity and narcotic action of mono-chloro-mono-bromo-methane with special reference to inorganic and volatile bromide in blood, urine and brain. J Ind Hyg Toxicol 29:382-89, 1947

64. Von Oettingen WF, Powell CC, Sharpless NE, Alford WC, Pecora LJ: Relation Between the Toxic Action of Chlorinated Methanes and Their Chemical and Physicochemical Properties, NIH bulletin 191. Federal Security Agency, US Public Health Service, National Institutes of Health, 1949, 85 pp

65. Berger M, Fodor GG: [CNS disorders under the influence of air mixtures containing dichloromethane.] Zentralbl Bakteriol (Ref) 215:517, 1968 (Ger)

66. Heppel LA, Neal PA: Toxicology of dichloromethane (methylene chloride)--II. Its effect upon running activity in the male rat. J Ind Hyg Toxicol 26:17-21, 1944

67. Fodor GG, Prajsnar D, Schlipkoter HW: Endogenous CO formation by incorporated halogenated hydrocarbons of the methane series. Staub-Reinhalt Luft 33:260-61, 1973

68. Roth RP, Jia-Ruey Lo R, Drew RT: Dichloromethane inhalation and drug metabolizing enzymes--The effect of chemical treatment with mixed function oxidase inducing and inhibiting agents on carboxyhemoglobin formation. AMRL-TR-73-125, paper No. 22, in Proceedings of the 4th Annual Conference on Environmental Toxicology. Wright Patterson Air Force Base, Ohio, Aerospace Medical Research Laboratory, 1973, pp 279-89

69. Heppel LA, Neal PA, Perrin TL, Orr ML, Porterfield VT: Toxicology of dichloromethane (methylene chloride)--I. Studies on effects of daily inhalation. J Ind Hyg Toxicol 26:8-16, 1944

70. Haun CC, Vernot EH, Darmer KI Jr, Diamond SS: Continuous animal exposure to low levels of dichloromethane. AMRL-TR-130, paper No. 12, in Proceedings of the 3rd Annual Conference on Environmental Toxicology. Wright-Patterson Air Force Base, Ohio, Aerospace Medical Research Laboratory, 1972, pp 199-208

71. Weinstein RS, Boyd DD, Back KC: Effects of continuous inhalation of dichloromethane in the mouse--Morphologic and functional observations. Toxicol Appl Pharmacol 23:660-79, 1972

72. Thomas AA, Pinkerton MK, Warden JA: Effects of low level dichloromethane exposure on the spontaneous activity of mice. AMRL-TR72-130, paper No 14, in Proceedings of the 3rd Annual Conference on Environmental Toxicology. Wright-Patterson Air Force Base, Ohio, Aerospace Medical Research Laboratory, 1972, pp 223-27

73. MacEwen JD, Vernot EH, Haun CC: Continuous Animal Exposure to Dichloromethane. AMRL-TR-72-28, Systemed Corporation Report No. W-71005. Wright-Patterson Air Force Base, Ohio, Aerospace Medical Research Laboratory, 1972, 33 pp

74. Weinstein RS, Diamond SS: Hepatotoxicity of dichloromethane (methylene chloride) with continuous inhalation exposure at a low dose level. AMRL-72-130, paper No. 13, in Proceedings of the 3rd Annual Conference on Environmental Toxicology. Wright-Patterson Air Force Base, Ohio, Aerospace Medical Research Laboratory, 1972, pp 209-22

75. Thomas AA: Low ambient pressure environments and toxicity--A new approach to space cabin toxicology. Arch Environ Health: 11:316-22, 1965

76. Schutz E: [Effect of polyethyleneglycol 400 on percutaneous absorption of active ingredients.] Arch Exp Pathol Pharmakol 232:237-38, 1958 (Ger)

77. Schutz E: [The effects of organic liquids on the skin.] Arzneim Forsch 10:1027-29, 1960 (Ger)

78. Schwetz BA, Leong BKJ, Gehring PJ: The effect of maternally inhaled trichlorethylene, perchloroethylene, methyl chloroform and methylene chloride on embryonal and fetal development in mice and rats. Toxicol Appl Pharmacol 32:84-96, 1975

79. Butler TC: Reduction of carbon tetrachloride in vivo and reduction of carbon tetrachloride and chloroform in vitro by tissues and tissue constituents. J Pharmacol Exp Ther 134:311-19, 1961

80. Paul BB, Rubinstein D: Metabolism of carbon tetrachloride and chloroform by the rat. J Pharmacol Exp Ther 141:141-48, 1963

81. DiVincenzo GD, Hamilton ML: Fate and disposition of [14 C] methylene chloride in the rat. Toxicol Appl Pharmacol 32:385-93, 1975

82. Reynolds ES, Yee AG: Liver parenchymal cell injury--V. Relationships between patterns of chloromethane-C 14 incorporation into constituents of liver in vivo and cellular injury. Lab Invest 16:591-603, 1967

83. Heppel LA, Porterfield VT: Enzymatic dehalogenation of certain brominated and chlorinated compounds. J Biol Chem 176:763-69, 1948

84. Fowler JSL: Carbon tetrachloride metabolism in the rabbit. Br J Pharmacol 37:733-37, 1969

85. Van Dyke RA: On the fate of chloroform. Anesthesiology 30:257-58, 1969

86. Recknagel RO, Ghoshal AK: Lipoperoxidation as a vector in carbon tetrachloride hepatotoxicity. Lab Invest 15:132-48, 1966

87. Scholler KL: Modification of the effects of chloroform on the rat liver. Br J Anaesth 42:603-05, 1970

88. Fowler JSL: Chlorinated hydrocarbon toxicity in the fowl and duck. J Comp Pathol 80:465-71, 1970

89. Garner RC, McLean AEM: Increased susceptibility to carbon tetrachloride poisoning in the rat after pretreatment with oral phenobarbitone. Biochem Pharmacol 18:645-50, 1969

90. Ugazio G, Burdino E, Danni O, Milillo PA: Hepatoxicity and lethality of halogenoalkanes. Biochem Soc Trans 1:968-72, 1973

91. Reiner O, Uehleke H: [Carbon tetrachloride interaction with reduced microsomal cytochrome P-450 and haem.] Hoppe-Seyler's Z Physiol Chem 352:1048-52, 1971 (Ger)

92. Ullrich V, Schnabel KH: Formation and binding of carbanions by cytochrome P-450 of liver microsomes. Drug Metab Dispos 1:176-83, 1973

93. Dingell JV, Heimberg M: The effects of aliphatic halogenated hydrocarbons on hepatic drug metabolism. Biochem Pharmacol 17:1269-78, 1968

94. Sasame HA, Castro JA, Gillette JR: Studies on the destruction of liver microsomal cytochrome P-450 by carbon tetrachloride administration. Biochem Pharmacol 17:1759-68, 1968

95. Bucher DJ: Action of Chloroform and Its Chlorinated Analogues on Hemeproteins, PhD thesis. Berkley, Cal, University of California, 1968, 161 pp

96. Bucher DJ, Brown WD: Action of chloroform and its chlorinated analogs on hemoproteins. Biochem 10:4239-46, 1971

97. Nunes AC, Schoenborn BP: Dichloromethane and myoglobin function. Mol Pharmacol 9:835-39, 1973

98. Porter K, Volman DH: Flame ionization detection of carbon monoxide for gas chromatographic analysis. Anal Chem 34:748-49, 1962

99. Open Forum (Discussion by Dr. Fassett), in Toxicity of Halogenated Solvents, Aerosol Propellants, and Fire-Extinguishants, Session II, in Proceedings of the 3rd Annual Conference of Environmental Toxicology AMRL-TR-72-130. Wright-Patterson Air Force Base, Ohio, Aerospace Medical Research Laboratory, 1972, p 230

100. Kubic VL, Anders MW, Engel RR, Barlow CH, Caughey WS: Metabolism of dihalomethanes to carbon monoxide--I. In vivo studies. Drug Metab Dispos 2:53-7, 1974

