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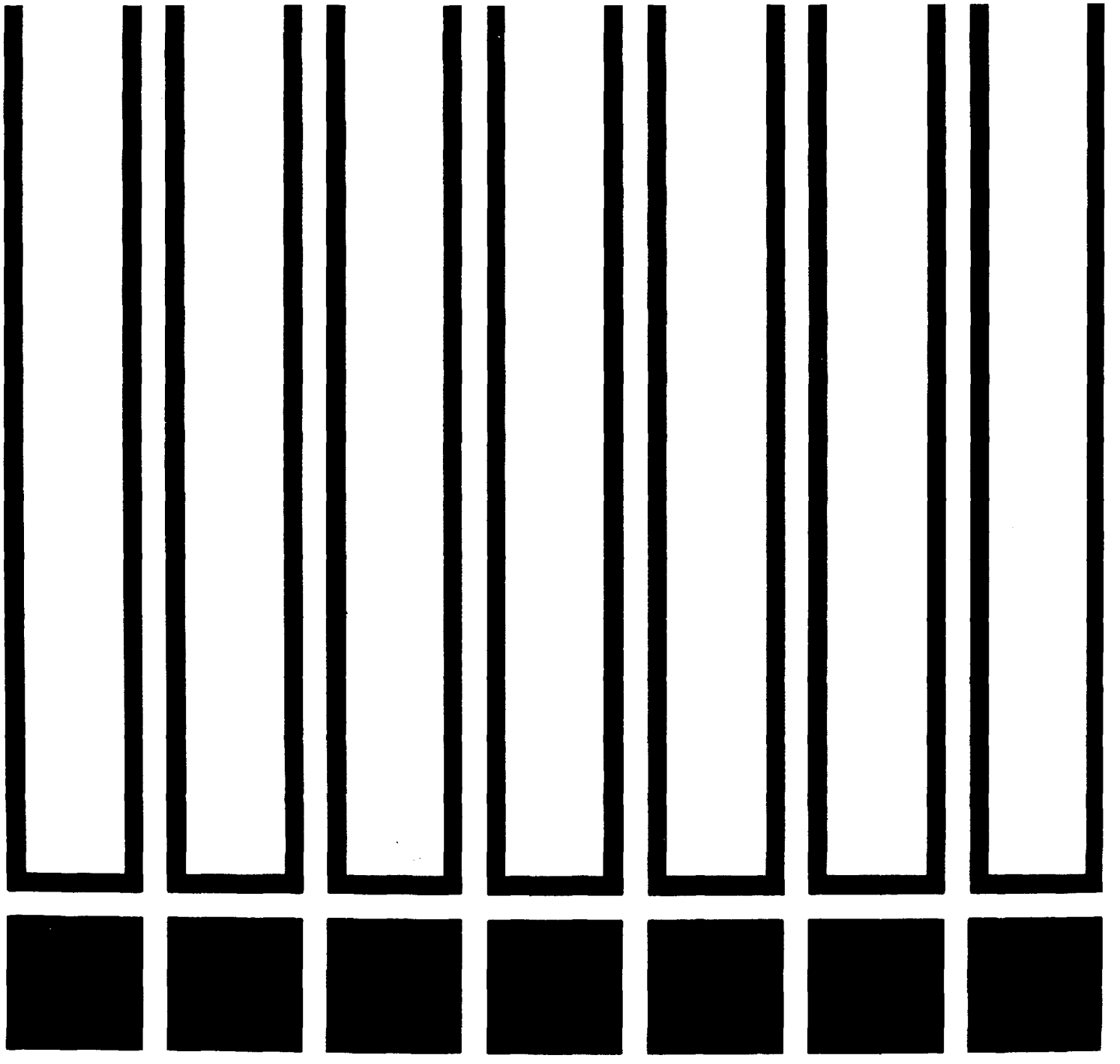
# CARBON TETRACHLORIDE



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

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# OCCUPATIONAL EXPOSURE TO CARBON TETRACHLORIDE

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health
1975

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# 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 carbon tetrachloride by members of my staff and the valuable, constructive comments by the Review Consultants on carbon tetrachloride, by the ad hoc committees of the American Industrial Hygiene Association and the Society of Occupational and Environmental Health, and 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 carbon tetrachloride. 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 Office of Research and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and recommended standard for carbon tetrachloride. 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

William D. Kelley
Assistant Director, Division of Laboratories and
Criteria Development

Robert N. Ligo, M.D.
Division of Technical Services

Frank L. Mitchell, D.O.
Office of Research and
Standards Development

Robert L. Peterson
Chief, Western Area Occupational
Health Laboratory

Charles Xintaras, Sc.D.
Division of Laboratories and
Criteria Development

Department of Labor Liaison:

Ching-Tsen Bien
Office of Standards

NIOSH REVIEW CONSULTANTS ON CARBON TETRACHLORIDE

Jay P. Bartlett, M.D., M.P.H.
Medical Consultant
California State Department of Health
Oakland, California 94123

Hervey B. Elkins, Ph.D.
Consultant in Industrial Toxicology and Industrial Hygiene Chemistry
Belmont, Massachusetts 03178

Adrian L. Linch
Consultant in Environmental Health
Everett, Pennsylvania 15537

Arnold W. Schaffer
Dow Environmental Health Services
Dow Chemical U.S.A.
Midland, Michigan 43640

Jeanne M. Stellman, Ph.D.
Presidential Assistant for Health and Safety
Oil, Chemical and Atomic Workers International Union
Denver, Colorado 80201

CRITERIA DOCUMENT: RECOMMENDATIONS FOR AN OCCUPATIONAL EXPOSURE STADARD FOR CARBON TETRACHLORIDE

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# I. RECOMMENDATIONS FOR A CARBON TETRACHLORIDE STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that worker exposure to carbon tetrachloride ($CCl_4$) in the workplace be controlled 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 the standard should therefore prevent adverse effects of carbon tetrachloride 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 carbon tetrachloride" is defined as exposure above half the time-weighted average (TWA) environmental limit. Exposures at lower environmental concentrations will not require adherence to the following sections, except that because liquid carbon tetrachloride is absorbed through the skin and because spills are extremely hazardous, Sections (3), (4)(b) and (c), (5) and (6)(d) shall be complied with wherever carbon tetrachloride is used.

## Section 1 - Environmental (Workplace Air)

(a) Concentration

Occupational exposure shall be controlled so that workers are not exposed to carbon tetrachloride in excess of 2 ppm (12.6 mg/cu m) determined as a time-weighted average (TWA) exposure for up to a 10-hour workday, 40-hour workweek.

(b) Sampling and Analysis

Procedures for sampling and analysis of workroom air for compliance with the standard shall be as provided in Appendices I and II or by any equivalent method.

Section 2 - Medical

(a) Comprehensive preplacement and annual medical examinations shall be made available to all workers exposed to carbon tetrachloride unless a different frequency is indicated by professional medical judgment 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 and interim medical and work history to include occurrence of nausea, vomiting, visual disturbances, and use of alcohol and barbiturates.

(2) A comprehensive medical examination, giving particular attention to kidneys, eyes (black and white and color visual fields), and appropriate tests of liver function.

(3) An evaluation of the worker's physical ability to safely wear a respirator.

(c) Employees shall be counseled regarding the increased hazards from working with carbon tetrachloride resulting from use of alcohol and barbiturates.

(d) Medical records shall be maintained for all persons employed in work involving exposure to carbon tetrachloride. All pertinent medical

records with supporting documents shall be maintained for 20 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 these records.

Section 3 - Labeling (Posting)

The following warning sign shall be affixed in a readily visible location on processing or other equipment, on carbon tetrachloride storage tanks, or containers, and at or near entrances to areas in which there is occupational exposure to carbon tetrachloride:

CARBON TETRACHLORIDE
WARNING!
INHALING VAPOR IS
HAZARDOUS TO HEALTH
Avoid breathing of vapor
Keep containers closed when not in use
Use only with adequate ventilation
MAY BE ABSORBED THROUGH SKIN
Avoid skin or eye contact

This sign shall also be printed in the predominant language of non-English-speaking workers. All employees shall be trained and informed of the hazardous areas with special instructions given to illiterate workers.

Section 4 - Personal Protective Equipment and Clothing

(a) Respiratory Protection

(1) Engineering controls shall be used wherever necessary and feasible to maintain carbon tetrachloride concentrations at or below the prescribed limit. Compliance with the permissible exposure limit 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 to concentrations in excess of the environmental limit for maintenance or repair activities.

(C) During emergencies when air concentrations of carbon tetrachloride 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 class of respirator to be used, the employer shall measure, when possible, the atmospheric concentration of carbon tetrachloride in the workplace initially and thereafter whenever process, worksite, climate, or control changes occur which are likely to increase the carbon tetrachloride concentration. This requirement shall not apply when only supplied-air, positive pressure respirators will be used.

(B) The employer shall ensure that no worker is being exposed to carbon tetrachloride in excess of the environmental limit because of improper respirator selection, fit, use, or maintenance.

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

TABLE I-1

RESPIRATOR SELECTION GUIDE FOR PROTECTION
AGAINST CARBON TETRACHLORIDE

| Concentrations of Carbon Tetrachloride | Respirator Type |
|---|---|
| 20 ppm or less | 1) Any supplied-air respirator.<br>2) Any self-contained breathing apparatus. |
| 100 ppm or less | 1) Any supplied-air respirator with a full facepiece, helmet or hood.<br>2) Any self-contained breathing apparatus with a full facepiece. |
| Greater than 100 ppm or entry and escape from unknown concentrations | 1) Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode.<br>2) A combination respirator which includes a Type C supplied-air respirator with a full facepiece operated in pressure-demand or other positive pressure or continuous-flow mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode. |
| Fire Fighting | Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode. |
| Escape | 1) Any gas mask providing protection against organic vapors.<br>2) Any escape self-contained breathing apparatus. |

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

(E) Respirators specified for use in higher concentrations of carbon tetrachloride are permitted in atmospheres of lower concentrations.

(F) Chemical cartridges and canisters shall not be used with carbon tetrachloride except for evacuation or escape.

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

(4) Where an emergency may develop that could result in employee injury from overexposure to carbon tetrachloride, 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 carbon tetrachloride, protective clothing shall be worn. The clothing shall be both impervious and resistant to carbon tetrachloride. 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 unless known to be safe. 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 defects prior to reuse.

(c) Eye Protection

Eye protection shall be provided for and worn by any employee engaged in an operation where carbon tetrachloride liquid or spray may

enter the eye. Chemical-type goggles, safety glasses with splash shields, or plastic face shields made completely of carbon tetrachloride-resistant materials shall be used. Suitable eye protection shall be in accordance with 29 CFR 1910.133.

Section 5 - Informing Employees of Hazards from Carbon Tetrachloride

All new and present employees in any carbon tetrachloride area shall be kept informed of the hazards, relevant symptoms, effects of overexposure, and proper conditions and precautions concerning safe use and handling of carbon tetrachloride.

A continuing educational program shall be instituted to ensure that all workers have current knowledge of job hazards, proper maintenance procedures, and cleanup methods, and that they know how to correctly use respiratory protective equipment and protective clothing.

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

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

Section 6 - Work Practices

(a) Handling and Storage

(1) Storage containers, piping, and valves shall be periodically inspected for leakage.

(2) Storage facilities shall be designed to contain spills and prevent contamination of workroom air.

(b) Contaminant Controls

(1) Suitable engineering controls designed to limit exposure shall be designed to prevent the accumulation or recirculation of carbon tetrachloride in the workroom and to effectively remove carbon tetrachloride 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 spray application of carbon tetrachloride such as in fumigation operations.

(c) Equipment Maintenance and Emergency Procedures

(1) Carbon tetrachloride hazard areas

Any space workers may enter where, because of its physical characteristics and sources of carbon tetrachloride, a volume of carbon tetrachloride could enter its atmosphere that would result in a vapor concentration in excess of the environmental limit, shall be considered a hazard area. Exits shall be plainly marked. Emergency exit doors shall be conveniently located and shall open into areas which will remain free of contamination in an emergency. At least 2 separate means of exit shall be

provided from each room or building in which carbon tetrachloride is stored or handled in quantities that could create a hazard.

(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, grain storage bins, or other confined spaces, which have contained carbon tetrachloride shall be thoroughly ventilated to assure an adequate supply of oxygen, tested for carbon tetrachloride and other contaminants, and inspected prior to each entry. Ventilation shall be maintained while workers are in the space.

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

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

(E) Personnel entering confined spaces shall be furnished with appropriate personal protective equipment and protected by a lifeline tended by another worker outside the space, who shall also be equipped for entry 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 concentrations of carbon tetrachloride which exceed the standard may occur. These instructions and procedures shall be printed both in English and in the predominant language of non-English-speaking workers, if any, unless they are otherwise trained and informed of the hazardous areas. Special instructions shall be given to illiterate workers.

(d) Showers and Eye Wash Fountains

Showers and eye wash facilities shall be provided and so located as to be readily accessible to workers in all areas where skin or eye splash with carbon tetrachloride is likely. If carbon tetrachloride is splashed on the skin, contaminated clothing shall be promptly removed and the skin washed with soap and water. If liquid carbon tetrachloride contacts the eyes, they shall be thoroughly irrigated with clean water, following which medical assistance shall be promptly provided. 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 shall not be 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 carbon tetrachloride based upon the following sampling and recording schedules:

(1) Samples shall be collected at least quarterly 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 shall require 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 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 or as indicated by a professional industrial hygienist.

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 |

(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 20 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.

# 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 carbon tetrachloride. 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 substances 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 recommended standard should not be the final goal.

These criteria for a standard for carbon tetrachloride are part of a continuing series of criteria developed by NIOSH. The proposed standard applies only to the processing, manufacture, and use of carbon tetrachloride as applicable under the Occupational Safety and Health Act of 1970. The standard was not designed for the population-at-large, and any extrapolation beyond occupational exposures is not warranted. It is

intended to (1) protect workers against development of systemic effects, and against local effects on the skin and eyes, (2) be measurable by techniques that are valid, reproducible, and available to industry and governmental agencies, and (3) be attainable with existing technology.

Carbon tetrachloride in liquid, aerosol, or vapor forms can be detrimental to health. It is readily absorbed by the skin and gastrointestinal tract in liquid form and by the lungs as a mist or vapor. The effects of exposure vary from temporary illness and discomfort to permanent severe injury. The risk from carbon tetrachloride exposure may be increased by the use of alcohol or barbiturates.

# III. BIOLOGIC EFFECTS OF EXPOSURE

## Extent of Exposure

Carbon tetrachloride ($CCl_4$), also known as tetrachloromethane, is a clear, colorless liquid having a moderately strong ethereal odor similar to that of chloroform. The more important physical properties are listed in Table XI-1. [1,2]

Two methods of carbon tetrachloride manufacture are chlorination of methane and direct chlorination of carbon disulfide. [2] Manufacture of carbon tetrachloride by 7 companies in the United States was reported by the US Tariff Commission for 1972. [3]

In the past, large quantities of carbon tetrachloride were used for drycleaning, degreasing, cleaning electrical parts, laboratory analyses, as a fire extinguisher, and in miscellaneous small applications. [1,4] Fairhall [4] calculated that 56.5% of the total 1946 US production of carbon tetrachloride, or approximately 82 million pounds, was used for making other halocarbons. In 1973, it was estimated that approximately 80% of the carbon tetrachloride produced in 1972 (997 million pounds [3] ) was used to make fluorocarbons and that about 200 workers were exposed by this use. (HL Smith, written communication, August, 1973). Grain fumigation, another major use of carbon tetrachloride, was estimated to consume approximately 16 million pounds in 1972, and it was estimated that about 25,000 workers were exposed. (S Calkins, written communication, September, 1973) Carbon tetrachloride production which was about 1 billion, 11 million pounds in 1970, [5] declined in the last 2 years for which data are

available to 997 million pounds in 1972. [3,6]

NIOSH estimates that 160,000 people are potentially exposed to carbon tetrachloride in their working environment.

## Historical Reports

Early studies of the effects of carbon tetrachloride on humans were made in England in connection with its use as an inhalation anesthetic. [7,8] In 1867, Smith [7] reported the results of 52 cases in which carbon tetrachloride was the anesthetic agent. He concluded that it was "useful in removing pain...while producing no nausea or sickness following its use."