101. Van Slyke DD, Hiller A, Weisiger JR, Cruz WO: Determination of carbon monoxide in blood and of total and active hemoglobin by carbon monoxide capacity. Inactive hemoglobin and methemoglobin contents of normal human blood. J Biol Chem 166:121-48, 1946

102. Carlsson A, Hultengren M: Exposure to methylene chloride--III. Metabolism of C14-labelled methylene chloride in rat. Scand J Work Environ Health 1:104-08, 1975

103. Collison HA, Rodkey FL, O'Neal JD: Determination of carbon monoxide in blood by gas chromatography. Clin Chem 14:162-71, 1968

104. Kassebart V, Angerer J: Influence of dichloromethane on the disappearance rate of ethanol in the blood of rats. Int Arch Arbeitsmed 33:231-36, 1974

105. White LD, Taylor DG, Mauer PA, Kupel RE: A convenient optimized method for the analysis of selected solvent vapors in the industrial atmosphere. Am Ind Hyg Assoc J 31:225-32, 1970

106. Cropper FR, Kaminsky S: Determination of toxic organic compounds in admixture in the atmosphere by gas chromatography. Anal Chem 35:735-43, 1963

107. Ramos H: Health Hazard Evaluation/Toxicity Determination--Cummins Northeastern Incorporated, Dedham, Massachusetts, PB-232 735, Report No. NIOSH-TR-110-74. Cincinnati, US Dept Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, March 1974, 7 pp

108. Vandervort R, Polakoff PL: Health Hazard Evaluation Report 72-84--Hazard Evaluation Services Branch, Division of Technical Services, Dunham-Bush, Incorporated, West Hartford, Connecticut. Cincinnati, US Dept Health, Education, and Welfare, Public Health Service, National Institute for Occupational Safety and Health, March 1973, 73 pp

109. Burton DJ, Shmunes E: Health Hazard Evaluation/Toxicity Determination--Chemetron Chemical, Organics Division, Newport, Tennessee, PB-229 233, Report No. NIOSH-TR-049-74. Cincinnati, US Dept Health, Education and Welfare, Public Health Service, National Institute for Occupational Safety and Health June 1973, 23 pp

110. Vandervort R, Lucas JB: Health Hazard Evaluation/Toxicity Determination--Owens-Corning Fiberglass Corporation, Huntingdon, Pennsylvania, PB-229 162, Report No. NIOSH-TR-060-74. Cincinnati, US Dept Health, Education, and Welfare, Public Health Service, National Institute for Occupational Safety and Health, August 1973, 10 pp

111. Gunter BJ, Lucas JB: Health Hazard Evaluation/Toxicity Determination Report 73-84-119--Head Ski Company, Boulder, Colorado, PB-232 723. Dept Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, March 1974, 20 pp

112. Markel HL Jr, Shama SK: Health Hazard Evaluation/Toxicity Determination--Whirlpool Corporation, Fort Smith, Arkansas, PB-232 721, Report NIOSH-TR 121-74. Cincinnati, US Dept Health, Education, and Welfare, Public Health Service, National Institute for Occupational Safety and Health, March 1964, 16 pp

113. Wagner WL: Health Hazard Evaluation/Toxicity Determination -- Schnadig Corporation, Cornelia, Georgia, PB-232 737, Report No. NIOSH-TR-127-74. Cincinnati, US Dept Health, Education, and Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, March 1974, 7 pp

114. Peterson JE, Hoyle HR, Schneider EJ: The analysis of air for halogenated hydrocarbon contaminants by means of absorption on silica gel. Am Ind Hyg Assoc Q 17:429-33, 1956

115. Williams FW, Umstead MB: Determination of trace contaminants in air by concentrating on porous polymer beads. Anal Chem 40:2232-34, 1968

116. Levadie B, Harwood JF: An application of gas chromatography to analysis of solvent vapors in industrial air. Am Ind Hyg Assoc J 21:20-24, 1960

117. Lugg, GA: Fujiwara reaction and determination of carbon tetrachloride, chloroform, tetrachloroethane and trichloroethylene in air. Anal Chem 38:1532-36, 1966

118. Otterson EJ, Guy CU: A method of atmospheric solvent vapor sampling on activated charcoal in connection with gas chromatography, in Transactions of the 26th Annual Meeting, American Conference of Governmental Industrial Hygienists, Philadelphia, April 25-28, 1964, pp 37-43

119. Saltzman BE: Direct reading colorimetric indicators, in Air Sampling Instruments for Evaluation of Atmospheric Contaminants, ed 4. Cincinnati, American Conference of Governmental Industrial Hygienists, 1972, pp S 22-23

120. Baretta ED, Stewart RD, Mutchler JE: Monitoring exposures to vinyl chloride vapor--Breath analysis and continuous air sampling. Am Ind Hyg Assoc J 30:537-44, 1969

121. Nelson GO, Shapiro EG: A field instrument for detecting airborne halogen compounds. Am Ind Hyg Assoc J 32:757-65, 1971

122. Cooper CV, White LD, Kupel RE: Qualitative detection limits for specific compounds utilizing gas chromatographic fractions, activated charcoal and a mass spectrometer. Am Ind Hyg Assoc J 32: 383-86, 1971

123. Fraust CL, Hermann ER: Charcoal sampling tubes for organic vapor analysis by gas chromatography. Am Ind Hyg Assoc J 27:68-74, 1966

124. Kupel RE, White LD: Report on a modified charcoal tube. Am Ind Hyg Assoc J 32:456, 1971

125. Cook WA: Maximum allowable concentrations of industrial atmospheric contaminants. Ind Med 14:936-46, 1945

126. American Conference of Governmental Industrial Hygienists: Report of the Sub Committee on Threshold Limits, in Proceedings of the 8th Annual Meeting, ACGIH, Chicago, April 7-13, 1946, pp 54-56

127. Methylene Chloride (Dichloromethane), in Documentation of Threshold Limit Values, rev ed. Cincinnati, American Conference of Governmental Industrial Hygienists, 1966, p 126

128. Dichloromethane (Methylene chloride, Methylene dichloride), (rev 1965), in Hygienic Guide Series. Am Ind Hyg Assoc J 26:633-36, 1965

129. Irish DD: Halogenated Hydrocarbons--I. Aliphatic, in Patty FA (ed): Industrial Hygiene and Toxicology, ed 2 rev; Toxicology (Fassett DW, Irish DD, eds). New York, Interscience Publishers, 1963, vol 2, pp 1257-59

130. Methylene Chloride (Dichloromethane), in Documentation of the Threshold Limit Values for Substances in Workroom Air, ed 3. Cincinnati, American Conference of Governmental Industrial Hygienists, 1971, pp 171-72

131. Gimadeev MM: Book Reviews: Functional disorders of the liver in those working with methanol in connection with a sanitary hygienic study of their working conditions. (Golubovskii IE, Kamchatnova VP, authors). Hyg Sanit 29:144-45, 1964

132. Methylene Chloride (Dichloromethane), in Supplemental Documentation of Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment, in Transactions of the 34th Annual Meeting of the American Conference of Governmental Industrial Hygienists, San Francisco, May 24-19, 1972, pp 188-90

133. Methylene Chloride, in Documentation of MAC in Czechoslovakia. Czechoslovak Committee of MAC, 1969, pp 118-20

134. Criteria for a Recommended Standard--Occupational Exposure to Carbon Monoxide, HSM 73-11000. US Dept of Health, Education, and Welfare, Health Services and Mental Health Administration, National Institute for Occupational Safety and Health, 1972, 115 pp

135. Atmospheric Carbon Monoxide Concentrations, in Air Quality Criteria for Carbon Monoxide, Publication No. AP-62. US Dept of Health, Education, and Welfare, Public Health Service, Environmental Health Service, National Air Pollution Control Administration, 1970, Chap 6, pp 6-1 to 6-30

136. Chlorine, Chemical Safety Data Sheet SD-80. Washington, DC, Manufacturing Chemists Association Inc, 1970, 20 pp

137. Methylene Chloride, Chemical Safety Data Sheet SD-86. Washington, DC, Manufacturing Chemists Association Inc, 1962, 11 pp

138. Methylene Chloride (Dichloromethane), Data Sheet 474. Chicago, National Safety Council, (no date), 4 pp

139. Methylene Chloride, Environmental Hazards Control Bulletin No. 25. US Dept Navy, Bureau of Medicine and Surgery, (no date), 3 pp

140. Rinzema LC, Silverstein LG: Hazards from chlorinated hydrocarbon decomposition during welding. Am Ind Hyg Assoc J 33: 35-40, 1972

141. Joint AIHA-ACGIH Respiratory Protective Devices Committee (EC Hyatt, Chmn): Respiratory Protective Devices Manual. American Industrial Hygiene Association and American Conference of Governmental Industrial Hygienists, 1963, 162 pp

142. American National Standard: Practices for Respiratory Protection, Z88.2-1969. New York, American National Standards Institute Inc, 1969, 31 pp

143. Nelson GO, Harder CA: Respirator cartridge efficiency studies--V. Effect of solvent vapor. Am Ind Hyg Assoc J 35:391-410, 1974

IX. APPENDIX I

SAMPLING PROCEDURE FOR

COLLECTION OF METHYLENE CHLORIDE

General Requirements

(a) Air samples representative of the breathing zone of workers should be collected to characterize the exposure from each job or specific operation at each work area.

(b) Samples collected should be representative of exposure of individual workers.

(c) Suggested records:

(1) The date and time of sample collection.

(2) Sampling duration.

(3) Total sample volume.

(4) Location of sampling.

(5) Temperature, pressure, and relative humidity at time of sampling.

(6) Other pertinent information.

Sampling

(a) Samples should be collected as near as practicable to the face of workers without interfering with freedom of movement.

(b) Samples should be collected to permit determination of TWA workday and ceiling exposures for every job involving exposure to methylene chloride in sufficient numbers to express the variability of the exposures

for the work situation. The minimum numbers of TWA's to be determined are listed in Section 7 of the recommended standard, according to the number of employees involved.

(c) Apparatus for Charcoal Tube Sampling

(1) Pump, battery-operated, complete with clip for attachment to the worker. Airflow through the pump should be within ±5% of the desired rate.

(2) Charcoal tubes: glass tube with both ends flame-sealed, 7 cm long with a 6-mm O.D., and a 4-mm I.D., containing 2 sections of 20/40 mesh activated coconut-shell charcoal separated by a 2-mm portion of urethane foam. The first is the adsorbing section and contains 100 mg of charcoal from coconut shells. The second, or reserve section, contains 50 mg. A 3-mm portion of urethane foam is placed between the outlet of the tube and the reserve section. A plug of glass wool is placed in front of the adsorbing section. The pressure drop across the tube when in use must be less than 1 inch of mercury at a flowrate of 1 liter/min.

(d) Calibration of Sampling Instruments

(1) Air sampling instruments should be calibrated with a representative charcoal tube in line, over a normal range of flowrates (50-1,000 ml/min). Calibration curves should be established for each sampling pump and should be used in adjusting the pump prior to field use. New calibration curves should be established for each sampling pump after making any repairs or modifications to the sampling system.

(2) The volumetric flowrate through the sampling system should be spot-checked and the proper adjustments made before and during each study to ensure obtaining accurate airflow data.

(e) Collection and Handling of Samples

(1) Immediately before sampling, break both ends of the tube to provide openings at least one-half the internal diameter of the tube (2 mm).

(2) The smaller section of charcoal is used as a reserve and should be positioned nearest the sampling pump.

(3) The charcoal tube should be placed in a vertical position during sampling.

(4) Tubing may be used to connect the back of the tube to the pump, but air being sampled should not be passed through any hose or tubing before entering the charcoal tube.

(5) The sample can be taken at flowrates of 50-1000 ml/min, depending on the pump. Total sample volumes of 5-100 liters are recommended, eg, a sample could be collected at 1,000 ml/min for 80 minutes to give a total sample volume of 100 liters, or at 50 ml/min for 10 hours to give a total sample volume of 30 liters. However, it is also recommended that each sample be less than 4 hours.

(6) The charcoal tubes should be capped with inert plastic caps immediately after sampling. Under no circumstances should rubber caps be used.

(7) One charcoal tube, to serve as an analytical blank, should be handled in the same manner as the sample tube (break, seal, and transport) except that no air is sampled through this tube.

X. APPENDIX II

ANALYTICAL PROCEDURE FOR DETERMINATION OF METHYLENE CHLORIDE

Principle of the Method

(a) A known volume of air is drawn through a charcoal tube to trap the methylene chloride vapor.

(b) The methylene chloride is desorbed from the charcoal with carbon disulfide.

(c) An aliquot of the desorbed sample is injected into a gas chromatograph.

(d) The area of the resulting peak is determined and compared with areas obtained from the injection of standards.

Range and Sensitivity

(a) The lower limit for detection of methylene chloride on a gas chromatograph with a flame ionization detector is 10 μg/sample at a 16 x 1 attenuation.

(b) The upper limit for methylene chloride is 5.0 mg/sample. This is the estimated amount of methylene chloride which the front section will hold before this compound breaks through to the reserve section of charcoal. If a particular atmosphere is suspected of containing a large amount of methylene chloride, it is recommended that a smaller volume of air be sampled.

Interferences

(a) Methylene chloride will not be trapped when the amount of water in the air is so great that condensation occurs in the charcoal sampling tube.

(b) Any compound which has the same retention time as methylene chloride with the chromatographic conditions described in this method could interfere. Most of these can be eliminated by altering operating conditions of the gas chromatograph.

Advantages of the Method

(a) This method is advantageous in that it provides one basic method for determining many different organic compounds.

(b) The sampling device is small, portable, and involves no liquids.

(c) The analysis of the tubes is accomplished by using a quick instrumental method.

Disadvantages of the Method

(a) The amount of sample which can be taken is limited by the weight of methylene chloride which the tube will hold before overloading.

(b) When the sample value obtained for the reserve section of charcoal exceeds 25% of that found on the front section, the possibility of appreciable sample loss exists.

(c) Other hydrocarbons in high concentrations may displace methylene chloride from the charcoal.

Apparatus

(a) Gas chromatograph equipped with a flame ionization detector.

(b) Stainless steel column (20 ft x 1/8 in) with 10% free fatty acid polymer stationary phase on 80/100 mesh, acid washed dimethyldichlorosilane treated Chromosorb W (or equivalent) solid support.

(c) A recorder and some method for determining peak area.

(d) Glass stoppered microtubes.

(e) Microsyringe of 10-μl capacity, and convenient sizes for making standards.

(f) Pipets. 0.5-ml delivery pipets or 1.0-ml pipets graduated in 0.1-ml increments.

(g) Volumetric flasks of 10-ml capacity or convenient sizes for making standard solutions.

Reagents

(a) Spectroquality carbon disulfide.

(b) Methylene chloride, preferably chromatoquality grade.

(c) Bureau of Mines Grade A helium.

(d) Prepurified hydrogen.

(e) Filtered compressed air.

Analysis of Samples

(a) All equipment used in the analysis should be washed in detergent followed by appropriate tap and distilled water rinses.

(b) Preparation: Each charcoal tube is scored with a file in front of the first section of charcoal and broken open. The glass wool is removed and discarded. The charcoal in the first (larger) section is transferred to a small stoppered test tube. The separating foam is removed and discarded; the second section is transferred to another similar test tube. These 2 sections are analyzed separately.

(c) Desorption: Prior to analysis, 0.5 ml of carbon disulfide is pipetted into each test tube to desorb methylene chloride from the charcoal.

EXTREME CAUTION MUST BE EXERCISED AT ALL TIMES WHEN USING CARBON DISFULIDE BECAUSE OF ITS HIGH TOXICITY AND FIRE AND EXPLOSION HAZARDS. IT CAN BE IGNITED BY HOT STEAM PIPES. ALL WORK WITH CARBON DISULFIDE MUST BE PERFORMED UNDER AN EXHAUST HOOD.

(d) Typical chromatographic operating conditions:

(1) 50 ml/min (70 psig) helium carrier gas flow.