Another early use of carbon tetrachloride was as a waterless shampoo. [9] Recommendations were made in 1909 in England to label carbon tetrachloride as a poison after a death resulted from its use for this purpose. [9] In some European countries, however, it continued to be used as a hair shampoo, resulting in further reports of serious illness and death. [10,11]

Health hazards from industrial use of carbon tetrachloride began to be reported in the early years of the twentieth century. In Germany, Lehmann [12] reported that he had received information in 1903 confirming that mental confusion, anesthesia, and other unwelcome effects occurred when new cleaning agents such as benzol and carbon tetrachloride were brushed on by hand.

In the United States, Hamilton [13] reported in 1915 that 4 men using carbon tetrachloride in the manufacture of rubber goods experienced nausea, vomiting, loss of appetite, loss of weight, weakness, and eye,

nose, and throat irritation. She also noted that men working without gloves were likely to develop dermatitis of the hands and arms.

Carbon tetrachloride was reported by Hall, [14,15] in 1921, to be an efficacious anthelmintic. Its use as an oral medication for this purpose stimulated considerable research into the pharmacologic and physiologic effects of carbon tetrachloride on humans. [16-18]

Effects of oral doses of carbon tetrachloride as a human anthelmintic administered to condemned prisoners in Ceylon were reported in 1922 and 1923. [16,17] Three condemned prisoners received 4 ml of carbon tetrachloride, two received 5 ml, and one received 5 ml plus an additional 3 ml 2 weeks later. The prisoners were executed 3-15 days after the administration of carbon tetrachloride. The livers of some showed no major microscopic or macroscopic changes upon autopsy, whereas the livers of others showed marked fatty degeneration. Although a dose-response relationship would be difficult to determine, it is significant that no fatalities occurred among the subjects within the 96 hours following ingestion of doses ranging from 3 to 8 ml of carbon tetrachloride.

In 1924, Wells [18] injected 1.5-2.5 ml of carbon tetrachloride through a tube into his duodenum to avoid eructation and began breath collection 10 minutes later. At this time the odor of carbon tetrachloride on his breath was unmistakable and he felt some dizziness. His method of determining carbon tetrachloride was reported to recover 97.8-99.5% of carbon tetrachloride from air experimentally blown through charcoal at rates of 1.0-13.4 liters/minute.

From the data presented by Wells, [18] average concentrations in his exhaled air for various periods after ingestion were calculated, and are

presented in Table XI-2. These data show that a large amount of the ingested carbon tetrachloride appeared in the exhaled breath and that it was detectable up to 36 hours after oral doses of 1.5-3 ml.

Effects on Humans

(a) Central Nervous System Effects

Carbon tetrachloride is a central nervous system depressant and this feature led to its early use as an anesthetic. [7,8] In many cases of ingestion and of occupational or accidental inhalation exposures to carbon tetrachloride, dizziness, headache, vertigo, giddiness, fatigue, and occasionally narcosis developed. [19-22]

Stevens and Forster [19] observed 17 cases of carbon tetrachloride poisoning between 1948 and 1953. In 7 of the cases they considered that there was neurological involvement, and headache, vertigo, weakness, blurring of vision, lethargy, and coma appeared soon after exposure. There were 2 fatalities among the 7 cases, and the brains of these were examined microscopically. One of these patients cleaned a sofa with a fluid containing carbon tetrachloride. Following his death 2 days after admission to the hospital, the brain showed scattered areas of demyelination with necrosis judged by the authors to be not unlike the lesions of acute perivenous encephalomyelitis. The other fatality was an alcoholic who died 7 days after washing parts of machines with carbon tetrachloride. In this man's brain the molecular layer of the cerebellar cortex was strikingly disorganized, and the Purkinje cells were pyknotic and greatly reduced in number. [19]

Similar Purkinje cell damage was reported by Cohen [20] in 1957 in 2

fatal cases from carbon tetrachloride ingestion that he described. Cohen [20] also reported finding patchy necrosis in the tissue connecting the cerebrum, cerebellum, and medulla oblongata, with cerebellar hemorrhages and extravasation of blood in the cerebrum. Other pathologic findings reported were liver necrosis and degeneration of the renal tubules.

Six workers in a motion picture film coating operation in which a solution of 85% carbon tetrachloride and 15% ethyl alcohol was used were the subject of a 1941 report by Heimann and Ford. [21] Carbon tetrachloride concentrations found with a portable combustion apparatus [23] in 6 samples of the work-environment air averaged 79 ppm (33-124 ppm). All 6 of the workers complained of fatigue after a "few" hours of work even though the work was not physically demanding. The sense of fatigue continued each workday, but disappeared on weekends. All of the men were given complete medical examinations, and medical histories were taken. Five of the 6 workers complained of nausea, and 4 experienced frequent vomiting. The authors [21] considered the fatigue of the workers to be the result of mild narcosis.

A soldier who cleaned bomb sights with carbon tetrachloride was reported in 1944 by Farrell and Senseman [22] to have had numbness, and ankle, knee, thigh, and wrist weakness. Physical and routine laboratory examinations were essentially negative except for the neuromuscular system. A fine spray of carbon tetrachloride was used to saturate a cloth wrapped around his fingers. He worked at the job 8 hours/day. The total exposure time and inhalation exposure concentrations were not reported. The case was diagnosed by the authors [22] as polyneuritis caused by absorption of carbon tetrachloride through the exposed skin. Following discontinuation

of the exposure, recovery was complete.

Experimental human studies of nervous system responses to inhaled carbon tetrachloride were reported by Lehmann and Schmidt-Kehl [24] in 1936. They used fans to distribute carbon tetrachloride spray throughout a 10-cubic meter room. The concentrations in the room were determined by hydrolysis of carbon tetrachloride with alkali in alcohol. The exposure concentrations ranged from 140 ppm (0.89 mg/liter) to 14,000 ppm (89 mg/liter). Exposures were for periods ranging from 50 seconds to 30 minutes. Two subjects usually were exposed at the same time and a total of 26 experiments were reported.

Perception of a light, transient odor was the only effect reported by Lehmann and Schmidt-Kehl [24] at 240 ppm (1.5 mg/liter) for 20 minutes. Dizziness and vertigo occurred after 10 minutes of exposure at concentrations of 600 ppm (4 mg/liter). Exposure at more than 600 ppm carbon tetrachloride resulted in increasingly severe effects that included headache, tiredness, giddiness, and salivation. Loss of consciousness occurred with exposure at 14,000 ppm (89 mg/liter) for 50 seconds. [24]

Responses reported by Davis [25] in a similar experiment included: none, with 5 hours of exposure at 75 ppm carbon tetrachloride; slight nausea after 30 minutes of exposure at 160 ppm; and nausea, vomiting, and headache after 30 minutes of exposure at 320 ppm.

Detection of a sweetish, not unpleasant odor was the only nervous system response to experimental carbon tetrachloride inhalation by human subjects observed by Stewart et al [26] and reported in 1961. The 6 individuals were exposed to carbon tetrachloride at a time-weighted average (TWA) concentration of 49 ppm (13-87 ppm) for 70 minutes. Odor was not

reported when 6 individuals were exposed on another occasion at a TWA concentration of 10.9 ppm (10-14.2 ppm) for 180 minutes. The exposures were conducted in a room 11 x 12 x 7.5 feet. The source of carbon tetrachloride was a 90-mm crystallization dish covered with a folded towel. A fan circulated carbon tetrachloride vapor throughout the room. The concentrations reported were obtained by sampling the room air at head height and passing the vapor through a continuously recording halide meter. The subjects did not report nausea, lightheadedness, or irritation during the exposures at either concentration, and impairment of equilibrium was not found when measured by the Romberg test and the heel-to-toe test during exposure.

(b) Eye Effects

Bilateral peripheral constriction of the visual color fields was found in 5 men examined by Wirtschafter [27] and reported in 1933. The men were employed in drycleaning establishments, and were exposed to carbon tetrachloride vapor 8-10 hours daily for 4, 5, 6, 10, and 26 weeks preceding examination. In 3 of the 5 cases, a delay of a few days to 3 weeks elapsed between first exposure and the onset of nausea, vomiting, dizziness, headache, and weakness. Three of the men complained of subsequently developing visual disturbances, which prompted the study of visual color fields. In one case, the color fields gradually returned to normal within 5 weeks after removal from exposure.

Marked optic atrophy of the right eye and a receding choked disc of the left eye were reported in 1950 by Smith [28] in a man who had cleaned silver bars for 8 months with a rag soaked in carbon tetrachloride. His visual impairment was noticed one week after termination of the job, and

medically confirmed on hospitalization 4 months later. At this time, the physical examination, apart from the eyes, gave negative results. Abnormalities were not found by electroencephalograms, skull and sinus roentgenograms, or tests for syphilis, blood sugar, or urea nitrogen. His vision improved somewhat during the following 3 years while he was not exposed to carbon tetrachloride.

Two other cases of visual disturbances were observed by Smith, [28] in which the exposures included other chemicals in addition to carbon tetrachloride. A man who dipped razor cutting heads in a solution containing carbon tetrachloride and gasoline and spread them on a cloth in front of him for inspection developed headaches and dizziness after about 4 months of this work. The illness progressed during 16 months to include weakness, irritability, nausea, muscle cramps, mental confusion, disorientation, and memory loss, and finally blurred vision. Laboratory and physical findings were normal, except for visual tests. The final diagnosis was bilateral optic neuritis. The second case was a woman who used a solution of 20% carbon tetrachloride and 80% naphtha as a spot remover in a dressmaking factory. When hospitalized for blurring vision, her eyes showed marked constriction of the visual fields with scotomata. Other physical and laboratory findings were normal. The diagnosis was retrobulbar neuritis. [28]

Bilateral diminished vision in a man was reported by Gray [29] to have developed after 11 years of mixing chemicals, especially carbon tetrachloride, in the manufacture of polishes. In this case, jaundice, nausea, vomiting, weakness, and weight loss developed 2 months after the onset of blurred vision. At this time a slight enlargement of the liver,

elevated icteric index, positive van den Bergh, and slight hypochromic anemia were found. The patient improved following removal from carbon tetrachloride exposure.

(c) Liver and Kidney Effects

Acute and chronic exposures to carbon tetrachloride have resulted in liver and kidney damage. [29-36] Mortality from carbon tetrachloride exposure was most often the result of pathologic effects on the liver and kidneys and subsequent organ failure. Moderate-to-heavy alcohol consumption was a concomitant variable in many cases of carbon tetrachloride poisoning with liver or kidney injury.

Two cases of industrial poisoning from carbon tetrachloride used as a cleaning agent were reported by Franco [30] in 1936. In one case, carbon tetrachloride was used to clean ink from stencils, and in the other, for cleaning electrical condensers on a boat. In one case, the diagnosis was necrotizing nephrosis and, in the other, acute nephritis. This was one of the first reports to recognize renal injury from carbon tetrachloride poisoning instead of, or in addition to, hepatic dysfunctions.

Between 1948 and 1957, Guild et al [31] examined 20 patients suffering from carbon tetrachloride poisoning (16 by inhalation and 4 by ingestion). Exposure times varied from 30 minutes to 11 hours; exposure concentrations were not reported. Following carbon tetrachloride exposure, dizziness, nausea, and vomiting commonly occurred within 1-6 hours. All 20 patients developed anuria 1-7 days (average 3 days) after exposure. Eighteen of the patients had no previous history of renal disease. Three of the 16 people exposed by inhalation and 2 of the 4 ingestion cases died. Autopsy findings in 4 of the 5 fatalities included acute renal tubular and

hepatic centrilobular necroses. The cause of death in the fifth case was clinically determined to be severe hepatic insufficiency. [31] Eleven of the 16 people exposed by inhalation and all 4 who had ingested carbon tetrachloride had clinical and laboratory evidence of moderate to severe hepatic dysfunction. Alcohol was consumed daily in large quantities by 16 of the 20 patients.

A history of chronic alcoholism was common to 3 cases of carbon tetrachloride intoxication with kidney and liver involvement observed in 1939 by Smetana. [32] Autopsy of one patient who died 10 days after ingestion of an unknown amount of carbon tetrachloride showed centrilobular liver necrosis, jaundice, ascites, and nephrosis. Autopsy findings in another man who died 9 days after an exposure of several hours to carbon tetrachloride at unknown concentrations while cleaning furniture and draperies included nephrosis, fatty degeneration of the liver, and centrilobular liver necrosis. A clinical diagnosis of toxic hepatitis, acute renal tubular damage, toxic myocarditis, and possible cirrhosis of the liver was made on the third patient who was hospitalized 3 days after cleaning dresses with carbon tetrachloride for 3 hours in a close, stuffy room.

Fatal uremia was reported in 1942 by Ashe and Sailer [33] as the cause of death of a man exposed to carbon tetrachloride while cleaning machinery in an elevator shaft. Death occurred 17 days after a 4-hour exposure. Degeneration of the tubular epithelium of the nephrons, centrilobular liver necrosis, and fatty degeneration of the ganglion cells of the globus pallidus were found at autopsy.

Carbon tetrachloride poisoning in a felt manufacturing plant was the subject of a report in 1932 by McGuire. [34] The 7 employees cleaned the felt by passing it through an open vat that contained a 33% mixture of carbon tetrachloride which was warmed. The other components of the solution were not reported. Extent of the skin exposure was not indicated. The men, all of whom were wine drinkers, complained of nausea and vomiting 1-3 days following institution of the soaking procedure. Other complaints included burning sensations of the eyes or mouth, headache, and diarrhea. Four of the 7 workers experienced kidney "irritation," diagnosed as acute nephritis in one. Two of the 7 men had definite liver enlargement with jaundice.

Liver function and enzyme activity were compared with microscopic findings obtained by liver biopsy in a 1960 report by Lachnit and Pietschmann [35] of 2 cases of acute carbon tetrachloride intoxication. One case involved a laborer who used carbon tetrachloride for 3 hours to clean a machine in a relatively large and well-ventilated room. He developed nausea, giddiness, stomach pains, fever, and 3 days after exposure he was hospitalized. His liver was slightly enlarged and sensitive to pressure. Serum glutamic-oxaloacetic transaminase (SGOT) was 6,000 units/ml and serum aldolase was 300 units (1 unit = 0.001 extinction decrement/minute/ml serum). The enzymes returned to normal values (10-33 units/ml) 10-15 days after intoxication. Large areas of centrilobular necrosis were found in a liver biopsy on the 8th day after intoxication. The surrounding liver cells appeared normal. The other man had assisted in the cleaning operation and had not been so directly exposed. He developed the same, but less severe, clinical symptoms and was hospitalized on the

12th day after exposure. At that time, SGOT of 80 units and serum aldolase of 21 units were found. Hepatic cells showing degenerative changes and nuclei of different sizes were found in a liver biopsy on the 22nd day after exposure. [35]

Three workers acutely exposed to carbon tetrachloride and hospitalized with jaundice, nausea, and dizziness were described by Barnes and Jones [36] in 1967. One of the cases was associated with the delivery process (concentrations of carbon tetrachloride were in excess of 30 ppm), another case occurred when an employee drained water from a carbon tetrachloride storage tank (carbon tetrachloride concentrations of 75-600 ppm with the "main" level at 210 ppm), and the third case occurred when an employee cleaned sludge from a carbon tetrachloride tank. Abnormal liver function was found in all 3. Findings in a liver biopsy from one of the workers taken 3 weeks after the episode were considered by the authors [36] to be consistent with toxic hepatic injury from carbon tetrachloride poisoning.