(2) 65 ml/min (24 psig) hydrogen gas flow to detector.

(3) 500 ml/min (50 psig) airflow to detector.

(4) 200 C injector temperature.

(5) 200 C manifold temperature (detector).

(6) 60 C isothermal oven or column temperature.

(e) Injection: The first step in the analysis is the injection of the sample into the gas chromatograph. To eliminate difficulties arising

from blowback or distillation within the syringe needle, the solvent flush injection technique is employed. The 10-μl syringe is first flushed with carbon disulfide several times to wet the barrel and plunger. Three μl of carbon disulfide are drawn into the syringe to increase the accuracy and reproducibility of the injected sample volume. The needle is removed from the carbon disulfide solvent and the plunger is pulled back about 0.2-μl to separate the solvent flush from the sample with a pocket of air to be used as a marker. The needle is then immersed in the sample and a 5-μl aliquot is withdrawn, taking into consideration the volume of the needle, since the sample in the needle will be completely injected. After the needle is removed from the sample and prior to injection, the plunger is pulled back a short distance to minimize evaporation of the sample from the tip of the needle. Duplicate injections of each sample and standard should be made. No more than a 3% difference in area is to be expected.

(f) Measurement of Area: The area of the sample peak is determined and preliminary sample results are read from a standard curve prepared as discussed below.

Determination of Desorption Efficiency

It is necessary to determine the percentage of methylene chloride on the charcoal that is removed in the desorption process. Since this percentage may vary with the amount of absorbed methylene chloride, a desorption efficiency curve is determined once for a given compound provided the same batch of charcoal is always used.

Activated charcoal, equivalent to the amount in the first section of the sampling tube (100 mg), is measured into a 2-inch long tube, with an inside diameter of 4 mm, flame-sealed at one end. This charcoal must be from the same batch as that used in obtaining the samples and can be obtained from unused charcoal tubes. The open end is capped with inert plastic. Known amounts of the compound are injected directly into the activated charcoal with a microliter syringe, and the tube is capped with more inert plastic. It is recommended that the amounts of methylene chloride applied vary from 0 μg to 10 mg.

At least 5 tubes are prepared in this manner and allowed to stand at least overnight to ensure complete adsorption of methylene chloride onto the charcoal. These 5 tubes will be referred to as the "desorption samples." A parallel blank tube should be treated in the same manner except that no methylene chloride is added to it. The desorption samples and blanks are desorbed and analyzed in exactly the same manner as previously described.

The same number of desorption standards are prepared for analysis by injecting identical volumes of methylene chloride into 0.5 ml of carbon disulfide with the syringe used in the preparation of the desorption samples. These are analyzed with the desorption samples.

A desorption efficiency curve is constructed. The desorption efficiency for each amount of methylene chloride applied to the charcoal equals the difference between the peak area of the desorption sample and the peak area of the blank divided by the peak area of the corresponding desorption standard, or

$$\text{desorption efficiency} = \frac{\text{area of sample} - \text{area of blank}}{\text{area of standard}}$$

Calibration and Standards

It is convenient to prepare standards in terms of mg methylene chloride per 0.5 ml of carbon disulfide because samples are desorbed in this amount of carbon disulfide. To minimize error due to the volatility of carbon disulfide, 20 times the weight can be injected into 10 ml of carbon disulfide. For example, to prepare a 0.3 mg/0.5 ml standard, 6.0 mg of methylene chloride is injected into exactly 10 ml of carbon disulfide in a glass-stoppered flask. The density of methylene chloride (1.326 g/ml) is used to convert 6.0 mg into microliters for easy measurement with a microliter syringe. A series of standards is prepared, varying in concentration over the range of interest (10 μg-10 mg) and analyzed under the same gas chromatographic conditions and during the same time period as the unknown samples. Curves are established by plotting concentration versus average peak area.

Calculations

(a) The weight in mg corresponding to the peak area is read from the standard curve. No volume corrections are needed, because the standard curve is based on mg methylene chloride/0.5 ml carbon disulfide, and the volume of sample injected is identical to the volume of the standards injected.

(b) Separately determine the weights of methylene chloride on the front and reserve sections of the charcoal tube.

(c) Corrections must be made to the methylene chloride weights determined on both the front and reserve sections for the weights of the

respective sections of the blank charcoal tube.

(1) Subtract the weight of methylene chloride found on the front section of the blank charcoal tube from the weight of methylene chloride found on the front section of the sample charcoal tube to give a corrected front section weight.

(2) Subtract the weight of methylene chloride found on the reserve section of the blank charcoal tube from the weight of methylene chloride found on the reserve section of the sample charcoal tube to give a corrected reserve section weight.

(3) Add the corrected amounts of methylene chloride present on the front and reserve sections of the sample tube to determine the total measured methylene chloride in the sample.

(4) Divide this total weight by the corresponding desorption efficiency to obtain M, the total mg per sample.

(d) Convert the liters of air sampled (V) to volume (V') at standard conditions of 25 C and 760 mm Hg, as follows:

$$V' = \frac{298VP}{760\ (T+273)}$$

where:

V' = volume of sampled air in liters at 25 C and 760 mm Hg

V = measured volume of sampled air in liters

P = barometric pressure in mm Hg, measured at time of sampling

T = temperature of air in degree Celsius, measured at time of sampling

(e) The concentration of methylene chloride in the sampled air can be expressed in various ways using M, the weight of methylene chloride obtained in (c)(4) and V', the standardized sample volume, obtained in (d), as follows:

(1) mg/liter = m/v'

(2) mg/cu m = μg/liter = 1,000 m/v'

(3) ppm = 288 M/V'

XI. APPENDIX III

MATERIAL SAFETY DATA SHEET

General instructions for preparing a Material Safety Data Sheet (MSDS) are presented in this Chapter. The examples used in the text are for illustrative purposes and are not intended to apply to any specific compound or product. Applicable information about a specific product or material shall be supplied in the appropriate block of the MSDS.

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the guidelines in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the

material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, ie, "100 ppm LC50 rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources of publications such

as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute Inc. Flammable or reactive data could be flash point, shock sensitivity, or other brief data indicating nature of the hazard.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 degrees Fahrenheit (21.1 degrees Celsius); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flash point and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the

product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a time-weighted average (TWA) concentration, as a permissible exposure, or by some other indication of an acceptable limit. Other data are acceptable, such as lowest LD50, if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

> Skin Contact--single short contact, no adverse effects likely; prolonged or repeated contact, irritation, and cracking. Readily absorbed through the skin with severe systemic effects.
>
> Eye Contact--some pain and mild transient irritation; no corneal scarring.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed workers.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect workers assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill," or "incineration." Warnings such as "comply with local, state, and federal anti-pollution ordinances" are proper but not sufficient. Specific procedures should be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If Necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Specify respirators as to type and NIOSH or US Bureau of Mines approval class, ie, "Supplied air," "Organic vapor canister," "Suitable for dusts not more toxic than lead," etc. Protective equipment must be specified as to type and materials of construction.

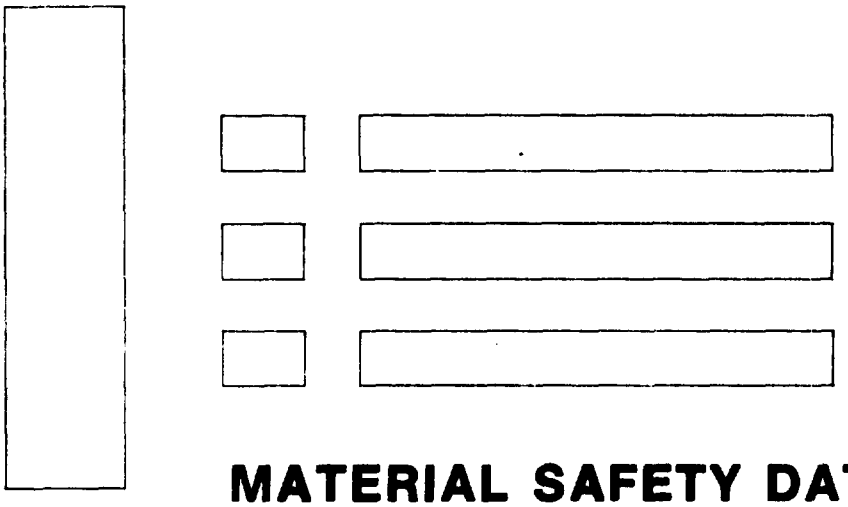
(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to workers potentially exposed to the hazardous material. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.



MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION	
MANUFACTURER'S NAME	REGULAR TELEPHONE NO. EMERGENCY TELEPHONE NO.
ADDRESS	
TRADE NAME	
SYNONYMS	

II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA			
BOILING POINT, 760 MM HG		MELTING POINT	
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE	
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O, % BY WT	
% VOLATILES BY VOL		EVAPORATION RATE (BUTYL ACETATE=1)	
APPEARANCE AND ODOR			

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	
FLAMMABLE LIMITS IN AIR, % BY VOL.	LOWER		UPPER
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARD			

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN

INHALATION

INGESTION

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY
STATEMENTS

OTHER HANDLING AND
STORAGE REQUIREMENTS

PREPARED BY

ADDRESS

DATE

XII. TABLES AND FIGURE

TABLE XII-1

SELECTED PROPERTIES OF METHYLENE CHLORIDE

Chemical Abstract serial number	000075092
Synonyms	Dichloromethane Methylene bichloride Methylene dichloride Methylene chloride
Molecular formula	CH2C1 2
Formula weight	84.94
Boiling point (760 mg Hg)	40 C (760 mm Hg)
Melting point	95-97 C
Vapor density	2.93 (air = 1)
Density of saturated vapor	2.06 (air = 1)
Density	1.326 g/ml (20C)
Solubility	2.0 g/100 ml water at 20 C; soluble in ethanol, ethyl ether, acetone and carbon disulfide
Explosive limits in oxygen	15.5-67% by volume
Flash point	None
Autoignition temperature	624 - 662 C
Relative evaporation rate	14 (water = 1) 71 (ether = 100)

Vapor pressure

Temp F	Temp C	mm Hg
50	10	230
68	20	349
77	25	436
86	30	511
95	35	600

Conversion factors (25 C; 760 mm Hg)	1 mg/liter = 1 g/cu m = 288 ppm 1 ppm = 3.48 mg/cu m = 3.48 μg/liter
Concentration in saturated air	550,000 ppm (25 C)

Adapted from references 1,4,5,6,7

TABLE XII-2

BREATH CONCENTRATIONS OF SUBJECTS DURING AND AFTER EXPOSURE AT REST FOR 2 HOURS AT 100 ppm OF METHYLENE CHLORIDE

Time, min	No.	Mean	Range
Breath concentrations during exposure, ppm			
15	4	39.5	31.4-45.4
30	4	42.9	35.2-49.0
45	4	42.3	34.0-50.0
60	4	45.6	37.4-56.2
75	4	48.2	34.9-58.2
90	3	48.7	40.0-55.4
105	4	47.3	37.6-57.4
120	4	47.0	37.2-58.1
Breath concentrations after exposure, ppm			
0*	5	20.9	19.0-22.8
2	5	11.9	9.8-13.5
5	5	8.8	6.9-12.3
10	5	7.0	5.1-9.8
20	5	4.8	3.9-5.8
30	5	3.7	2.9-4.8
40	5	3.3	2.6-4.6
50	5	2.9	1.9-3.9
60	5	2.6	1.9-3.6
120	5	1.4	0.6-2.0
180	5	0.7	0.3-1.3
240	5	0.3	0.0-0.6
300	5	0.1	0.0-0.2

* First measurement after leaving exposure chamber

Adapted from DiVincenzo et al, [48] additional data supplied by authors

TABLE XII-3

BREATH CONCENTRATIONS OF SUBJECTS DURING AND AFTER EXPOSURE FOR 4 HOURS AT 100 ppm OF METHYLENE CHLORIDE

Time, min	No.	Mean	Range
Breath concentrations during exposure, ppm			
30	5	33.8	24.8-45.9
60	5	36.4	24.8-52.5
120	5	35.1	27.5-45.5
180	4	36.4	28.6-40.8
240	5	39.0	31.8-51.9
Breath concentrations after exposure, ppm			
0*	5	21.6	19.1-23.8
2	5	13.7	12.3-17.1
5	5	9.6	8.3-11.9
10	5	7.7	6.0-9.2
20	5	5.4	5.1-6.6
30	5	4.6	3.7-5.9
40	5	4.2	3.3-5.9
50	5	3.3	2.6-3.9
60	5	3.2	2.3-4.2
120	5	1.7	1.2-2.5
180	5	1.0	0.7-1.3
240	5	0.8	0.4-1.1
300	3	0.4	0.2-0.7
360	3	0.4	0.2-0.7

* First measurement after leaving exposure chamber

Adapted from DiVincenzo et al, [48] additional data supplied by authors

TABLE XII-4

BREATH CONCENTRATIONS OF SUBJECTS DURING AND AFTER EXPOSURE FOR 2 HOURS AT REST AT 200 ppm OF METHYLENE CHLORIDE

Time, min	No.	Mean	Range
Breath concentrations during exposure, ppm			
10	7	69.5	50.0-95.0
20	7	71.8	58.0-96.0
30	7	73.7	50.0-96.0
40	6	71.0	55.0-91.0
50	7	76.2	44.0-98.0
60	7	76.2	53.0-105.0
75	7	81.2	56.0-114.0
90	7	80.7	58.0-107.0
105	7	89.4	54.0-120.0
120	7	88.4	71.0-113.0
Breath concentrations after exposure, ppm			
0*	7	38.0	25.0-51.0
2	7	25.3	16.0-38.0
5	6	22.2	16.0-28.0
10	7	16.0	11.0-20.0
20	7	11.4	7.0-15.0
30	6	9.0	7.0-10.0
40	5	7.7	5.4-9.5
50	6	5.5	3.9-6.8
60	7	5.0	3.0-7.8
120	7	2.2	1.4-3.3
180	7	1.1	0.4-1.6
240	7	0.8	0.4-1.4
300	7	0.5	0.1-0.8
360	6	0.2	0.1-0.5

* First measurement after leaving exposure chamber

Adapted from DiVincenzo et al, [48] additional data supplied by authors

TABLE XII-5

BREATH CONCENTRATIONS DURING EXPOSURE OF SUBJECTS EXPOSED AT REST OR EXERCISE FOR 2 HOURS AT 100 ppm OF METHYLENE CHLORIDE

Time, min	No.	Status	Methylene chloride, ppm	
			Mean	Range
10	4	resting	28.2	15-39
15	4	exercise	39.7	29-49
25	4	resting	33.5	25-40
30	4	exercise	45.5	33-56
40	4	resting	38.5	30-48
45	4	exercise	47.0	35-56
55	4	resting	36.2	26-47
60	4	exercise	48.2	35-59
70	4	resting	38.2	30-47
90	4	exercise	49.5	35-59
100	4	resting	40.2	33-47
120	4	resting	42.0	32-47

Adapted from DiVincenzo et al, [48] additional data supplied by authors

TABLE XII-6

BREATH CONCENTRATIONS AFTER EXPOSURE OF INDIVIDUALS WHO EXERCISED WHILE EXPOSED FOR 2 HOURS AT 100 ppm OF METHYLENE CHLORIDE VAPOR

Time, min	No.	Methylene chloride, ppm	
		mean	range
0	4	29.0	22.0-37.0
2	4	17.5	14.0-20.0
5	4	14.8	12.0-18.0
10	4	12.5	9.0-15.0
20	4	8.0	7.0-9.0
30	4	7.6	6.0-9.9
40	4	5.7	4.0-8.6
50	3	4.8	3.3-7.6
60	4	4.2	3.0-7.4
120	4	2.6	2.0-4.0
180	2	1.0	0.9-1.2
240	3	0.9	0.7-1.5
300	2	0.2	0.2-0.4
360	3	0.2	0.1-0.4