Enlarged livers and elevated icteric indices, but no indications of kidney injury, were found by Gray [29] in 4 workers who had been chronically exposed to carbon tetrachloride for from 2 months to 11 years. The worker with the longest exposure was a chemical mixer. The other 3 workers, including 2 with a history of heavy chronic alcohol consumption, used carbon tetrachloride to clean machinery. Both kidney and liver damage were observed by Gray [29] in 3 other cases of carbon tetrachloride poisoning where exposure had been for 1-2 days in electric motor cleaning operations. One of these acutely poisoned patients with a history of heavy chronic alcohol consumption died following the carbon tetrachloride exposure. [29]

A foreman and another man who occasionally worked with him on the maintenance of telephone relay equipment within the German railway system frequently experienced nausea and stomach distress as reported by Dellian and Wittgens in 1962. [37] Sixteen measurements of carbon tetrachloride concentrations ranged from 10 to 100 ppm in various locations. The foreman, 54 years of age, had worked 4 years in the maintenance section using carbon tetrachloride on the average of 3 days/week. During the 4th year, colic in his right upper abdomen led to his incapacity to work. Clinical studies excluded the possibility of gall bladder infection. Laparoscopy confirmed that both lobes of the liver were enlarged and yellow-red in color with indistinct markings. Coarse fatty degeneration, undeveloped borders, and moderate infiltration of the periportal areas were found on microscopic examination of liver tissue. The SGOT was elevated and sulfobromophthalein (BSP) retention was increased. Fourteen months after this examination, a greater degree of fatty liver degeneration was found on biopsy, but SGOT had returned to normal. Kidney findings were normal at all examination times. There was no history of alcohol abuse or predisposing disease known to affect the liver. The investigators concluded that the effects were related to chronic exposure to carbon tetrachloride. [37]

In 1961, Stewart et al [26] reported that exposures to carbon tetrachloride at 10 or 11 ppm for 180 minutes did not affect liver or kidney function based on normal urinary urobilinogen, SGOT, and 15-minute phenolsulfonphthalein. However, exposure at 49 ppm for 70 minutes may have had some effect on liver function shown by a reduction of serum iron 1 or 2 days later in 2 of 4 subjects in whom it was measured.

Primary hepatic epithelioma secondary to cirrhosis was diagnosed at autopsy of a military fireman who had been extensively exposed to carbon tetrachloride from fire extinguishers during an unspecified number of years. [38] One particular day, he and an assistant were ordered to use a carbon tetrachloride extinguisher to destroy a swarm of wasps that had located in an enclosed space. Both men became intoxicated, and the assistant was hospitalized with nephritis. The fireman who suffered some "indisposition" was not hospitalized, but he began to feel very weak and nauseated the next day. The following day these symptoms became more pronounced and somnolence and anorexia developed. On the 6th day after exposure he developed hematuria which lasted 4 days, at which time he felt better and returned to work. During the next 4 years, 10-day episodes of anorexia, fatigue, fever, hematuria, and conjunctival subicterus occurred at intervals of 4-6 months. Four years after the acute poisoning, the fireman was hospitalized with weakness, fever, epigastric pain, cramps, and diarrhea. A bright pink liver with small nodules resembling micronodular cirrhosis and an enlarged spleen were seen by laparoscopy. The diagnosis of hepatic cirrhosis with portal hypertension was confirmed by splenoportography and laparoscopy. There were no known etiological factors such as icteric antecedents or heavy alcohol usage. Microscopic examination of biopsy material showed cirrhosis and an early epithelioma of the liver. The epithelioma was glandiform with clear cells. Lymph vessels under the thickened Glisson capsule were increased in number and inflamed. Five months after the surgery the patient was thin, subicteric, and asthenic, with abdominal pain and a hard, enlarged liver. Two months later he died from a ruptured neoplastic lobe. Irregular cirrhosis with early

hepatic cancer on the cirrhotic areas of the entire right lobe was found at autopsy. Cancerous pylephlebitis was also observed.

Johnstone [39] reported in 1948 that a woman who had been exposed to carbon tetrachloride for 17 months developed cancer of the liver. The woman was an assistant to a metallurgist and several times a day she dipped a sponge into a small open dish of carbon tetrachloride to clean the metal. After 2 months, she became increasingly fatigued and exhibited periodic jaundice. After 13 months of employment, she sought medical aid and was hospitalized. A markedly enlarged liver with nodular cirrhosis was found in an exploratory operation. Following a short recuperation, she returned to work for 4 months at which time she was forced to stop work because of extreme weakness, marked jaundice, and increasing weight. She died 3 years after the beginning of her employment. A cancer of the liver was found at autopsy. The type of cancer was not specified and results of laboratory studies were not reported. Five years prior to her employment, she had suffered "biliary colic," pain at the angle of the right scapula, and she had been studied for "gall bladder disease." Whether these factors had etiological significance was not discussed by the author. [39]

Hepatocellular carcinoma was reported by Tracey and Sherlock [40] in 1968 as the diagnosed cause of death of a 59-year-old man 7 years after acute poisoning with carbon tetrachloride. When he returned to his apartment from a cocktail party he noted the odor of carbon tetrachloride which had been used earlier that day to clean the rug. He slept in the apartment and 5 days later developed nausea, vomiting, and diarrhea. He became jaundiced and anuric on the 10th day. At this time, the liver was found to be enlarged 3 fingerbreadths below the costal margin. There was

no history of previous jaundice, symptoms of hepatic decompensation, or portal hypertension, but the patient, who had been in good health all his life, admitted to having several alcoholic drinks daily.

He remained almost completely anuric for 4 days and remained in the hospital for 9 weeks. Four years later when he was seen again, he had been in good health and had abstained from alcohol since his hospitalization. Clinical tests at this time were normal. A smooth, enlarged, nontender liver palpable 3 fingerbreadths below the right costal margin was found. He was readmitted to the hospital 3 years later with a history of anorexia, weight loss, nausea, vomiting, and diarrhea. His liver was enlarged 4 fingerbreadths below the right costal margin and a 6 x 6 cm tender mass was felt in the right epigastrium. A hepatocellular carcinoma was found by liver biopsy. He died five months later. The liver was extensively involved with tumors, and only a small amount of normal tissue remained. There was a moderate amount of fibrosis, but the parenchymal cell structure was so disrupted by tumors that no classification of the cirrhosis could be made.

(d) Carbon Tetrachloride in Blood and Exhaled Air

In 1951, Hamburger et al [41] reported that a concentration of carbon tetrachloride in the blood of 32 mg/liter was found at autopsy of a woman who died 11 days after cleaning her hair with carbon tetrachloride. In 1958, Hamburger [42] reported carbon tetrachloride concentrations in the blood of 0.09-2.30 mg/liter in 9 individuals hospitalized 1-5 days after they had become anuric from carbon tetrachloride poisoning. Among 6 other individuals examined after being anuric from carbon tetrachloride poisoning for 6 or more days, carbon tetrachloride was found in the blood of only

one. In this individual, carbon tetrachloride in the blood was 1.4 mg/liter on the 10th day of anuria. The case histories were described in detail by Richet et al. [43] Carbon tetrachloride was determined by reaction with pyridine in alkali as described by Fabre et al. [44]

A man who had a history of chronic alcohol consumption became oliguric after cleaning tiles in his bathroom for about 30 minutes with carbon tetrachloride. In a breath sample obtained 10 days after exposure, Markham [45] reported a carbon tetrachloride concentration of 4 mg/liter. The analytical method was not given.

During 6 exposures of 30 minutes' duration to carbon tetrachloride at 650-1,600 ppm (4.1, 4.2, 6.7, 8.6, 9.6, and 10.2 mg/liter), Lehmann and Schmidt-Kehl [24] collected expired air with an aspiration device and determined residual carbon tetrachloride concentrations. The respective percentages absorbed (61.0, 64.3, 57.2, 61.1, and 57.0) were calculated from the concentrations of carbon tetrachloride in inhaled air and those found in exhaled air.

Carbon tetrachloride was measured by Stewart et al [26] in the exhaled air during 5 hours after the end of human exposures. The concentrations found at 25 minutes after a 70-minute exposure at 49 ppm were about 20 μg/liter and about 6 μg/liter when exposures had been at 10 or 11 ppm for 3 hours. Breath concentrations ranged between about 1.0 and 2.5 μg/liter at 5 hours after removal from exposure, regardless of exposure concentration.

A worker became dizzy, weak, nauseated, and finally unconscious during exposure to a mixture of vapors including carbon tetrachloride. Ten minutes later he was coherent, though uncoordinated, and nauseated.

Concentrations of carbon tetrachloride in his breath following the episode were reported by Stewart et al [46] in 1965. Thirty minutes after his collapse, a breath sample contained 9.5 ppm (60 μg/liter) carbon tetrachloride, determined by infrared analysis. Carbon tetrachloride was still detectable in the breath 15 days after the exposure. The data were not presented, but the authors [46] reported normal findings for urinalysis, complete blood cell counts, 24-hour urinary urobilinogen, and SGOT measured serially over 2 weeks.

Concentrations of carbon tetrachloride in exhaled breath of a woman who drank a "pint" of a solution containing 2 parts carbon tetrachloride and 1 part methanol were studied by Stewart et al [47] and reported in 1963. Gastric lavage was carried out soon after ingestion. The first expired air sample contained 2,000-2,500 μg/liter of carbon tetrachloride. A series of exhaled breath samples were analyzed for carbon tetrachloride over the following 19 days. The samples showed a progressive decrease in carbon tetrachloride concentration to about 1.2 μg/liter 19 days after the ingestion.

Studies of absorption of carbon tetrachloride through the skin of the thumb were reported by Stewart and Dodd [48] in 1964. Three subjects each immersed one thumb in carbon tetrachloride for 30 minutes, and the concentrations of carbon tetrachloride in the exhaled air of the subjects were determined at 10, 20, and 30 minutes of immersion. The concentration ranges in the exhaled air at these times were respectively 0.025-0.819, 0.25-3.27, and 0.69-5.23 μg/liter. Carbon tetrachloride was still measurable in exhaled air of these subjects 5 hours later.

(e) Clinical Observations with Alcohol and Carbon Tetrachloride

Among the case studies presented in previous sections of this chapter, alcohol consumption was frequently mentioned as a coexisting factor. The first serious effects of carbon tetrachloride as an anthelmintic for humans were observed when it was administered by Smillie and Pessoa [49] to 2 alcoholics in a group of 34 persons, 9-25 years of age; daily alcohol consumption was reported for 16 of the 20 cases of carbon tetrachloride poisoning discussed by Guild et al [31]; all of the 7 men studied by McGuire [34] were wine drinkers; the 3 cases reported by Smetana [32] were chronic alcoholics; and the 2 fatalities studied by Gray [29] were long-term alcohol addicts.

In addition to these cases, others have found alcohol to be a prominent factor in those hospitalized with carbon tetrachloride poisoning. Alcohol was considered in 1948 to be a predisposing factor in 8 of 10 cases studied by Abbott and Miller [50]; it was involved in 8 of 12 cases reported by Joron et al [51] in 1957, and in 17 of 19 cases discussed by New et al [52] in 1962. In the report by New et al, [52] the serious cases of renal failure all involved alcohol consumption, whereas alcohol was not a factor in the 4 cases with only liver or central nervous system involvement.

Thompson [53] mentioned the case of a known chronic alcoholic who frequently drank on his job of bottling carbon tetrachloride and who was seriously poisoned while his coworkers were not affected.

Epidemiologic Studies

Surveys of a number of industries that used carbon tetrachloride were reported by Elkins [54] in 1942. Carbon tetrachloride in the workroom air was collected in amyl acetate, decomposed to chloride by burning the solution, and the chloride was determined by silver nitrate titration. [55] Ranges of concentrations and their averages were reported, but the number of samples and sampling times were not. A survey of 5 drycleaning plants where carbon tetrachloride was used revealed the following effects and exposure concentrations:

(1) Nausea, vomiting, belching, drowsiness, headache, dizziness, and lassitude occurred among several women engaged in a spot cleaning operation after several days of exposure to carbon tetrachloride at an average of 35 ppm (10-80 ppm). In this plant, each woman used about one quart of solvent per day in a well-ventilated room.

(2) Workers in a drycleaning plant complained of feeling sick, but quantitative data about the type and frequency of symptoms or number of people involved were not reported. Carbon tetrachloride concentrations during operations that would produce the maximum amount of vapor averaged 65 ppm (35-115 ppm). The frequency and duration of the exposures at these concentrations were not reported. The symptoms were not completely alleviated when undescribed operational changes were made that reduced the average concentration to a reported 25 ppm.

(3) An unspecified number of workers in a drycleaning plant where carbon tetrachloride concentrations averaged 25 ppm (15-60 ppm) were reported to be seriously affected in some way.

(4) An operator of a drycleaning shop where measured carbon tetrachloride concentrations averaged 20 ppm (5-40 ppm) used a gas mask because he had been nauseated.

(5) Several women using small amounts of carbon tetrachloride for spot removal in a large, well-ventilated room were nauseated, and one woman's illness of several weeks was attributed to the exposure. No measurements of carbon tetrachloride in the air were made at the time the nausea and illness occurred, but Elkins [54] believed that only low concentrations could have occurred. After dilution of the carbon tetrachloride with an equal volume of naphtha and installation of a canopy hood over the work area, the concentration of carbon tetrachloride in the air was 5 ppm, and there were no further complaints.

In a survey of two plants where multigraph operators used carbon tetrachloride, Elkins [54] reported that:

(1) Nausea, loss of appetite, and loss of weight occurred in 4 persons in an office where ink was removed from multigraph machines using about 1 gallon of carbon tetrachloride daily. Carbon tetrachloride concentrations reported only for the worst conditions ranged from 40 to 375 ppm, with an average of 85 ppm. Concentrations of this magnitude were considered to occur only once in 2-3 weeks. The factors causing the worst environmental conditions were not explained, nor was the frequency of occurrence of the symptoms reported.

(2) Five multigraph operators who used slightly more than 1 quart of carbon tetrachloride daily in a relatively small area experienced nausea. No measurements of carbon tetrachloride concentrations were given for the conditions under which the nausea occurred. After installation of

general ventilation and apparent alleviation of symptoms, the concentrations of carbon tetrachloride were 10-25 ppm.

Smyth et al [56] and Smyth and Smyth [57] reported 8-hour time-weighted average exposure concentrations which they calculated from carbon tetrachloride determinations and job analyses for 73 workers employed in carbon tetrachloride and fire extinguisher manufacture, 10 workers in drycleaning plants, and 2 workers involved with other uses of carbon tetrachloride. The exposure concentrations were determined using a portable 50-cm interference refractometer. Summaries of the environmental data are shown in Tables XI-3, XI-4, and XI-5.

Carbon tetrachloride TWA exposures of the workers studied in these various plants (see Table XI-5) ranged from 5 to 117 ppm with peak exposures at 22-1,680 ppm. Hematology, liver and kidney function, and fields of vision were studied in 77 workers using carbon tetrachloride in 10 plants. The distribution of significant findings for visual fields, determined with a "simple" portable perimeter, and icteric indices are shown in Table XI-5. Nine of the men had definitely restricted visual fields. Four of these 9 workers were engaged in container-filling operations. An additional 26 men had slightly restricted visual fields, 40 had normal visual fields and the measurement was not made on 2 men. Thirteen of 67 men tested had elevated icteric indices. Hematology, kidney function studies, and other measures of liver function did not show significant results of exposure.

Ophthalmological studies of 108 people who were chronically exposed to carbon tetrachloride were conducted by Moeller. [58] A group of 46 people who were mostly locksmiths from various factories had exposures to

carbon tetrachloride varying from 1 hour daily to 1 hour weekly, for an average of 7.7 years. Another group of 62 people worked in a single, large locksmith shop where cleaning operations were performed at least 1-3 hours daily, without protective clothing, by dipping mops into buckets of carbon tetrachloride. Air analyses in this shop gave carbon tetrachloride concentrations of 6.4-9.5 ppm (40-60 mg/cu m).

Vision, ocular foreground (probably lens) and eye ground (fundi oculi), intraocular pressure, and corneal sensitivity were studied in the group of 46 workers. In this investigation, he found reduced corneal sensitivity in 28 of the workers, and temporal atrophy of the optic nerve in a 63-year-old subject who had been exposed to carbon tetrachloride for 27 years and to carbon monoxide for 33 years.

In the group of 62 workers and in a control group of 82 persons, Moeller [58] studied outer limits of the field of vision and color fields of vision on a spherical perimeter, instant adaptation on the recording nyctometer, dark adaptation on a recording adaptometer, sense of color with charts and an anomaloscope, near point measurement on a proximeter, and blind spots with a scotometer.

Among these workers, 43 had reduced corneal sensitivity, 4 had restricted outer limits of the visual fields for white, 4 had subnormal or questionable dark adaption curves, 15 had color limits of the visual field which clearly deviated from normal, and in 7 there were instrument detectable changes in color perception.

Kazantzis and Bomford, [59] in a 1960 report, described a factory in which quartz crystals and various pieces of equipment were cleaned with carbon tetrachloride. The carbon tetrachloride could be smelled in the

vicinity of the equipment as well as near another bench where plates were cleaned with a cloth dipped in beakers of carbon tetrachloride. The 3,000 sq ft room was divided by a partial partition. Concentrations of carbon tetrachloride were measured on both sides of the partition, both before and after the beakers were covered. Before they were covered, 67, 70, and 97 ppm were found on one side of the partition, and 45, 45, and 47 ppm on the other side. After the beakers were covered, the concentrations found were 0, and 8, and 9 ppm on the one side and less than 8 ppm on the other side.