Adapted from DiVincenzo et al, [48] additional data supplied by authors

TABLE XII-7

BLOOD CONCENTRATIONS OF METHYLENE CHLORIDE IN MAN
DURING AND FOLLOWING EXPOSURE AT 200 ppm FOR 2 HOURS

During Exposure			After Exposure		
Time, min	mg/liter range	No.	Time, min	mg/liter range	No.
10-12	0.511-0.666	3	60	0.356-0.422	4
30	0.032-1.399	4	120	0.178-0.266	4
50-80	1.130-2.000	4	180	0.111-0.200	4
120	1.780-2.200	4	240	0.066-0.155	4

Adapted from DiVincenzo et al, [48] additional data supplied by authors

TABLE XII-8

BLOOD CONCENTRATIONS OF METHYLENE CHLORIDE IN SUBJECTS AFTER EXPOSURE AT 100 ppm FOR 2 HOURS

Time, min	mg/liter
3	0.622
4	0.666
4	0.666
8	0.666
7	0.577
15	0.399
19	0.355
35	0.244
44	0.266
60	0.266
67	0.122
68	0.088
120	0.100
127	0.088
129	0.066

Adapted from DiVincenzo et al, [48] additional data supplied by authors

TABLE XII-9

URINARY EXCRETION OF METHYLENE CHLORIDE IN MAN AFTER EXPOSURE AT 100 ppm FOR 2 HOURS

Subject	Time of Collection after Exposure, min	Urine Volume ml	CH_2Cl_2 μg	24-Hour Total, μg
GDV	5	115	23.7	26.8
	125	165	3.1	
FJY	30	141	18.5	23.9
	285	97	5.4	
AI	5	125	16.4	21.0
	111	243	4.6	
TSE	5	165	18.6	18.6

Adapted from DiVincenzo et al [48]

TABLE XII-10

URINARY EXCRETION OF METHYLENE CHLORIDE IN MAN AFTER EXPOSURE AT 200 ppm FOR 2 HOURS

Subject	Time of Collection after Exposure, min	Urine Volume ml	CH_2Cl_2 μg	24-Hour Total, μg
GDV	12	185	52.2	63.7
	125	80	4.4	
	225	135	5.1	
	280	108	2.0	
FJY	12	153	57.4	69.9
	300	225	12.5	
BDA	62	235	92.8	101.8
	354	240	9.0	
CJT	5	210	63.5	82.1
	60	200	18.6	
WHJ	18	245	83.4	83.4
WJK	15	94	42.5	63.3
	120	80	13.4	
	300	133	7.4	
AW	10	204	84.6	106.7
	300	172	13.0	
	555	163	9.1	

Adapted from DiVincenzo et al [48]

TABLE XII-11

ENVIRONMENTAL CONCENTRATIONS OF METHYLENE CHLORIDE
IN THE ATMOSPHERE OF A PLASTIC FILM FACTORY

Working Location	No. of Samples	Range ppm	Average ppm
Charging mixers	7	153-965	372
Adding solvent	3	72-2,454	1,022
Adding solid plastic	4	1,642-4,896	3,142
Filtration process	15	29-1,210	331
Exchange of filter plant	14	464-1,699	901
Casting machine	121	32-1,414	297
Dryer	71	43-991	265
Water powered shut off	35	60-2,632	541
Dry powered shut off	10	109-622	317
Winding machine	16	81-567	213
Catwalk delivery room	2	61-86	72
Rear of cooler	12	1,823-3,781	2,913
CH_2Cl_2 regenerator	8	84-723	423

Adapted from Kuzelova and Vlasak [55]

TABLE XII-12

ENVIRONMENTAL CONCENTRATION OF METHYLENE CHLORIDE
IN A PLASTIC FILM FACTORY
CHARCOAL COLLECTION-GAS CHROMATOGRAPHIC ANALYSIS

Location	Time	Day 1 ppm	Day 2 ppm
Casting room			
Desk No. 1	3:30 pm	471	
	8:30 am		159
	10:30 am		172
	2:30 pm		219
Dryer	3:30 pm	566	
Front caster No. 2	3:40 pm	594	
	1:00 pm		404
Back caster No. 2	6:00 pm	412	
Stretcher	3:50 pm	300	
Utility table	6:20 pm	399	
Desk No. 2	11:50 am		610
Filter Room			
Filter	5:00 pm	845	
Mezzanine	8:30 pm	966	
Basement	1:00 pm		2,140
Winding room	5:00 pm	190	
Office	9:00 pm		326
Laboratory	4:20 pm	182	

Adapted from data supplied by Massachusetts Department of Labor and Industries (LD Pagnotto, written communication, December 1973)

TABLE XII-13

ALVEOLAR CARBON MONOXIDE CONCENTRATIONS (ppm) AND DERIVED CARBOXYHEMOGLOBIN (PERCENT) DURING AND AFTER EXPOSURE TO METHYLENE CHLORIDE

Hours Since Exposure Start	Item Measured	Subject 1	2	3	4	5	6	7
		During exposure values						
0*	CO	26	32	30	32	24	30	27
	COHb	4.4	3.3	5.0	5.3	4.1	5.0	4.6
2	CO	29	32	39	32	41	36	31
	COHb	4.9	5.3	6.4	5.3	6.8	6.0	5.2
4	CO	31	41	44	45	60	41	40
	COHb	5.2	6.8	7.2	7.4	9.6	6.8	6.6
6	CO	34	43	47	43	74	51	45
	COHb	5.7	7.0	7.7	7.0	11.5	8.3	7.4
8	CO	36	41	58	51	77	50	44
	COHb	5.7	6.8	9.3	8.3	12.0	8.1	7.2
		After exposure values						
9	CO	38	40	56	50	68	50	44
	COHb	6.3	8.1	9.0	8.1	10.7	8.1	7.2
11	CO	33	33	4zz	41	61	46	39
	COHb	5.5	5.5	7.5	6.8	9.7	7.5	6.4
15	CO	38	27	29	24	44	42	38
	COHb	4.7	4.6	4.9	4.1	7.2	6.9	6.3
24	CO	17	21	23	25	29	26	23
	COHb	3.6	3.6	3.9	4.2	4.9	4.4	3.9

* Beginning of workday

Adapted from Ratney et al [59]

TABLE XII-14

EFFECTS OF EXPOSURE TO METHYLENE CHLORIDE AT 5,000 ppm ON RUNNING ACTIVITY OF 5 RATS DURING 1 HOUR

Measurement	Rat Number					
Conditions	1	2	3	4	5	Average
	Revolutions / hour					
Preexposure 20-day average	725	186	928	482	518	568
Even days (no exposure)	1,251	483	1,152	1,019	366	
	803	309	1,349	918	549	
	343	1	403	541	232	
	525	29	885	738	257	
	568	207	293	620	477	
Average	698	226	816	765	376	576
Odd days during exposure	1	5	10	33	19	
	136	51	65	60	15	
	0	39	15	40	0	
	276	85	135	103	14	
	232	14	25	104	1	
Average	129	39	50	68	10	59
Odd days 30 min after exposure	68	169	746	167	13	
	375	109	468	551	338	
	173	12	92	246	54	
	219	14	259	432	477	
	1	190	404	328	161	
Average	167	99	394	345	209	243

Adapted from Heppel et al [66]

TABLE XII-15

LIVER AND BODY WEIGHTS OF MICE WITH CONTINUOUS INHALATION OF 5,000 ppm METHYLENE CHLORIDE

Day		Body weight grams		Liver wt/body wt g/100 g		Liver weight grams	
		Control	CH_2Cl_2	Control	CH_2Cl_2	Control	CH_2Cl_2
1	mean*	24.5	23.5	4.89	6.38	1.2	1.5
	SE	0.80	0.78			0.05	0.07
2	mean	25.3	20.7	5.14	7.25	1.3	1.5
	SE	0.55	0.50			0.05	0.05
3	mean	26.1	19.2	4.60	7.29	1.2	1.4
	SE	0.58	0.35			0.04	0.05
4	mean	26.5	19.4	4.91	7.22	1.3	1.4
	SE	0.45	0.37			0.04	0.05
7	mean	26.2	18.0	4.96	7.22	1.3	1.3
	SE	0.49	0.47			0.04	0.05