Five days after corrective action, 17 of 18 employees were interviewed and examined by Kazantzis and Bomford. [59] Fifteen of the 17 interviewees had experienced for up to 2 years one or more of the following: nausea, 15; anorexia, 12; vomiting, 7; flatulence, 7; gastric discomfort or distention, 10; and depressive symptoms of headache or giddiness, 10. Nausea had usually developed on Tuesday or Wednesday of each week and vomiting on Thursday or Friday. One affected individual had previously been studied in the hospital because of the severity of his symptoms. The only physical or clinical abnormality found was an SGOT measurement of 76 units/ml. After his return to work and 5 days after the corrective measures were taken, SGOT measured in this individual and in 7 coworkers was normal. At the same time, the fundi and visual fields were normal in the 17 individuals studied; no abnormalities were found in the urine; and no other abnormal physical signs were discovered except for abdominal tenderness without guarding in 3 men. All workers were symptom-free within one week and there were no recurrences up to 6 months later.

In 1967, Barnes and Jones [36] reported a comparative study of exposed and unexposed workers in a plant where carbon tetrachloride was

used in the manufacture of polyfluorohydrocarbons. Sixteen of the plant's employees who handled carbon tetrachloride and 11 others who worked in sections of the plant remote from carbon tetrachloride were studied. The process was automated and enclosed, but intermittent exposure occurred when carbon tetrachloride was delivered by road tanker and discharged into receiving tanks and when the pipes and tanks were periodically cleaned and repaired.

Urinary urobilinogen was found in 6 of those handling carbon tetrachloride, and there was protein in the urine of 3 others of this group. Both the average zinc turbidity and average thymol turbidity of the exposed group were elevated compared to those of the control group. Serum bilirubin averaged 1.36 mg% (0.45-4.0) compared to the control group average of 0.46 mg% (0.20-0.60). The SGOT averaged 37.3 (25-48) Sigma Frankel (SF) units in the exposed group and 32.7 (27-38) SF units in the control group. [36]

An epidemic of carbon tetrachloride poisoning in a parachute plant in which 137 people became ill with sudden onset of abdominal cramping, nausea, and vomiting over a 10-day period in early December 1943 was described by Doyle and Baker. [60] Health records showed that a great many employees had frequent or even constant headaches and that complaints of gastric distress had been especially prevalent for several weeks. All 675 or more employees in the plant had a waxy, "anemic appearance," and the great majority complained of constant headaches, "sour stomach," weakness, and colds. Food, water, and infectious diseases were carefully ruled out as causative factors.

The investigators [60] found that carbon tetrachloride, labeled 99.005%, used for cleaning the parachutes, was constantly present in open

containers on each of 30-40 tables covering half of the 120 by 300 feet of floor space. Gauze pads were soaked in carbon tetrachloride and then rubbed against soiled areas of parachutes. Of the 137 persons who became acutely ill, 135 were engaged in this task. To remedy the situation, the number of open containers of carbon tetrachloride was reduced to 9, windows and doors were opened as much as possible, the building was thoroughly aired between shifts, and the carbon tetrachloride containers were kept covered when not in use. No measurements of carbon tetrachloride in the air had been made before these corrective measures were taken. One afternoon, one week later, 2 room air samples taken between 2 work tables, rather than in the breathing zone of workers, contained 163.6 and 193.5 ppm of carbon tetrachloride. A halogenated hydrocarbon detector was used for the determinations.

Rabes [61] reported in 1972 on a study of 51 workers exposed to carbon tetrachloride for 3-27 years in an electrical plant where turbines and generators were overhauled and cleaned. The process occurred 2-3 times/year and lasted about 14 days each time. Carbon tetrachloride was the only solvent ever used in these cleaning operations. During each 8-hour cleaning shift, a tank containing 20-30 liters of carbon tetrachloride was uncovered and the stripped-down components of the electrical equipment were cleaned in and around it. Special ventilation was not used. The author [61] noted that it was difficult to determine the carbon tetrachloride exposure but that, as an indication, in a 19-month period the maintenance section used 18,100 kg of carbon tetrachloride. Carbon tetrachloride concentrations of 6.3 ppm (40 mg/cu m, or 40 μg/liter) were found at the beginning of a work shift, and of 9.5 ppm (60 mg/cu m) after 5

minutes of work in an unspecified location in the plant. Work clothes sprinkled with carbon tetrachloride were seldom changed.

Fifty-one exposed workers and a comparison group of 27 unexposed workers were given clinical examinations, and laboratory analyses of blood and urine were made. [61] All test subjects (exposed and comparison) were evaluated for previous diseases affecting the liver and for occupational contact with other hepatotoxic substances. The 51 subjects were classified according to years of exposure to carbon tetrachloride, ie, 1-5, 6-10, 11-15, 16-20, or greater than 20. Table XI-6 shows the calculated average biochemical measurements used to evaluate liver function. Serum iron and glutamic dehydrogenase (GDH) were increased in the carbon tetrachloride-exposed group compared to the control group. Both indicators of liver changes were increased by a statistically significant amount after 5 years of exposure to carbon tetrachloride--23% increase for serum iron and 92% increase for GDH. In order to exclude distortion of the data due to previous liver damage, the test subjects were classified into 2 additional groups, those with and those without previous liver damage. Analysis of the data in this way excluded previous liver damage as a significant factor in the results.

Animal Toxicity

(a) Effects of Liquid Carbon Tetrachloride

Centrilobular liver necrosis was found in dogs after ingestion, inhalation, subcutaneous and intraperitoneal injection, and rectal administration of carbon tetrachloride by Gardner et al [62] and reported in 1924. A single 0.5 ml/kg oral dose of carbon tetrachloride produced frank,

fresh central necrosis in the livers of 2 dogs killed 48 hours after administration. Pathologic changes were not found in the kidneys of these 2 dogs. With carbon tetrachloride doses of 0.05, 0.1, and 0.25 ml/kg, indefinite microscopic signs of pathologic changes including swelling and paleness of parenchymal cells were seen in the liver. No gross or microscopic abnormalities were seen in 2 dogs killed 48 hours after a single dose of 0.01 ml/kg. Centrilobular necrosis of the liver was found in rabbits administered oral doses ranging between 0.1 and 6 ml/kg.

Monkeys given 1-2 ml/kg of carbon tetrachloride by stomach tube on 3 days/week showed no evidence of incipient fibrosis after 176 days, [62] but marked accumulation of fat in the center of the liver lobules, and vacuolation and swelling of liver cells were found by microscopic examination. Of 15 liver function tests, only 30-minute BSP retention reflected liver damage. The normal range of BSP retention was given as 0.35-1.5%. BSP retention of 8.2-8.5% was found in 4 monkeys after 15 doses; 14.0-27.0% was found after 31 or 32 doses; and 18.0% was found in 1 monkey after 52 doses.

The intensity and character of damage and repair occurring simultaneously in kidneys and liver were studied by Lundh. [63] Long-Evans strain rats were injected subcutaneously with carbon tetrachloride as follows: the first group received 1 injection of 0.4 ml/kg; the second group received 1 injection of 4 ml/kg; and the third group received 0.4 ml/kg every 3 days over periods of 72 hours-12 weeks. Animals in the single injection groups were autopsied serially at 2, 4, 8, 16, 20, 24, 30, 36, 42, 48, 72, 96, 120, and 168 hours. Animals in the multiple injection group were autopsied serially at 72 hours and at 2, 3, 4, 5, 6, 7, 8, 10, and 12 weeks.

Marked swelling of the renal tubular epithelium and collapse of Bowman's space occurred 2 hours after injection of 4 ml/kg of carbon tetrachloride. In the livers, disappearance of small arterioles and medial necrosis of larger arteries were seen at 4 hours after injection. Severe renal damage was still seen at 48 hours and a normal state had not been completely attained at 120 hours after injection of carbon tetrachloride. [63] Severe destructive changes were still present at 120 hours in the liver parenchyma.

Degeneration of the cytoplasm of the proximal tubular cells of the kidneys was found 4 hours after the single 0.4 ml/kg injection of carbon tetrachloride. At this time, liver cells around the central vein were eosinophylic. The degenerative changes in the kidney became maximal 16-24 hours after the injection, and at 48 hours, the kidneys had regained normal microscopic appearance. Liver damage progressed slowly from the central cells to the rest of the liver and from eosinophilic and granular changes to marked vacuolation and eventually cellular death. Maximum liver damage was observed 36-48 hours after injection of carbon tetrachloride and cellular regeneration was complete at 120 hours.

Until 2 weeks after the start of injections, the nephrotoxic and regenerative patterns found in the group of animals given carbon tetrachloride doses of 0.4 ml/kg at 72-hour intervals were similar to those found in the group given a single dose. At 2 weeks, the regenerative processes were not complete between injections, and dilation of renal tubules with flattening and atrophy of proximal tubular cells was seen. The liver cells did not recover between any of the injections and fibrotic and cirrhotic changes began at about 2 weeks.

Ornithine carbamoyl transferase (OCT) activity was found to vary in relation to the severity of liver damage in a study reported by Musser and Spooner [64] in 1968. Wistar rats were given carbon tetrachloride at a dose of 0.125 mg/g by intraperitoneal injection and killed by decapitation at various intervals 4-120 hours after injection. Autopsies were performed immediately after death and serum and tissue OCT determinations were made. Liver cell damage determined by microscopic examination was graded on a 1-4 scale, ranging from scattered individual cell necrosis to confluent areas of necrosis. The index of liver cell damage increased with time after injection to a maximum at 48 hours, then decreased to 0, ie, normal, at 120 hours. Serum OCT was significantly elevated at 8 hours after injection of carbon tetrachloride, maximum at 48 hours, and still abnormally high at 96 hours. The lowest level of tissue OCT was at 24 hours and the highest at 46 hours. After 48 hours, the tissue OCT decreased toward normal levels but rose significantly at 120 hours. Serum OCT levels at various times after carbon tetrachloride administration are shown in Table XI-7.

The effects on serum OCT activity of 33 solvents, including carbon tetrachloride, were reported by DiVincenzo and Krasavage [65] in 1974. Carbon tetrachloride was dissolved in corn oil and administered by intraperitoneal (IP) injection to mature male guinea pigs in doses of 5, 25, 50, 75, and 150 mg/kg. Twenty-four hours after the injections, 2 ml of blood was withdrawn by heart puncture from anesthetized animals, and serum OCT activity was determined spectrophotometrically. Each animal was killed after blood sampling by an overdose of diethyl ether and the liver was removed and examined. Control serum OCT values were 2.02 (SD of 1.61) International Units (IU) with a reported range of 0 to 8.9 IU. The value

of 8.9 IU suggested to the authors some incipient liver damage in an unexposed, presumably healthy animal. Carbon tetrachloride doses of 5, 25, 50, 75, and 150 mg/kg gave average serum OCT activity of 3.8, 37.1, 63.5, 53.5, and 64.4 IU, respectively. Liver damage and lipid accumulation were found after all doses except 5 mg/kg. [65]

Absorption of liquid carbon tetrachloride through the skin was studied by Lapidus [66] and McCord. [67] Lapidus [66] studied carbon tetrachloride in the blood, liver, and brain of 4 rabbits after immersion of one ear of each rabbit in carbon tetrachloride. Ear immersion times were 5, 6, 8, and 9 hours, and precautions were taken to avoid inhalation of carbon tetrachloride vapor. Substantial amounts of carbon tetrachloride were found in the blood (12-13 mg/100 g), liver (0-90 mg/g), and fat (0-300 mg/g). A trace of carbon tetrachloride was found in the brain of the rabbit whose ear was immersed for 9 hours, but none was found in the brains of the other rabbits. The analytical method required at least 5 mg of carbon tetrachloride in a sample.

McCord [67] administered carbon tetrachloride under a leak-proof bandage placed on the clipped abdominal skin of 3 animals (species not stated). Three times daily for 7 or 8 days, he injected either 7.5, 1.6, or 1.2 ml/kg of carbon tetrachloride under the bandages. The first animal (7.5 ml/kg/injection) died on the 7th day, the second (1.6 ml/kg/injection) died on the 8th day, and the third (1.2 ml/kg/injection) was killed after the 7th day. Autopsies were limited to macroscopic observations. Subcutaneous necrosis was evident in the areas where the carbon tetrachloride had been applied, the livers showed a dark purplish mottling, and inflammation was seen throughout the body of each animal.

(b) Chronic Inhalation Effects

An experiment was reported by Prendergast et al [68] in which 15 rats, 15 guinea pigs, 3 rabbits, 2 dogs, and 3 monkeys were exposed to carbon tetrachloride at 82 ppm for 8 hours/day, 5 days/week for a total of 30 exposures. The report also included the results of exposing similar groups of animals to carbon tetrachloride at 10 ppm or 1.0 ppm for 90 days or a total of 2,160 hours of continuous exposure. Weight losses or decreased growth occurred with all species under each exposure condition except for rats at 1 ppm.

The lungs of all animals repeatedly exposed at 82 ppm showed interstitial inflammation or pneumonitis and a high percentage of the livers of all species except dogs had a mottled appearance. Fatty changes were most severe in the livers of guinea pigs, then rats, then rabbits, then dogs, and least severe in monkeys. Livers of guinea pigs exposed at 82 ppm showed fatty infiltration, fibrosis, bile duct proliferation, hepatic cell degeneration and regeneration, focal inflammatory cell infiltration, alteration of lobular structure, and early portal cirrhosis. Three guinea pigs died during the experiment, 1 each after 20, 22, and 30 exposures, and 1 monkey died after seven exposures. [68]

Exposures at 10 ppm for 90 days of continuous exposure resulted in a "high incidence" (not explained) of enlarged and discolored livers in all species except dogs. [68] Liver changes were found in all species by microscopic examination. The changes included fibroblastic proliferation, collagen deposition, hepatic cell degeneration and regeration, and alteration of the structure of the liver lobule. Liver fat content of exposed guinea pigs averaged 35.4% (SD of 10.7%) compared to the control

average of 11.0% (SD of 3.6%). [68] Liver enzymatic activities of rats and guinea pigs, the most affected species, were normal except for a moderate reduction in succinic dehydrogenase. The other enzymes studied were reduced nicotinamide adenine dinucleotide (NADH), reduced nicotinamide adenine dinucleotide phosphate (NADPH), lactic dehydrogenase (LDH), and glucose-6-phosphate dehydrogenase (G6PD).

Specific pathological changes attributable to the continuous exposure at 1.0 ppm were not observed. The fat content of the livers of the guinea pigs averaged 9.7% (SD 2.4%) compared to 11.0% (SD 3.6%) in controls. [68]

Smyth et al [56] and Smyth and Smyth [57] reported on monkeys, rats, and guinea pigs exposed to carbon tetrachloride for 8 hours/day, 4-6 days/week for periods of time up to 321 days. Carbon tetrachloride atmospheres were obtained by metered dilution of air saturated with carbon tetrachloride at different temperatures. Monkeys were exposed at 50 and 200 ppm, and rats were exposed at 50, 100, 200, and 400 ppm. Guinea pigs were first exposed at 50, 100, 200, and 400 ppm. Since all guinea pigs exposed at 100, 200, or 400 ppm died by 94 days of age (Table XI-8), the diet was changed and other guinea pigs were exposed at 25, 50, 100, and 200 ppm. The death rate of guinea pigs fed the new diet continued to be high (Table XI-8). Optic nerve degeneration was found in 1 or 2 guinea pigs exposed at each concentration, and fatty degeneration was found in the ocular muscle of 3 to 6 guinea pigs at each concentration. Mortality was not a significant outcome of exposure of rats and monkeys to the various concentrations of carbon tetrachloride.

Rats were killed periodically for study. Initially the 5 groups of rats each contained 24 animals. Evidence of regeneration of liver cells and of interstitial cell proliferation was found after 126 exposures at 50 ppm and developing liver cirrhosis was evident after 189 exposures. Splenocytes were increased in rats after 121 exposures. Some damage to the myelin sheath of the sciatic nerve was seen in a rat after 96 exposures, and in another after 121 exposures. Degenerative changes were seen in the eye muscles of 3 rats. There was some evidence of kidney damage in rats exposed at 50 ppm, but it was not marked in any animal. At 100 ppm, liver, kidney, and nerve damage similar to that observed at 50 ppm became apparent after 20 exposures but did not develop to a greater extent than in rats exposed at 50 ppm. Splenocytes were increased after 49 exposures and increased pigment, not seen in rats exposed at 50 ppm, became noticeable in rats after 107 exposures at 100 ppm. Some necrosis was seen in rat livers by these investigators [56,57] after 20 exposures at 200 ppm. Cellular regeneration was apparent after 115 exposures, and cirrhosis after 150 exposures. Other pathological developments that occurred at lower exposure concentrations also occurred in rats at 400 ppm but they were more severe with the increased exposure. Two rats were found with optic nerve degeneration.

The exposure history of the monkeys is shown in Table XI-9. Fatty changes without evidence of degeneration were found in the livers after 62 exposures at 50 ppm. After 188 exposures at this concentration, there was evidence of adaptation and the livers appeared less abnormal than had been observed earlier, and after 225 exposures and 28 days' rest, the liver appeared practically normal. The kidneys appeared normal at 188 days, but

cloudy swelling was seen at 225 days; this improved with 28 days of rest. Spleen and nerve tissue appeared normal in all the monkeys exposed at 50 ppm.

At 200 ppm, evidence of liver damage with marked increase in interstitial cells and cellular infiltration into septa was observed after 62 exposures. After 225 exposures, this degeneration had not progressed, no cirrhosis was found, and there was no evidence of regeneration. The liver of a monkey examined 28 days after the last of 225 exposures appeared normal. In the kidneys of monkeys, light granular swelling without definite tubular degeneration was seen after 62 exposures at 200 ppm. There was increased secretion in the tubules, but little or no cell detritus and no desquamated cells. The animal examined 28 days after the last of 225 exposures had normal kidneys except for increased tubular secretion. There were some slight fatty changes in the ocular muscle and in the sciatic nerve. Other organs appeared normal. [56, 57]

In a chronic exposure study reported by Adams et al, [69] guinea pigs and rats were exposed at 5, 10, 25, 100, 200, and 400 ppm for 7 hours/day, 5 days/week for up to 184 exposures over a period of 258 days. The number of animals involved in each exposure and the number of animals surviving each exposure were not always reported. Eight or 9 guinea pigs of each sex were apparently used at most concentrations. Fifteen rats of each sex were used at concentrations of 25 ppm or more, 20 of each sex at 10 ppm, and 23 females and 26 males were exposed at 5 ppm. Numerous biochemical and organ weight measurements and microscopic findings were reported but it was not possible to determine from the report which measurements were omitted at the different concentrations. Consistent

responses in guinea pigs that were reported were increased liver weights at all exposure concentrations, a moderate amount of fatty degeneration at 10 ppm and above, and a moderate amount of liver cirrhosis at 25 ppm or more. Increased liver weights of rats occurred at all exposure concentrations of 10 ppm or more, accompanied by fatty degeneration. Liver cirrhosis was not detected in rats at exposures below 50 ppm.

Chronic exposures of rabbits were also studied by Adams et al. [69] One or 2 rabbits of each sex were reported to have survived exposures at 10, 25, 50, and 100 ppm. Liver weights were not increased by exposure at 10 ppm, but were increased by exposures at 25 ppm or more. Moderate fatty degeneration of the liver with cirrhosis developed after 178 exposures in 248 days at 25 ppm. Effects observed at lower concentrations were also observed at 50 and 100 ppm. In addition, decreased growth and increased kidney weights were observed and blood clotting time, indicative of liver injury, increased 1.5-2 times by exposures to carbon tetrachloride at 50 and 100 ppm. [69]

Some indications of microscopic liver changes were seen in 2 monkeys exposed to carbon tetrachloride at 100 ppm by Adams et al. [69] Body weight loss was the only abnormal finding reported in monkeys exposed to carbon tetrachloride at 50 ppm and no abnormal findings were reported in 2 others exposed at 25 ppm. The monkeys were exposed 148-198 times for 7 hours each time.

(c) Carcinogenesis

Induction of hepatomas in mice of the C3H and A strains was reported by Edwards [70] in 1941. The mice were fed 0.1 ml of a 40% solution of carbon tetrachloride in olive oil by stomach tube 2 or 3 times/week for a

total of 23-58 feedings and autopsied 2-147 days after the last feeding. (Body weights were not given, but if the mice weighed about 25 grams, the doses would have been about 1.5 ml/kg body weight.) This dose caused liver necrosis, and eventually cirrhosis. Hepatomas were found in 126 of 143 C3H strain mice and in all 54 A strain mice. The normal incidences of hepatomas in mice of comparable age (11-12 months) were 10% in the C3H strain and 0.5% in the A strain. Administration of olive oil to control animals did not increase the incidence of hepatomas above normal.

Subsequent reports of the experiment in 1942 by Edwards and Dalton [71] and Edwards et al [72] included more data from these strains and also data on 3 additional strains (Y, C, and L) that had normal hepatoma incidences of less than 2% at 12-16 months of age. Hepatoma incidences of 60, 82, and 47% in Y, C, and L strains, respectively, were reported after carbon tetrachloride treatment. Aliquots of mice were killed periodically after one or more doses of carbon tetrachloride, and all were killed before one year of age. Regenerative processes were observed throughout the experiment and atypical mitotic forms such as triple mitoses were frequent. Large cells with a peculiar, faintly basophilic reticulated cytoplasm and small nuclei were seen often in the livers of mice treated for one month or more. These cells were concentrated along strands of fibrous tissue. The hepatic tumors, described in detail by the investigators, [71] were usually multiple, as many as 10 in each liver. Neither invasion of blood vessels by hepatoma nor metastases were seen. Neither adenocarcinomas nor hemangioendotheliomas were present in any of the livers. The authors did not find evidence that tumors were induced in any other organ.

Rudali and Mariani [73] conducted an experiment in which 30 XVII Ivry strain mice were fed by stomach tube 0.1 ml of a 40% solution of carbon tetrachloride in oil, 2-3 times/week. Spontaneous liver tumors had not been observed up to this time in this strain of mice which was used by the Institut de Radium. Twenty-one animals were used to study the progress of the lesions for up to 66 days. Nine animals were given 48 carbon tetrachloride doses over 118 days. These 9 animals were autopsied after 132, 143, 232, 234, and 310 days. Microscopic adenomas were found in the first 4 mice. In each of the 5 mice killed after 310 days, macroscopic tumors were found and 4 of these had signs of malignancy. No metastases were found.

Effects of size and spacing of multiple doses of carbon tetrachloride on induction of hepatomas were reported by Eschenbrenner [74] in 1944. Doses of carbon tetrachloride administered were 1.6, 0.8, 0.4, 0.2, and 0.1 ml/kg body weight. Each dose was dissolved in olive oil and 0.005 ml/kg of the solution was administered by stomach tube. At each dose level, 5 groups of strain A mice were used to vary the intervals between doses by 1, 2, 3, 4, or 5 days. Each mouse was given 30 doses. Each of the doses had been found previously to cause central necrosis of the liver lobules. All animals were examined for hepatomas 150 days after the first dose. One mouse with hepatoma was found among 60 mice dosed daily. Eighteen mice with hepatomas were found among 60 mice dosed every other day, and with this dosing interval, there was an increased incidence of hepatomas as the magnitude of the individual doses of carbon tetrachloride increased. With intervals of 3 days between doses, 37 mice with hepatomas were found among 60 treated mice, and there was no apparent relationship to

the magnitude of the individual doses. With intervals of 4 days between doses, 55 mice with hepatomas were found among 75 treated mice, and again there was no relationship to the magnitude of the individual doses. Twenty-five mice with hepatomas were found among 44 mice treated at 5-day intervals, and there appeared to be a relationship to the magnitude of the individual doses. No hepatomas were found among 28 control mice that received olive oil without carbon tetrachloride. Three spontaneous hepatomas which differed from the induced tumors in color and microscopic characteristics were found, one in a control animal and 2 in experimental animals.

Eschenbrenner and Miller [75] reported in 1946 that single oral doses of carbon tetrachloride of 12.5 μl/kg or more caused liver cell necrosis in both male and female strain A mice. Doses of 6.25 μl/kg did not result in any observations of liver cell necrosis. Doses of 12.5 μl/kg resulted in observable liver cell necrosis in 1 of 8 mice examined. All higher doses caused liver cell necrosis in all mice examined. The investigators then administered 120 daily doses of 6.25, 12.5, 25, or 50 μl/kg. Each dose of carbon tetrachloride was dissolved in olive oil and 5 ml/kg of the solution was administered by stomach tube. The mice were examined one month after the last dose when they were 9 months old. No hepatomas were found in the mice given the nonnecrotizing doses of 6.25 μl/kg. All mice given the higher, necrotizing doses had hepatomas. Other groups of mice were given 30 necrotizing carbon tetrachloride doses of 100, 50, or 25 μl/kg at 4-day intervals. Very small hepatomas were found by microscopic examination in 2 of 10 mice given doses of 25 μl/kg. Larger

hepatomas were found macroscopically in two-thirds of the mice given the higher doses at 4-day intervals.

Transplantation of tumors induced by carbon tetrachloride has succeeded in some cases. One hepatoma from an A strain mouse was successfully transplanted and the subcutaneous transplants were invasive. [71] This tumor, which was first transplanted 6 months after the donor animal had received the last of 36 doses of carbon tetrachloride, was carried through at least 4 transplant generations. Transplantation of 7 other tumors, 3 from strain A and 4 from C3H mice, was unsuccessful in this experiment. The number of carbon tetrachloride doses and the examination times relative to the last dose were not reported for other mice of strain A and mice of strain C3H from which 7 hepatoma transplants were unsuccessfully attempted. [71]

Andervont and Dunn [76] reported in 1952 that there were no successes with 1-4 transplantations of each of 8 hepatomas that were induced in I strain mice by 22 weekly 0.25-ml oral doses of 4% carbon tetrachloride in olive oil (approximately 0.4 ml/kg). The mice were 3-9 months old when the experiment started. The ages of the donor mice at the time the transplantations were made were not reported.

In a later experiment with C3H mice, reported in 1955 by Andervont and Dunn, [77] and in 1958 by Andervont, [78] 28 of 30 tumors from carbon tetrachloride treated mice grew when transplanted. The mice had received, one week apart, two 0.2-ml oral doses of a 2% solution of carbon tetrachloride in olive oil (approximately 0.16 ml/kg), and subsequently they received, at weekly intervals, 17 doses of a 3% solution of carbon tetrachloride. The ages of the mice at the beginning of the experiment

were 3.5-7.5 months. [78] The time intervening between the last dose of carbon tetrachloride and the transplantation of the tumors was not given. However, for the tumors described in detail, the ages of the donor mice were given as 11, 12, 12, and 14 months indicating that as much as 2.5-5 months could have elapsed between the end of dosing and the tumor transplantation. The C3H strain had a substantial incidence of spontaneous hepatomas, 10% at 11-12 months of age, [70] and up to 50% at older ages, [70,78] and the spontaneous hepatomas of this strain had been successfully transplanted. [76]

Successful transplantation of hepatomas induced by carbon tetrachloride in a strain of mice in which spontaneous hepatomas had not been observed was reported by Leduc and Wilson [79] in 1959. Carbon tetrachloride was administered to BUB strain mice by stomach tube in doses of 0.1 ml of a 40% solution in olive oil, 3 times/week for a total of 45-66 doses. About 1/3 of the mice were given iv 0.2 ml/day thorotrast, a thorium containing x-ray contrast medium, on 3 days before carbon tetrachloride administration was started and X-ray pictures were taken at 2-4 week intervals for detection of tumors. No hepatomas were found in 20 control mice examined 192-514 days after injection of thorotrast only, but hepatomas were found in mice treated only with carbon tetrachloride. Two transplantations were attempted from mice that had not been given thorotrast but had been treated for 50-52 weeks with carbon tetrachloride. These transplants which were made 12 days and 11 weeks after the last carbon tetrachloride dose were not successful. Successful transplantations were made of 5 hepatomas from a thorotrast-treated mouse that had been given 45 doses of carbon tetrachloride and killed 8 months after the last

dose. The authors commented on the ability of thorotrast to cause vascular tumors in the liver and other organs, but concluded from their data that thorotrast did not have an important role in development and transplantability of these hepatomas.

Hepatocellular carcinomas, less than 5 mm in size, were found and reported in 1967 by Reuber and Glover [80] in Buffalo strain rats given carbon tetrachloride subcutaneously twice weekly for 12 weeks at a dose of 0.65 ml/kg. In another study reported by Reuber and Glover [81] in 1970, male rats of the Japanese, Osborne-Mendel, Wistar, Sprague-Dawley, and Black strains were injected subcutaneously twice weekly until death with carbon tetrachloride at a dose of 1.3 ml/kg. The carbon tetrachloride was in corn oil solution. The Osborne-Mendel rats survived up to 105 weeks, Japanese rats up to 78 weeks, Wistar rats up to 68 weeks, Black rats up to 18 weeks, and Sprague-Dawley rats up to 16 weeks. Carcinomas were not observed in the Black and Sprague-Dawley rats, all of which died with severe liver cirrhosis at an early age. Some of the rats of the 3 longer-lived strains developed liver cell carcinomas; the frequency of carcinoma was 12 of 15 in Japanese rats, 8 of 13 in Osborne-Mendel, and 4 of 12 in Wistar rats. Incidences of carcinomas greater than 5 mm in these groups, were 8, 4, and 1, respectively.

Development of liver cell carcinomas in male and female Syrian golden hamsters after 30 weekly doses of a 5% solution of carbon tetrachloride in corn oil administered by stomach tube was reported in 1961 by Della Porta et al. [82] Ten hamsters of each sex were used in the experiment. They were initially 12 weeks old. During the first 7 weeks, the carbon tetrachloride dose was 0.0125 ml, and during the remaining 21

weeks of administration it was 0.00625 ml. Since the animals weighed about 100 grams, the doses were about 0.125 and 0.0625 ml/kg. One female died at the 10th week of administration, and 3 females and 5 males died or were killed between the 17th and 28th weeks. After all the doses were administered, the survivors were kept under observation for 25 additional weeks. During this time, 3 females died between weeks 41 and 54, and the rest were killed at week 55. Necrotic changes and hemorrhages involving the regenerated parenchyma were found in livers of animals that died within 48 hours of treatment. All animals that died during the time the doses were being given showed changes consistent with postnecrotic cirrhosis. One or more liver-cell carcinomas were found in each of the 5 males and 5 females examined 43-55 weeks after the first carbon tetrachloride dose.

Costa et al [83] exposed albino rats for up to 7 months at an unspecified inhalation concentration of carbon tetrachloride. The rats were killed serially 2-10 months after beginning of exposure. Thirty rats completed the experiment. Twelve of the rats were found to have adenocirrhosis and 10 had liver nodules measuring up to 1 cm which were microscopically diagnosed as incipient or established liver carcinomas. Established carcinomas were found in 5 livers and incipient carcinomas were found in 5 others.

(d) Teratogenesis and Mutagenesis

Smyth et al [56] and Smyth and Smyth, [57] in their chronic exposure study, observed 3 generations of rats exposed at 50, 100, 200, or 400 ppm carbon tetrachloride. The numbers of animals in the second and third generations were few, and there was evidence of reduced fertility at 200 and 400 ppm. There was no report of incidences of embryonic or fetal abnormalities.

Schwetz et al [84] reported the effects of repeated exposures to carbon tetrachloride on rat embryo and fetal development. Groups of pregnant Sprague-Dawley rats were exposed at 300 and 1,000 ppm for 7 hours a day on days 6 through 15 of gestation. Day 0 of pregnancy was considered to be the day on which sperm was seen in vaginal smears. Concentrations of carbon tetrachloride in the exposure chambers were continuously monitored by combustion analysis. In addition, an infrared spectrophotometer with a multipath gas cell was used 3 times daily to analyze the chamber air and substantiate the concentration calculations.

A significant decrease in fetal body weights and crown-rump lengths as compared with controls was found when pregnant rats were exposed at 300 and 1,000 ppm on days 6 through 15 of gestation. Fetuses showed no anatomical abnormalities by gross examination but the incidence of microscopic sternebral anomalies was significantly increased by exposure at 1,000 ppm. Subcutaneous edema was found in 33% of the control litters, 59% of the litters from dams exposed at 300 ppm, and 50% of the litters from dams exposed at 1,000 ppm. The authors concluded that carbon tetrachloride was not teratogenic.