* 13-20 female mice/group

Adapted from Weinstein et al [71]

TABLE XII-16

EFFECTS OF 4 WEEKS OF CONTINUOUS EXPOSURE AT 1,000 ppm METHYLENE CHLORIDE ON DOG HEMATOLOGY, LIVER ENZYMES, AND BSP RETENTION

	Preexposure		After 4 weeks	
Item Measured*	Control	Exposed	Control	Exposed
Hematocrit, vol %	42.8	45.1	41.9	55.5
Hgb, g %	14.9	16.0	14.5	18.3
RBC, millions	6.3	6.8	6.3	7.7
WBC, thousands	14.0	11.3	14.0	11.4
Reticulocytes, %	0.2	0.6	0.9	0.1
ICDH, Sigma units	279	118	193	352
SGPT, Sigma-Frankel units	33.2	24.9	28.8	102.3
BSP, % retention	5.5	6.0	3.25	6.5

* Values are means of 8 animals, except BSP values are means of 4
Adapted from MacEwen et al [73]

TABLE XII-17

THE EFFECT OF CONTINUOUS EXPOSURE AT 25 AND 100 ppm OF METHYLENE CHLORIDE ON MOUSE LIVER MICROSOMAL CYTOCHROMES

CH_2Cl_2 Exposure Group	nM cytochrome/mg microsomal protein		
	P-450	b5	P-420
	30 Exposure days		
Control	0.866	0.860	0.507
25 ppm	0.815	0.780	0.455
100 ppm	0.511**	0.642**	0.227**
	60 Exposure days		
Control	0.959	0.990	0.504
25 ppm	0.984	0.981	0.460
100 ppm	0.708*	1.173	0.842
	90 Exposure days		
Control	0.848	0.815	0.506
25 ppm	0.867	0.854	0.419
100 ppm	0.653**	0.944**	0.646**

* $P<0.05$; ** $P<0.01$

Adapted from Haun et al [70]

TABLE XII-18

METHYLENE CHLORIDE INHALATION EXPOSURES AND EFFECTS

Author	Concentration ppm	Exposure Variables	Effects
		Humans - experimental	
Stewart et al [39] [41]	50-1,000	1 to 7.5 hrs/day 5 days/wk	COHb percentages proportional to exposure concentration and time.
Forster et al [43]	50-500	7.5 hrs 5 days/wk	Increased affinity of Hgb for oxygen in proportion to exposure concentration.
	100 and 500	7.5 hrs/day 5 days/wk	Blood lactic acid increased slightly from exercise at 500 ppm, not 100 ppm.
Fodor & Winneke [37]	317 and 751	4 hrs	Depressed CFF, decreased auditory vigilance performance.
Winneke [38]	317, 470 751	3-5 hrs	Decreased performance of CFF, auditory vigilance, psychomotor tasks.
		Humans - occupational	
Collier [35]	Unknown	1 subject, 13 yrs intermittent	Irregular, severe leg and arm pains, hot flashes, vertigo stupor, poor night vision, anorexia, precordial pain, rapid pulse, short of breath, fatigue, 4,910,000 rbc, 6,200 wbc; punctuate basophilia of of 3,500/million improved 6 wks after removal from work.
Collier [35]	Unknown	1 worker, 20 yrs intermittent	Drowsy, pains in head, tingling in hands and feet.

TABLE XII-18 (CONTINUED)

METHYLENE CHLORIDE INHALATION EXPOSURES AND EFFECTS

Author	Concentration ppm	Exposure Variables	Effects
Moskowitz & Shapiro [50]	Unknown	4 workers, acute exposure, probably 1-3 hrs	3 workers hospitalized with eye, lung, and respiratory tract irritation, reduced Hgb and RBC counts; 1 worker died veins of pia-arachnoid conspiciously engorged.
Hughes [51]	Unknown	4 hrs	Oppressive odor, irritation of eyes, excessive fatigue, weakness, sleepiness, light headedness, chilly sensations, nausea, shortness of breath, substernal pain, weakness, dry rales in chest, pulmonary edema.
Kuzelova & Vlasak [55]	28-4,896	33 workers, average of 2 yrs exposure	Headache, fatigue, irritation of upper respiratory tract, conjunctiva, neurasthenic disorders, mild acute poisoning in 3, with unconsciousness in 1, sweet taste, heart palpitations.
Weiss [58]	660-3,600	1 worker, several hrs/day for 5 yrs	After 3 yrs: burning pain around heart, restlessness, feeling of pressure, palpitations, forgetfulness, insomnia, feeling of drunkeness. After 5 yrs: auditory and visual hallucinations, slight erythema of hands and underarms, diagnosed as having toxic encephalosis.
Ratney et al [59]	159-219 (average 183)	4 workers, 3 investigators	Increased alveolar CO at end of work day.

TABLE XII-18 (CONTINUED)

METHYLENE CHLORIDE INHALATION EXPOSURES AND EFFECTS

Author	Concentration ppm	Exposure Variables	Effects
		Animals	
Flury & Zernik [60]	14,500	2 hrs	Mice, death.
	10,000	2 hrs	Mice, narcosis.
	4,000	6 hrs	Dogs, light narcosis after 2.5 hrs; rabbits after 6 hours.
	6,000	6 hrs	Guinea pigs, light narcosis in 2.5 hrs, rabbits and cats in 3/4 hrs, dogs in 2 hrs.
Svirbely et al [63]	12,795-16,897	7 hrs	Mice LC50 = 16,188 ppm.
Muller [61]			Mice LC50 = 14,400 ppm.
Lazarew [62]			Mice LC50 = 17,400 ppm.
von Oettingen et al [64]	15,000 and 20,000		Dogs, loss of pupillary and corneal reflexes after 10-20 min, complete muscular relaxation after 25-35 min, reduction in blood pressure, rapid narcosis at 20,000 ppm.
	40,000		Dogs, loss of pupillary and corneal reflexes after 10-20 min, complete muscular relaxation after 16 min; 3 of 5 dogs died from progressive heart failure due to cardiac injury.

TABLE XII-18 (CONTINUED)

METHYLENE CHLORIDE INHALATION EXPOSURES AND EFFECTS

Author	Concentration ppm	Exposure Variables	Effects
Berger & Fodor [65]	25,000-28,000	1.5 hrs	Rats, electrical activity stopped after 1.5 hrs.
	16,000-18,000	6 hrs	Rats, initial excitement followed by deep narcosis, decreased EMG tonus, decreased EEG activity, breathing difficulties, tremor, electrical activity stopped after 6 hrs.
	5,000-9,000	8 hrs	Long sleeping phase lacking desynchronization phases.
	2,800	14 hrs	Rats, decreased proportion of REM sleep to total sleep.
Fodor & Winneke [37]	3,000, 1,000 and 500	24 hrs	Rats, suppressed REM sleep, increased time between two REM periods, linear relation between dose and response.
Heppel & Neal [66]	5,000	30 min/ day	Rats, decreased running activity.
Weinstein et al [71]	5,000	7 days	Mice, initial increase in physical activity followed by decrease in food and water intake, lethargy, increased liver to body weight ratio and liver fat, mild fatty infiltrations, hydropic degeneration of centrilobular cells.
Fodor et al [67]	100 or 1,000	3 hrs	Rats, increased blood CO measurements.