The conception rates, numbers of implantations, and litter sizes were normal, even though maternal body weights were significantly less than control body weights. [84]

(e) Metabolism and Mechanism of Action

When carbon tetrachloride is administered to mammals, it is metabolized to a small extent. The metabolites include chloroform, hexachlorethane, and carbon dioxide. [85-87] Some of the carbon tetrachloride metabolic products also are incorporated into fatty acids by

the liver and into liver microsomal proteins and lipids. [88,89] A consequence of carbon tetrachloride breakdown is lipoperoxidation in the liver. [90-92] The initial pathological injury occurs in the endoplasmic reticulum. [93] Within the endoplasmic reticulum cytochrome P-450, [94] protein synthesis, [95] and glucose-6-phosphatase [96] are markedly depressed within the first 6 hours.

The acute liver necrotic action of carbon tetrachloride is dependent upon its metabolic breakdown as evidenced by (1) little effect of carbon tetrachloride in chickens and ducks, neither of which metabolize it [97]; (2) the increased carbon tetrachloride effects from alcohols, chlorinated hydrocarbons, and barbiturates which increase its metabolism [98-101]; and (3) decreased activity of glucose-6-phosphatase and aminopyrine demethylase in the whole animal after carbon tetrachloride administration but insensitivity of these enzymes to the physical presence of carbon tetrachloride in vitro. [102]

McCollister et al [85] found that about 1/2 of the carbon-14 from labeled carbon tetrachloride inhaled by monkeys at 46 ppm for 139-300 minutes was later excreted in the expired air, mostly as carbon tetrachloride, and less than 5% as carbon dioxide. Only small amounts of labeled carbon appeared in the urine, not as carbon tetrachloride but either as urea or as an unidentified nonvolatile substance.

Butler [86] found that small amounts of chloroform were excreted in exhaled air of dogs after inhalation of carbon tetrachloride, and that the conversion could take place in tissue homogenates. Fowler [87] showed that both chloroform and hexachlorethane were metabolites of carbon tetrachloride administered to rabbits. Gordis [88] found

trichloromethylated fatty acids present in labeled liver lipid after feeding a mixture of chlorine-36 and carbon-14 labeled carbon tetrachloride to rats, and Rao and Recknagel [89] found a small amount of labeling of rat microsomal proteins and lipids after administering carbon-14 labeled carbon tetrachloride.

The metabolism of carbon tetrachloride is dependent upon microsomal hydroxylating enzyme systems such as cytochrome P-450. Reduction of cytochrome P-450 and probably of other microsomal enzymes by feeding low protein diets to rats decreased metabolism to carbon dioxide, [103] and decreased toxicity of carbon tetrachloride (the LD50 of orally administered carbon tetrachloride increased from 6.4 to 14.7 ml/kg). [104] Pretreatment with phenobarbital to stimulate cytochrome P-450 increased metabolism of orally administered carbon tetrachloride to carbon dioxide, markedly increased fat in the liver, and increased plasma concentrations of bilirubin compared to rats given only similar doses of carbon tetrachloride. [100,101]

Preexposure to DDT also has been shown to increase both the P-450 content of rat liver cells and the toxicity of carbon tetrachloride. [100, 104] Ethanol administration increased the activity of the liver hydroxylating enzyme system. Ethanol pretreatment increased the necrotic liver injury from carbon tetrachloride, but had less effect on the liver fat accumulation caused by carbon tetrachloride. [98,99,105,106]

Dogs chronically treated with phenobarbital for 12 months then given a single dose of carbon tetrachloride were similarly much more affected than dogs given only carbon tetrachloride as indicated by increased liver triglyceride content, increased diene conjugates, and increased SGOT. [90]

Carbon tetrachloride was found to promote lipid peroxidation in the liver of rats at oral doses of 0.3-1.0 ml/kg, but not at doses of 0.1 ml/kg. [91] Hashimoto et al [92] compared the lipid peroxidation in the liver of a woman who died with massive liver necrosis after drinking carbon tetrachloride with that of the liver from a victim who died from a traffic accident. They concluded on the basis of liver lipid conjugated dienes that extensive peroxidative degeneration had occurred as a result of the carbon tetrachloride poisoning.

(f) Effects of Alcohol with Carbon Tetrachloride

Robbins [107] conducted a series of experiments in which he measured the concentration of carbon tetrachloride in the exhaled air of dogs absorbing carbon tetrachloride from the alimentary canal under various conditions. Carbon tetrachloride in the exhaled air was determined by the thermal conductivity method (which was said to be accurate within 100-200 ppm). He found that when 10 or 50 ml of carbon tetrachloride was administered simultaneously with 40 ml of alcohol, the carbon tetrachloride concentrations in the exhaled air were considerably greater than when the carbon tetrachloride was administered alone. The concentration of the administered alcohol was not given. The author found that absorption of carbon tetrachloride was increased when given with alcohol but he did not consider that the increased toxicity was due to the increased absorption.

A higher mortality and more extensive liver necrosis in dogs was found when Gardner et al [62] administered 4 ml of 95% ethyl alcohol orally with 4 ml carbon tetrachloride than when carbon tetrachloride was given alone. The enhancing effect of alcohol did not occur when the carbon tetrachloride administered was 0.05 or 0.10 ml/kg.

Cornish and Adefuin [98] conducted a series of experiments to determine the effects of ethyl alcohol ingestion on carbon tetrachloride toxicity using serum enzymes (SGOT, SGPT, and isocitric dehydrogenase) and liver morphology as toxicity determinants. In all experiments, 2 groups of 6 rats each were used. In each experiment 5 ml/kg of ethyl alcohol was administered orally to the 6 rats of one group; the 6 rats of the other group did not receive any alcohol. Except for the alcohol treatment, the 2 groups of rats in each experiment were treated alike.

Exposures to carbon tetrachloride for 2 hours at 10,000 ppm caused marked degenerative fatty infiltration of the livers of all exposed animals, whether or not they were given ethanol. With exposure to carbon tetrachloride for 2 hours at 1,000 ppm, the livers showed degenerative fatty infiltration, but necrosis was not observed, and there were no increases in serum enzyme activities. Effects similar to these were observed when ethanol was administered 2 hours before exposure to carbon tetrachloride at this level. However, when ethanol was administered 16-18 hours before the carbon tetrachloride exposure, more severe effects were found. In addition to degenerative fatty infiltration, there was liver cell necrosis, and the activities of all 3 serum enzymes were elevated at 48 hours after exposure.

Carbon tetrachloride exposures for 2 hours at concentrations of 250 ppm or less caused no changes from controls in either serum enzyme activities or liver morphology. When ethanol was administered 16-18 hours before the carbon tetrachloride exposures at 100 and 250 ppm, a slight increase in liver lipid was found by microscopic examination. With exposures to carbon tetrachloride at 25 or 50 ppm for 2 or 8 hours, no

changes from controls were found, with or without ethanol pretreatment.

Ethanol treatments without carbon tetrachloride exposure caused no changes from controls in the serum enzymes or liver structure.

Correlation of Exposure and Effect

Symptoms referable to gastrointestinal and central nervous disturbances have been found to occur early in exposure to carbon tetrachloride and at relatively low levels of exposure. [24,31,33,54] Nausea, vomiting, belching, drowsiness, and headaches were found by Elkins [54] in surveys of workers exposed at 10-25 ppm in one factory and at 35 ppm (10-80) in another. Similar effects were found by Kazantzis and Bomford [59] in workers exposed to carbon tetrachloride between 45 and 97 ppm. These effects subsided when concentrations were reduced to 9 ppm or less.

Eye irritation and dysfunction were reported in some cases of occupational exposures to carbon tetrachloride. [27-29,56-58] Smyth et al [56] and Smyth and Smyth [57] found restricted visual fields in 4 workers whose 8-hour TWA exposures were estimated at 7, 10, 10, and 24 ppm with peak exposures of 66, 26, 173, and 232 ppm, respectively.

Various eye abnormalities were found by Moeller [58] in 62 workers in a locksmith shop where carbon tetrachloride concentrations of 6.4-9.5 ppm were found. Details of the sampling and analysis were not reported. Among the 62 workers, 70% had reduced visual fields and 15 individuals had visual color fields deviating from normal. Similar eye abnormalities were reported in other occupational cases where the air concentrations of carbon tetrachloride were not measured. [27-29]

Impaired function and kidney and liver tissue changes have been

reported in cases of both acute and chronic exposure to carbon tetrachloride. [20,26,30-40,53,61] Renal tubular necrosis and severe centrilobular liver necrosis were found in autopsy examinations of 4 fatalities among 20 cases of carbon tetrachloride exposures studied by Guild et al. [31] In all 20 cases, anuria developed 1-7 days following exposure.

Elevated serum transaminases and an enlarged discolored liver with fatty degeneration were observed in a 54-year-old man who had been using carbon tetrachloride in his work for 4 years. [37] Air samples at 16 locations in the plant contained carbon tetrachloride at concentrations of 10-100 ppm. No predisposing diseases or other etiological factors were found in a review of the patient's medical history.

Elevated serum aldolase and SGOT were compared with tissue changes in 2 men exposed to an unspecified amount of carbon tetrachloride. [35] In both cases, serum enzymes were elevated when the men were hospitalized with gastrointestinal and central nervous system symptoms resulting from carbon tetrachloride exposure. Large areas of centrilobular necrosis were found in one man and degenerative cellular changes were found in the other man in liver biopsies.

Increased serum iron and GDH were found in 51 workers with 5 or more years of periodic exposure to carbon tetrachloride. [61] Air samples in the work area contained carbon tetrachloride concentrations of 6.3 ppm at the beginning of a workshift and 9.5 ppm, 5 minutes after the beginning of the work period. The data were not sufficient to determine whether the environmental concentrations were always near the reported range. Serum iron and GDH were the only findings in clinical examinations and a series

of biochemical studies of the 51 exposed workers which varied from findings in a comparison group of 27 persons. The serum iron was elevated 23% and the GDH was elevated 92%. [61]

Serum iron was depressed in 2 of 4 subjects experimentally exposed by Stewart et al [26] at 49 ppm carbon tetrachloride for 70 minutes, but was not depressed in any subjects exposed at 10 or 11 ppm carbon tetrachloride for 180 minutes.

Zinc and thymol turbidity, serum bilirubin, and SGOT were elevated in a group of workers in a polyfluorocarbon manufacturing plant who handled carbon tetrachloride, compared to workers who did not handle carbon tetrachloride. [36] Urobilinogen was found in the urine of 6 of 16 carbon tetrachloride handlers and in none of the nonhandlers of carbon tetrachloride. No estimate of the exposure of the 16 workers was reported.

Smyth et al [56] and Smyth and Smyth [57] noted elevated icteric indices in 11 workers with estimated 8-hour TWA exposures of 26-39 ppm. Icteric indices were normal in 11 other workers with estimated 8-hour TWA exposures of 5-24 ppm.

Three human cases of hepatic carcinoma, 2 after repeated exposure, and 1 after a single exposure, have been reported. [38-40] In each case, the diagnosis was confirmed at autopsy. The extent of the exposure to carbon tetrachloride in these cases was only reported qualitatively and no definitive causal relationship between carbon tetrachloride and the resultant carcinomas was established, but data from animal studies show that carcinomas have resulted in a variety of experimental animals with various routes of intake. [70-83]

Reuber and Glover [81] found carcinomas greater than 5 mm occurring in 3 strains of rats injected 1-2 times a week with 1.3 ml/kg of carbon tetrachloride subcutaneously until the animals died. Japanese, Osborne-Mendel and Wistar strain rats had carcinoma frequencies of 80%, 60%, and 33%, respectively; the incidences of carcinomas greater than 5 mm were 53%, 30%, and 8%, respectively.

Established and incipient carcinomas were found by Costa et al [83] in albino rats exposed by inhalation to carbon tetrachloride for up to 7 months. The concentrations of carbon tetrachloride were not reported. Twelve of 30 rats surviving the experiments had adenocirrhosis and liver nodules measuring as large as 1 cm. Incipient or established carcinomas were found in 10 of these.

Liver damage within the first 120 hours after a single 0.125 ml injection of carbon tetrachloride was directly related to serum OCT activity in rats. [64] In guinea pigs serum OCT activity reflected liver damage but there was no dose-response relationship with doses of 5, 25, 50, 75 and 150 mg/kg. [65]

Intermittent carbon tetrachloride exposures (7 or 8 hours/day, 5 days/week) had adverse effects on guinea pigs and rats at concentrations of 10 ppm and guinea pigs at 5 ppm. [69] Female guinea pigs exposed to carbon tetrachloride at 5 ppm had increased liver weights relative to body weights after 143 exposures.

Both guinea pigs and rats exposed at 10 ppm for 7 hours/day, 5 days/week, 136 times, had increased liver weights and liver lipid contents compared to controls. [69] Fatty degeneration of the livers was also observed. These effects were more pronounced at 25 and 50 ppm. Exposures

at 50 ppm caused depression of growth, increased liver and kidney weights, and increased total liver lipid content. Fatty degeneration and cirrhosis of the liver, and swelling of the renal tubules were also observed. [69]

Intermittent exposures by Smyth et al [56] and Smyth and Smyth [57] of rats and guinea pigs to carbon tetrachloride at concentrations of 50 and 100 ppm affected liver weight, liver lipid content, and kidney weights. Fatty degeneration and cirrhosis of the liver, evidence of regeneration of liver cells, and some swelling of the kidneys were also observed.

Four monkeys exposed 5 hours/day, 4-6 days/week to carbon tetrachloride at 50 ppm had slight fatty liver changes at 62 days, evidence of adaptation at 188 days, and practically normal livers 28 days after the last of 225 exposures.

Continuous exposure of guinea pigs, monkeys, rats, and dogs to carbon tetrachloride at 10 ppm for 90 days caused depressed growth in all species. [68] Monkeys had an emaciated appearance and suffered hair loss. All animals, except the dogs, had enlarged or discolored livers, but the tissue structure was not well described or compared to controls. The enzymatic activities of the livers of the rats and guinea pigs, the most affected species, were normal; however, the fat content of the livers of exposed guinea pigs was 35% compared to 11% in the controls.

In a similar experiment, where the same species were exposed continuously for 90 days at 1 ppm, there were no signs of toxicity during testing. [68]

Absorption of liquid carbon tetrachloride through the skin of humans and animals has been demonstrated experimentally. [48,66,67] Lapidus [66] found carbon tetrachloride in the blood, liver, and fat of 4 rabbits after

each had had 1 ear immersed in carbon tetrachloride. The immersion times for the 4 rabbits were 5, 6, 8, and 9 hours.

Human subjects who each immersed one thumb in liquid carbon tetrachloride for 30 minutes had measurable amounts of carbon tetrachloride in exhaled air 5 hours later. [48] The investigators concluded that the amount of carbon tetrachloride that could penetrate the skin depended on the type of skin, the area exposed, and the duration of exposure. Using the data from the experimental exposure of 1 thumb, they estimated that the amount of carbon tetrachloride absorbed during topical exposure of both hands for 30 minutes would be equivalent to a vapor exposure of about 10 ppm for 3 hours.

Absorption of liquid carbon tetrachloride through the skin could have been a contributing factor in many occupational cases. [22,45,54,56,57,59,60] However in most reports it was not considered by the investigators, although its occurrence was evident because of the nature of the work being performed.

Alcohol was a concomitant factor in many of the human cases of carbon tetrachloride poisoning, especially in cases where severe liver and kidney damage occurred. [31,32,34,50-53] That ingestion of ethyl alcohol can increase the hepatoxicity of carbon tetrachloride has been demonstrated by animal experiments. Marked degenerative fatty infiltration and early centrilobular liver necrosis were found in rats given ethyl alcohol (5 ml/kg) orally 16-18 hours before exposure to carbon tetrachloride at 1,000 ppm for 2 hours. These changes did not occur in controls exposed only to carbon tetrachloride. [98] With 2-hour exposures to carbon tetrachloride at 100 ppm, SGOT activity was increased in rats given alcohol before

exposure, but not in those which were not given alcohol. Serum enzymes or liver tissue were not altered in rats pretreated with alcohol and exposed at 25 or 50 ppm carbon tetrachloride for 2 or 8 hours.

Similar potentiating or augmenting effects including increased liver enzyme activity, increased liver triglyceride content, and increased carbon tetrachloride metabolism were found when carbon tetrachloride exposure occurred together or in temporal proximity with exposure to barbiturates or chlorinated hydrocarbons such as DDT. [90,94,103,104]

A summary of concentration response data for inhalation exposures to carbon tetrachloride is presented in Table XI-10.

# IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION OF EXPOSURE

## Environmental Concentrations

In 1935, Smyth and Smyth [57] reported concentrations of carbon tetrachloride in the air of 23 drycleaning establishments, 5 carbon tetrachloride manufacturing plants, 3 fire extinguisher manufacturing plants, and 5 plants where carbon tetrachloride was either repacked or used in chemical processes, one of which used a mixture of 30% carbon tetrachloride and 70% ethylene dichloride. Fifteen of the drycleaning plants used an unspecified mixture of carbon tetrachloride and trichloroethylene in open type drycleaners. A portable 50-cm interference refractometer, calibrated for the appropriate mixture, was used for all determinations. The measurements, which were essentially instantaneous observations of carbon tetrachloride concentrations, were taken at intervals of 10 seconds to 5 minutes, depending on the variation of the process. The method was not specific for carbon tetrachloride. Tables XI-3 and XI-4 summarize the concentrations found in different workplaces in plants where the exposure was to carbon tetrachloride. Average carbon tetrachloride concentrations were 59-84 ppm near closed systems, 21-650 ppm near half-closed systems, and 72-300 ppm near open processes. In general, most concentrations were less than 100 ppm, but on some excursions they were as high as 7,900 ppm. [57]

A study of carbon tetrachloride concentrations in a film-coating room of a motion picture plant, using a portable combustion apparatus, [23] was reported by Heimann and Ford. [21] The coating wax was carried in a solution of 85% carbon tetrachloride and 15% ethyl alcohol. Carbon

tetrachloride exposure concentrations of 33, 61, 67, 72, 117, and 124 ppm (average, 79 ppm) were found.

The Kentucky Bureau of Industrial Hygiene investigated an outbreak of an illness resembling food poisoning in a parachute factory in 1944 and discovered that it was associated with the use of carbon tetrachloride for cleaning the parachute fabric. [60] One week after measures were taken to alleviate the situation, air samples were taken with a halogenated hydrocarbon indicator commonly used in plant surveys at that time and the carbon tetrachloride concentrations found in the vicinity of the inspection tables were 163 and 194 ppm.

Concentrations of carbon tetrachloride at which workers were exposed in 7 plants using carbon tetrachloride for various purposes were studied by Elkins. [54] The samples were collected in amyl acetate, the solution was burned, and the liberated chloride was determined by titration with silver nitrate. [55] The findings in these plants are summarized in Table IV-1.

In 1959, Elkins [108] published additional data on carbon tetrachloride exposure concentrations found in 30 work places. These data are presented in Table IV-2.

Breathing zone exposures to carbon tetrachloride were studied with a portable halide meter in a plant where carbon tetrachloride was used in the manufacture of polyfluorocarbon refrigerants. [36] The process was virtually automated and enclosed, but exposures of workers occurred when road tankers were unloaded or when storage tanks were cleaned or repaired. Draining of contaminated water from a carbon tetrachloride storage tank resulted in exposure concentrations in excess of 600 ppm. Fitters dismantling recovery columns during a maintenance operation were exposed to

carbon tetrachloride at 75-600 ppm, with "the main" exposure level at 210 ppm. Concentrations of carbon tetrachloride in the breathing zone of a tank-truck driver on top of the tanker and during the hose-connecting process ranged up to 30 ppm.

TABLE IV-1

CONCENTRATIONS OF CARBON TETRACHLORIDE IN 7 INDUSTRIAL PLANTS

| Type of Operation | $CCl_4$ Concentration, ppm Average | Range |
|---|---|---|
| Drycleaning (spotting) | 35 | 10-80 |
| Drycleaning | 65 | 35-115 |
| Drycleaning | 25 | 15-60 |
| Drycleaning | 20 | 5-40 |
| Multigraph cleaning | 85 | 40-375 |
| Multigraph | -- | 10-25 |
| Unspecified | 25 | 10-30 |

Derived from Elkins [54]

Paulus et al [109] surveyed the fumigation procedure used by government employees involved in shelled corn storage. The fumigant used was composed of 80% carbon tetrachloride and 20% carbon disulfide. Carbon tetrachloride concentrations were determined in the bins after fumigation with a halide detector. Because of wide fluctuations in the halide meter responses at higher concentrations, the ratio of carbon tetrachloride to carbon disulfide in duplicate samples was used to estimate carbon tetrachloride concentrations during application. The data presented in Table IV-3 show that during fumigation, when the fumigators wore full-face gas masks with organic vapor canisters, about 40% (14 of 36 measurements)

TABLE IV-2

CONCENTRATIONS OF CARBON TETRACHLORIDE IN 28 PLACES OF WORK

| Type of Operation | Concentration, ppm Avg. | Max. | Comment |
|---|---|---|---|
| Balloon cementing | 40 | 50 | No illness |
| | 65 | 70 | Nausea |
| | 45 | 45 | |
| Carburetor jet testing | 115 | 130 | Illness reported |
| Cement mixing | 25 | ... | Illness reported |
| Drycleaning | 20 | 40 | Nausea |
| | 25 | 30 | Complaints |
| | 25 | 60 | Complaints |
| | 35 | 155 | Much illness |
| | 35 | 45 | Illness |
| | 10 | 15 | |
| | 120 | 200 | Compensation case |
| | 45 | 90 | |
| | 65 | 115 | |
| | 10 | 30 | |
| Gasoline tank cementing | 15 | 25 | No illness |
| | 30 | 35 | No illness |
| | 40 | 50 | |
| Gas mask cleaning | 3 | ... | |
| Jewel cleaning | 40 | 45 | Nausea |
| Metal cleaning | 45 | 95 | |
| Motor cleaning | 50 | 70 | |
| Multigraphing | 15 | 25 | |
| | 80 | 375 | Illness |
| | 190 | 225 | Illness |
| Nozzle cleaning | 10 | 16 | |
| Pitch spraying | 20 | 40 | |
| Tape coating | 25 | 30 | Complaints |
| Jacket cleaning | 130 | 350 | Serious illness |
| Broaching | 30 | 40 | Nausea, vomiting |

Derived from Elkins [108]

TABLE IV-3

FREQUENCY OF OCCURRENCE OF CCl 4 CONCENTRATIONS
IN BREATHING ZONES OF GRAIN FUMIGATORS

| Concentration Range, ppm | Operation | | |
|---|---|---|---|
| | Spraying (masks) | Tending Equipment | Inspecting Bins |
| 0-25 | | 15/43 | 18/33 |
| 26-50 | | 9/43 | 2/33 |
| 51-150 | | 9/43 | 12/33 |
| 151-375 | | 7/43 | 1/33 |
| 375+ | | 3/43 | |
| 0-1,500 | 14/36 | | |
| 1,501-4,500 | 8/36 | | |
| 4,501-15,000 | 9/36 | | |
| 15,000+ | 5/36 | | |

Adapted from Paulus et al [109]

of the estimated concentrations were reported to range from 0 to 1,500 ppm. Five of the 36 measurements were estimated at more than 15,000 ppm.

Workers tending the equipment did not wear respiratory protection. About 33% (15 of 43 measurements) of the estimates of the concentrations to which they were exposed ranged from 0 to 25 ppm and 3 of the 43 estimates were greater than 375 ppm. Workers inspecting previously fumigated grain bins also did not wear respiratory protection. About 50%, (18 of 33 measurements) of the directly measured concentrations at which they were

exposed were in the range of 0-25 ppm and only 1 measurement was greater than 150 ppm.

Environmental Sampling and Analytical Method

(a) Collection Methods

Most analytical methods are dependent on the effectiveness and reproducibility of the uptake of carbon tetrachloride 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, which has been used as a collection medium, is a polar adsorbent and shows pronounced selectivity in adsorbing polar molecules, particularly in preference to nonpolar molecules such as carbon tetrachloride. [110] A laboratory study indicated that water vapor in the workroom could displace carbon tetrachloride when sampling more than 3 liters of air through 1-inch silica gel tubes. [111]

More recently, activated charcoal has been used as a collection medium in conjunction with analysis by gas chromatography. [112] Charcoal is nonpolar and will generally adsorb organic vapors in preference to water vapor resulting in less interference from atmospheric moisture than with silica gel. [111]

Williams and Umstead [113] reported the use of porous polymer beads as a collection medium. With this sampling method, the same column was used for sample collection and gas chromatographic analysis. This method consolidated collection and analysis into one operation, but only one analysis could be made on each sample. The method has not been developed for field use.

Liquids have been used to collect chlorinated hydrocarbons from contaminated atmospheres. Elkins et al [55] used amyl acetate in a sampling train to collect carbon tetrachloride from sampled air. Midget impingers containing m-xylene have been used for collection in conjunction with gas chromatographic analysis. [114] Bubbler bottles containing a pyridine solution have been used for collection in conjunction with colorimetric analysis. [115] Impingers and bubblers present hazards from glassware and chemicals when used in personal sampling units for collection of breathing zone samples.

Other investigators have collected grab samples of contaminated atmospheres directly in a variety of containers ranging from plastic bags to hypodermic syringes. [116]

(b) Desorption Methods

When solid collection media are used, it is necessary to desorb the collected contaminant from the medium. Desorption from charcoal was studied by Otterson and Guy. [116] They recommended the use of different desorbing agents depending upon the comparative gas chromatograph retention times for the desorber and the contaminant. Carbon disulfide was determined to be the best desorbent for carbon tetrachloride collected in charcoal tubes.

(c) Analysis

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

(1) Chemical methods

The 3 chemical methods that have been used extensively are: 1) dechlorination of collected vapor samples with strong alkalis followed by titration of the chloride ion (alkaline hydrolysis) [108]; colorimetric measurement of the reaction products of carbon tetrachloride and pyridine heated in alkali solution (Fujiwara reaction) [117]; and 3) direct reading colorimetric indicators. [118]

The dechlorination method (alkaline hydrolysis) requires collection of the carbon tetrachloride-contaminated air by a suitable collection medium followed by alkaline hydrolysis in isopropyl alcohol, and titration of the liberated chloride with silver nitrate. [108] The percentage of chlorine hydrolyzed is determined by comparison between samples and known controls. A disadvantage is that it is not specific for carbon tetrachloride.

In the colorimetric analytical method based on the Fujiwara reaction, a stream of air containing carbon tetrachloride is passed through a bottle containing pyridine. [117] Potassium hydroxide and methylethyl ketone are then added to an aliquot of the sample, and this mixture is heated in a boiling water bath, cooled during a fixed time period, and the color developed is determined with a 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. [118] These are glass tubes packed with solid chemicals that change color when a measured and controlled flow of air containing carbon tetrachloride passes through the packed material. Depending on the type of detector

tube, the air may be drawn directly through the tube and compared with a calibration chart, or the air may be drawn into a pyrolyzer accessory prior to the detection tube. [118] In either case, the analysis is not specific for carbon tetrachloride since liberated halogen ions produce the stain and any halogen or halogenated compounds will interfere. Regulations on detector tubes (42 CFR 84.50) provide that measurements with colorimetric indicator tubes shall be correct within ±25% of the values read. There are commercially available detector tubes which fulfill this criterion.

(2) Physicochemical methods

Photodetection (halide meters), [119] infrared spectrometry, [120] and gas chromatography [116] are among the analytical methods that are based on the physicochemical properties of carbon tetrachloride.

Halide meters are made to detect the increased brightness of an a-c arc across metal electrodes when they are enveloped by an atmosphere contaminated with halogenated compounds other than fluorides. These instruments are sensitive to all halogens and halogenated compounds except fluorides and consequently they are not specific for carbon tetrachloride. Halide meters are suitable for continuous monitoring if carbon tetrachloride is the only halogenated contaminant present in the sampled air. [119]

An infrared spectrophotometer in conjunction with a suitable recorder can be used to record concentrations relatively instantaneous or continuously. With this method, concentrations are measured directly and it is not necessary to collect individual samples or to transport them to a laboratory for analysis. Infrared spectrophotometry has been used for continuous monitoring of industrial operations for chlorinated hydro-

carbons. There is the need to ensure 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] Infrared analysis is subject to interferences from other air contaminants and these interferences are not easily detected or resolved without substantial knowledge of infrared spectrophotometry.

Gas chromatography provides a quantitative analytical method which can be specific for different chlorinated hydrocarbons. [121] Every compound has a specific retention time in a given chromatograph column, but several compounds in a mixture may have similar retention times. This problem is easily overcome by altering the stationary phase of the chromatograph column or by changing the column temperature or other analytical parameters. Altering conditions will usually change the retention times and separate the components.

A mass spectrometer can be used subsequent to gas chromatography to more positively identify the substance present in a gas chromatographic peak. Linked gas chromatograph-mass spectrometer instruments perform this identification automatically. A charcoal capillary tube has been used to trap and transfer the material associated with a gas chromatographic peak to a mass spectrometer for qualitative identification when only unlinked units were available. [122]

(d) Conclusions and Recommendations

(1) Compliance Method

Based on review of air sampling and analytical methods, it is recommended that carbon tetrachloride in air samples be collected with activated coconut shell charcoal, desorbed with carbon disulfide, and

analyzed by gas chromatography. Although this system of measurement is indirect and requires collection and desorption prior to analysis, it has the following attributes:

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

(B) Estimation of exposure with personal samplers is easily achieved.

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

(D) Carbon tetrachloride can be identified in combination with many other compounds.

(E) At the sample volumes recommended, ie, 5-80 liters, interference by moisture is minimal.

(F) Sampling tubes and personal pumps are commercially available.

(2) Monitoring Methods

Exposure to carbon tetrachloride associated with its continuous and constant use can be monitored by infrared spectrophotometry or, if it is the only halogenated hydrocarbon in the workroom air, halide meters can be used. Air from representative work sites can be drawn directly into the infrared spectrophotometer or halide meter by a multiprobe sampling apparatus. A time-location study of the workroom at the different probe locations can be used to estimate peak, ceiling, and TWA exposures to carbon tetrachloride.

Direct reading colorimetric tubes (gas detection tubes) can be used as an inexpensive way to monitor carbon tetrachloride concentrations. The tubes must be used as instructed by the manufacturer.

Biologic Evaluation of Exposure

Carbon tetrachloride was found by Hamburger et al [41] in the blood of patients who had developed anuria following carbon tetrachloride poisoning. They used the reaction of carbon tetrachloride with pyridine as described by Fabre et al [44] for whole blood. The concentrations in the blood of 9 individuals ranged from 0.09-2.30 mg/liter. No information was available about the amount of carbon tetrachloride which had been absorbed by these patients. [43] Carbon tetrachloride was not detected by infrared analysis by Stewart et al [26] in the blood or urine of subjects exposed to carbon tetrachloride at 49 ppm for 70 minutes or 10-11 ppm for 180 minutes. The minimum amount of carbon tetrachloride added to either blood or urine which could be detected by the method they used was 5 ppm (5 mg/liter). There was no measurable excretion of carbon tetrachloride in the urine of monkeys exposed to carbon-14 labeled carbon tetrachloride at 46 ppm for up to 344 minutes by McCollister et al. [85] The concentration of carbon tetrachloride in the blood of these monkeys ranged up to 3.1 mg/liter. Most of the carbon tetrachloride absorbed by these monkeys was excreted unchanged in the expired air. Wells [18] found that most of the carbon tetrachloride he ingested was exhaled. He was able to measure carbon tetrachloride in his exhaled air up to 38.5 hours after he ingested 3 ml of carbon tetrachloride.

Carbon tetrachloride was measured by Stewart and Dodd [48] in the exhaled air of 3 human subjects who each immersed one thumb in beakers of carbon tetrachloride. The concentration ranges in the exhaled air were 0.03-0.09, 0.3-3.3, and 0.7-5.8 μg/liter at 10, 20, and 30 minutes of immersion, respectively. The thumbs were removed from the liquid at the end of 30 minutes and breath samples collected 5 hours later still had measurable amounts of carbon tetrachloride (0.1 μg/liter).

Concentrations of carbon tetrachloride in exhaled air of human subjects were studied by Stewart et al [26] during 5 hours following exposures to carbon tetrachloride at 49 ppm for 70 minutes and at 10-11 ppm for 180 minutes. Twenty-five minutes after the end of exposure at 49 ppm, carbon tetrachloride averaged about 20 μg/liter in the exhaled air, and in the subjects exposed to 10-11 ppm it averaged about 6 μg/liter. Five hours after the exposures, carbon tetrachloride ranged from 1 to 2.5 μg/liter regardless of the exposure concentration.