TABLE XII-18 (CONTINUED)

METHYLENE CHLORIDE INHALATION EXPOSURES AND EFFECTS

Author	Concentration ppm	Exposure Variables	Effects
Heppel et al [69]	5,000	7 hrs/day 5 days/wk up to 6 mo	Various experimental animals, no effect.
	10,000	4 hrs/day	Various animals, incoordination, conjunctival irritation, shallow respiration, pulmonary congestion, edema with focal extravasation of blood, some fatty degeneration.
MacEwen et al [73]	1,000	14 wks continuous	Various experimental animals, increased hematocrit, Hgb, RBC, bilirubin; weight loss, mild centrilobular fat.
	5,000	14 wks continuous	High mortality, pneumonia, fatty liver, icterus, splenic atrophy, edema of meninges, renal tubule vascular changes.
Haun et al al [70]	25	2-8 wks continuous	Various experimental animals, no overt toxicity, nonspecific tubular degenerative and regenerative changes.
	100		Altered cytochromes P-450, P-420, and b5, fatty infiltration of the liver, nonspecific tubular degenerative and regenerative changes, elevated COHb.
Thomas et al [72]	25	14 wks continuous	Mice, increased activity.
Weinstein & Diamond [74]	100	10 wks continuous	Elevated liver fat, decreased hepatocyte glycogen, centrilobular fatty infiltration.

TABLE XII-19

ENVIRONMENTAL CONCENTRATIONS OF METHYLENE CHLORIDE
SILICA GEL COLLECTION - ALKALINE HYDROLYSIS
Summary of 1968 - 1972 Data

Locations Sampled	No. of Samples	Range ppm	Mean ppm
Casting room*			
Desk No. 1	13**	55-310	169
Dryer	6	120-495	270
Front caster No. 2	14	88-495	196
Back caster No. 2	12	75-380	217
Stretcher	7	190-346	250
Front caster No. 1	2	82-146	114
Utility table	1	250	250
Desk No. 2	3	70-180	132
Filter room			
Filter	4	190-590	381
Mezzanine	2	157-180	168
Basement	7	155-400	197
Winding room		140-215	188
Office	3	35-57	46

* Chlorofrom concentrations in the casting room, 16-73 ppm
** This location considered typical of general room air
Adapted from data supplied by the Massachusetts Department of Labor and Industries (LD Pagnotto, written communication, December 1973)

TABLE XII-20

COMPARISON BETWEEN ENVIRONMENTAL CONCENTRATIONS OF METHYLENE CHLORIDE IN A PLASTIC FILM PLANT MEASURED BY 2 COLLECTION AND ANALYTICAL METHODS

Location	1968-1972 Averages of Silica Gel-Alkaline Hydrolysis		1973 Charcoal-Gas Chromatography Day 1		Day 2	
	ppm	no.	ppm	no.	ppm	no.
Casting Room						
Desk No. 1	169	13	471	1	183	3
Dryer	270	6	566	1	-	
Dryer	270	6	566	1	-	
Front Caster No. 2	196	14	594	1	404	1
Back Caster No. 2	217	12	412	1	-	
Stretcher	250	7	300	1	-	
Utility Table	250	1	399	1	-	
Desk No. 2	132				610	
Filter Room						
Filter	381	4	845	1	-	
Mezzanine	168	2	966	1	-	
Basement	197	7	-	1	2,140	
Winding Room	188	5	190	1	-	
Office	46	3	-		326	1

Adapted from data supplied by the Massachusetts Department of Labor and Industries (LD Pagnotto, written communication, December 1973)

TABLE XII-21

THERMAL DECOMPOSITION PRODUCTS OF METHYLENE CHLORIDE VAPOR

CH_2Cl_2 concentration, ppm	Type of combustion	Concentration of Combustion Products, ppm			
		HCL	$COCl_2$	Cl_2	CO_2
	5 minutes after ignition				
10,000	open gas flame	310	80	-	-
23,000	open gas flame	1,130	150	-	-
202-374	kerosene flame	-	32	-	-
52,000	hot iron surface	1,300	20	-	-
	30 minutes after ignition				
10,000	open gas flame	810	320	-	10,000
23,000	open gas flame	270	440	-	13,000
202-374	kerosene flame	-	77	-	-
57,000	hot electric wire	650	90	-	-
	Nonspecified after ignition time				
570,000	wood fire	45,500	580	-	-
	Welding Operations				
730	tungsten arc	10	1	4	-

Adapted from references 34,53,140

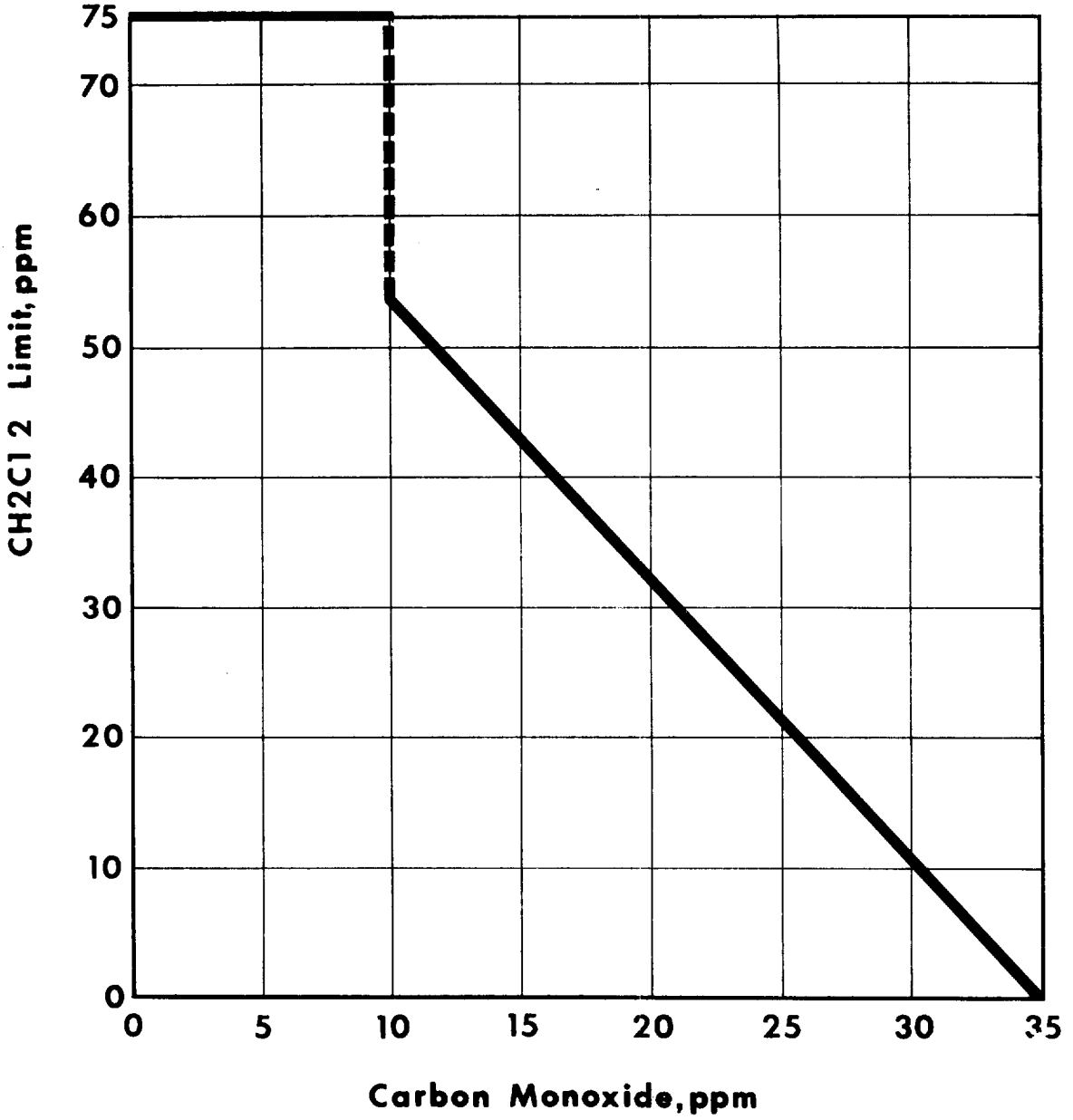


FIGURE XII-1. Methylene Chloride TWA exposure limits as functions of carbon monoxide exposure concentrations

U.S. GOVERNMENT PRINTING OFFICE: 1977—757-057/5741

U. S. GOVERNMENT PRINTING OFFICE 1989/648-164/00513

HEW Publication No. (NIOSH) 76-138