Concentrations of carbon tetrachloride in the breath of 2 patients who were accidentally exposed to carbon tetrachloride, 1 by inhalation and the other by ingestion, were studied by Stewart et al. [46,47] The amount of carbon tetrachloride absorbed was not known in either case. The initial concentration of carbon tetrachloride in the breath of the inhalation case following the exposure was 56 μg/liter. Carbon tetrachloride was still detectable in the patient's breath 2 weeks later. In the ingestion case, the concentration of carbon tetrachloride found in the breath about 3 hours after the ingestion was 2.0-2.5 mg/liter. A series of breath samples showed a progressive decrease in carbon tetrachloride concentration to 1.2 μg/liter. Analytical methods for carbon tetrachloride in air may be

sensitive enough to evaluate exposures by breath analysis at the recommended environmental standard, but experimental data to determine this have not been found. Carbon tetrachloride has a long life in the body and a variety of exposure conditions can result in the same exhaled breath concentrations. Data from experimental animals must be obtained and correlated with human data in order to estimate the magnitude of carbon tetrachloride exposure from concentrations in the breath. However, as a complement to air sampling, breath analysis can be useful to qualitatively determine carbon tetrachloride exposure.

# V. DEVELOPMENT OF STANDARD

## Basis for Previous Standards

The Sub-Committee on Threshold Limits of the National Conference of Governmental Industrial Hygienists (NCGIH) published a list in 1942 entitled, "Maximum Permissible Concentrations of Atmospheric Contaminants as Recommended by Various State Industrial Hygiene Units." [123] Thirteen states were listed as recommending 100 ppm for carbon tetrachloride. The listing was presented without comment other than that the tabulated values were not to be construed as recommended safe concentrations.

Various standards for carbon tetrachloride were the subject of discussion at the 7th Annual Meeting of NCGIH in 1944. [124] Manfred Bowditch, Director, Massachusetts Division of Occupational Hygiene, gave "temporary indisposition," indicated by nausea, as reason for a standard lower than 100 ppm. (Some of the data that were the basis for this statement were published by Elkins [54] in 1942, and by Bowditch [125] in 1943.) He reported that as a consequence, the Division of Occupational Hygiene of the Massachusetts Department of Labor and Industries proposed lowering the standard for carbon tetrachloride to 40 ppm. Other governmental agencies also considered 100 ppm ineffective and recommended a lower standard. [124,126]

A list of maximum allowable concentrations of atmospheric industrial contaminants compiled by Cook [126] in 1945 included the carbon tetrachloride values of 7 governmental agencies. These are presented in Table V-1.

TABLE V-1

CARBON TETRACHLORIDE STANDARDS OF GOVERNMENTAL AGENCIES

| Agency | MAC, ppm |
|---|---|
| California Industrial Accident Commission | 100 |
| Connecticut Bureau of Industrial Hygiene | 100 |
| Massachusetts Department of Labor and Industries | 50 |
| New York State Department of Labor | 75 |
| Oregon State Board of Health | 50 |
| Utah Department of Health | 100 |
| United States Public Health Service | 100 |

Derived from Cook [126]

These concentrations were all recommended as allowable for prolonged exposures, usually assuming a 40-hour workweek. [126]

In addition to tabulating these values, Cook [126] reported 100 ppm to be an accepted or tentative value based on the work published by Smyth et al [56] in 1936. However, in his discussion of carbon tetrachloride, Cook [126] wrote that since that publication there was an increasing amount of evidence of injury to health at lower concentrations and he recommended that exposures be at less than half the 100 ppm then being used.

The American Conference of Governmental Industrial Hygienists (ACGIH) (formerly NCGIH) adopted a list of "Maximum Allowable Concentrations of Air Contaminants for 1946" which was prepared by the Sub-Committee on Threshold Limits [127] and selected a value of 50 ppm for carbon tetrachloride based on Cook's recommendation. [126]

The ACGIH Committee on Threshold Limits reported in 1949 that it had received comments from outside the Conference that a value of 50 ppm for carbon tetrachloride was too low. [128] On the other hand, carbon tetrachloride was included in a list of substances for which a reduction of the limit had been suggested by members of the Conference.

The ACGIH recommended a TLV of 25 ppm for carbon tetrachloride in 1953. [129] A preface to future tables of threshold limits was adopted which defined the values as "maximum average atmospheric concentration of contaminants to which workers may be exposed for an 8-hour working day without injury to health." [129] The preface was modified in 1958 and included the statement that "They [threshold limit values] represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day after day, without adverse effect." [130]

The American Standard Maximum Acceptable Concentration of Carbon Tetrachloride (ASA Z37.17-1957), published in 1957, was 25 ppm for exposures not exceeding 8 hours daily with the understanding that variations should fluctuate around 10 ppm. [131] The 25 ppm was understood to be a ceiling below which all concentrations were to fall. It was partly based on the animal experiments reported by Adams et al [69] and partly on industrial experiences of members of the Committee.

The Documentation of Threshold Limit Values [132] which was published in 1962 by the ACGIH referred to the reports of Adams et al, [69] Heimann and Ford, [21] Kazantzis and Bomford, [59] and Elkins [54] in its support of the TLV for carbon tetrachloride of 25 ppm. From these data, it was considered that 25 ppm was low enough to prevent irreversible injury. [132]

At the annual meeting of the ACGIH in 1962, the Threshold Limit Committee recommended reducing the TLV for carbon tetrachloride to 10 ppm because there were "increasing indications" that exposure to carbon tetrachloride at 25 ppm was excessive. [133]

Tables of "Permissible Levels of Toxic Substances in the Working Environment" for many countries were published by the International Labour Office in 1970. [134] The reported carbon tetrachloride standards are presented in Table V-2. The USSR values (MAC) are absolute values never to be exceeded. They are set at a value which will not be expected to produce in any exposed person any disease or other detectable deviation from normal. Some other countries tend to follow this concept in setting their standards, while still others tend to follow the concepts of the ACGIH. The intent is indicated for some of the standards presented in Table V-2.

TABLE V-2

CARBON TETRACHLORIDE STANDARDS OF 10 COUNTRIES

| Country | Standard mg/cu m | Standard ppm | Qualifications |
|---|---|---|---|
| Czechoslovakia | 50 | 8 | Normal MAC |
| | 250 | 40 | Single short exposure |
| Finland | 160 | 25 | 8 hours continuous exposure |
| Hungary | 20 | | 8-hour average |
| | 100 | | 30 minutes |
| Japan | 10 | | |
| Poland | 20 | | |
| Rumania | 50 | | |
| UAR and SAR | | 100 | |
| USSR | 20 | | MAC |
| Yugoslavia | 65 | 10 | |

Derived from reference 134

The most recent documentation of the threshold limit values was published by the ACGIH in 1971. [135] The reports of Heimann and Ford, [21] Elkins, [54] Barnes and Jones, [36] Kazantzis and Bomford, [59] Markham, [45] Adams et al, [69] and Stewart et al [26] were referred to in support of the TLV of 10 ppm which had been adopted in 1962. Information that some workmen experienced nausea when average daily carbon tetrachloride exposures approached 25 ppm, whereas no difficulties were experienced at 10 ppm, based on a personal communication to the Committee, was used as additional support for the TLV. The TLV of 10 ppm was recommended with the caution that peak exposures, even of short duration, should not exceed 25 ppm.

The Occupational Safety and Health Administration, US Department of Labor, adopted ANSI standard Z37.17-1967 [136] as the federal standard for carbon tetrachloride (29 CFR 1910.1000). This standard is 10 ppm for an 8-hour TWA exposure, with an acceptable ceiling exposure concentration of 25 ppm, and an acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift of 200 ppm for 5 minutes in any 4 hours.

This ANSI standard was based on human experience and extensive animal investigations. References cited to support it were Adams et al, [69] Stewart et al, [26] Stewart et al, [46] Stewart and Dodd, [48] von Oettingen, [137] and Irish. [138]

Basis for Recommended Environmental Standard

The recommended environmental standard is based on reports of liver and eye changes found in workers chronically exposed to carbon tetrachloride. [13,20,22,27-29,36,37,39,41,50,56,57,59,61] Concentrations

of carbon tetrachloride to which the workers had been exposed were not available in some of the reports and were not extensively documented in any of them. However, the findings of liver and eye damage at the carbon tetrachloride concentrations reported are supported by comprehensive studies of animals chronically exposed to carbon tetrachloride, 7 hours/day, 5 days/week for up to 2 years. [56,57,69]

Elkins [54] found that workers' symptoms of gastrointestinal and central nervous system disturbances generally were alleviated when exposures were reduced below 20 ppm. He did not, however, report studies which would detect liver injury. The observations of Kazantzis and Bomford [59] support those of Elkins, [54] but they also did not make measurements to detect chronic liver injury.

Alcohol consumption was common both in fatalities and in severe cases of liver and kidney involvement from carbon tetrachloride exposure. [29,31,32,34,40,49-53] Observations that alcohol enhances the hepatotoxic effect of carbon tetrachloride have been verified by animal studies. [98,99,106,107] Two-hour exposures of rats to carbon tetrachloride at 100 ppm, 16-18 hours after they were given ethyl alcohol, increased SGOT activity compared to that of either control rats exposed to carbon tetrachloride at 100 ppm without alcohol pretreatment or rats given only ethyl alcohol. The toxicity from single 8-hour exposures to carbon tetrachloride at 25 and 50 ppm was not increased by pretreatment of the rats with ethyl alcohol. [98]

Elevated icteric indices and enlarged livers were found by Gray [29] in 4 workers who had used carbon tetrachloride in their work for from 2 months to 11 years. The carbon tetrachloride concentrations to which these

workers were exposed were not reported, but Smyth et al [56] and Smyth and Smyth [57] found elevated icteric indices in 11 workmen chronically exposed at 8-hour TWA concentrations estimated at 26-39 ppm. In the same investigation, they [56,57] did not find elevated icteric indices in 14 other workmen with estimated 8-hour TWA exposures at 5-24 ppm.

Elevated serum transaminases, elevated BSP retention, and an enlarged, discolored liver with fatty degeneration were found by Dellian and Wittgens [37] in a man who had been using carbon tetrachloride in his work for 4 years. Carbon tetrachloride concentrations found at 16 locations in the plant where the man worked were 10-100 ppm. Two other workers reported chronic symptoms of central nervous system and gastrointestinal disorders.

Elevated SGOT was found by Kazantzis and Bomford [59] in a man who worked in an environment where measured carbon tetrachloride concentrations were between 45 and 97 ppm. The SGOT returned to normal after corrective measures reduced carbon tetrachloride concentrations to less than 10 ppm. Of 18 employees in the factory, 17 reported having had symptoms of central nervous system or gastrointestinal disturbances before these corrective measures were taken.

Statistically significant increases were found in zinc and thymol turbidity, SGOT, and serum bilirubin, indicative of liver injury, in a group of 16 workers who handled carbon tetrachloride compared to a group of 11 workers who did not handle it in a modern plant manufacturing polyfluorocarbons. [36] Urinary urobilinogen was normal in the unexposed workers but was positive in 6 of the 16 exposed workers. There was no report of concentrations of carbon tetrachloride in the factory.

The durations of exposure to carbon tetrachloride and biochemical test data of 51 workers were compared by Rabes. [61] The workers had used carbon tetrachloride for 3-27 years to clean equipment in an electrical generating plant. Carbon tetrachloride was the only solvent used in the cleaning process which occurred 2-3 times a year. Each cleaning process required about 14 days. Concentrations of carbon tetrachloride in the work environment, determined from 2 measurements taken on 1 day, were 6.3 ppm at the beginning of a work shift and 9.5 ppm at the end of the work shift.

Biochemical test data from the 51 exposed workers were classified into 5 groups according to the number of years of employment and compared with 27 unexposed workers. Serum iron and GDH changes indicative of liver injury were found in the exposed workers. The average serum GDH value of the group exposed for 3-5 years was increased 92% above the average of the control group, and for the group exposed 20 or more years, it was increased 182%. Serum iron of the group exposed for 3-5 years was increased 40% and 25.5% for the total group of exposed workers. [61]

Restricted visual fields and other eye abnormalities have occurred with occupational exposures to carbon tetrachloride. [13,20,22,27-29,56-58] Smyth et al [56] and Smyth and Smyth [57] described 9 cases of definitely restricted visual fields and 26 cases of slightly restricted visual fields in 77 workmen exposed to carbon tetrachloride. Of the 9 cases of definitely restricted visual fields, 4 occurred in workmen for whom estimated 8-hour TWA exposures were 7, 10, 10, and 24 ppm with respective estimated peak exposures of 66, 22, 173, and 232 ppm. Moeller [58] found a high percentage of restricted visual fields in 62 workmen who dipped cleaning mops into buckets of carbon tetrachloride without skin or eye

protection. The measured concentrations of carbon tetrachloride in the air were in the 7-10 ppm range. The fundi and visual fields were normal in 17 individuals examined by Kazantzis and Bomford [59] after exposures at 45-97 ppm for up to 2 years.

The indications of liver changes in workers chronically exposed to carbon tetrachloride at estimated concentrations of 5-10 ppm were based on only 2 environmental measurements, [61] so it is unlikely that their exposures were confined to the 5-10 ppm range. However, the possibility that liver involvement, as reported, could have occurred is supported by other occupational observations reported by Barnes and Jones, [36] Dellian and Wittgens, [37] Smyth et al, [56] Smyth and Smyth, [57] and Moeller, [58] and by animal experimentation. The finding of degenerative fatty changes in the livers of both rats and guinea pigs exposed to carbon tetrachloride at 10 ppm for 7 hours/day, 5 days/week for 26 weeks suggests that the present standard TWA of 10 ppm for an 8-hour workday is too high.

Pathologic changes have been found in animals exposed 7 hours/day, 5 days/week to carbon tetrachloride at 5 ppm or more. [69] Increased liver weights relative to body weights were found in female guinea pigs after 143 exposures to carbon tetrachloride at 5 ppm. Guinea pigs may be more sensitive to carbon tetrachloride than other species, [56,57] and in this study, [69] rats were the only other species exposed at 5 ppm. However, increased liver weights and fatty degeneration of the liver were found in both rats and guinea pigs exposed at 10 ppm, 7 hours/day, 5 days/week for 136-139 exposures. Total lipid, neutral fat, and esterified cholesterol in livers of these animals were more than twice the control values. Cirrhosis of the liver and fatty degeneration of the liver, nerves (optic and

sciatic), and eye muscle were found in guinea pigs intermittently exposed at 25 ppm. [57,69] Fatty degeneration of the liver without cirrhosis was found in rats and rabbits intermittently exposed at 25 ppm. [69] Liver cirrhosis and degenerative changes in the eye muscle and sciatic nerve were found by Smyth et al [56,57] in rats after chronic exposures to carbon tetrachloride at 50 ppm.

When exposure concentrations were below 100 ppm, Adams et al [69] did not find significant liver effects in monkeys. However, Smyth et al [56] and Smyth and Smyth [57] did observe fatty changes without degeneration in the livers and degenerative changes in the eye muscle of monkeys exposed at 50 ppm for 8 hours/day, 4-6 days/week for 62 days. Fatty degeneration of the liver and slight cloudy swelling of the kidney tubules were found by Adams et al [69] in 2 monkeys exposed at 100 ppm.

Three cases of liver cancer in humans following carbon tetrachloride exposure were found in the literature. [38-40] In these cases a definitive causal connection could not be made to carbon tetrachloride. However, in all three cases there was evidence of severe liver injury from acute exposures to carbon tetrachloride.

Hepatomas following administration of carbon tetrachloride to a variety of experimental animals have been reported. [70-83] They have been found in animals following inhalation, ingestion, or subcutaneous or intrarectal administration of carbon tetrachloride.

Hepatomas induced by carbon tetrachloride were successfully transplanted between mice of the same strain. [77,79] Transplantations of hepatomas from a single host were successful when 8 months had elapsed

between carbon tetrachloride administration and tumor transplantation, but were unsuccessful when only 11 weeks or less had elapsed. [79]

Carcinomas larger than 5 mm were found in livers of 3 strains of rats subcutaneously injected, twice weekly until they died, with doses of 1.3 ml/kg carbon tetrachloride. [81] Carcinomas were found in 12 of 15 Japanese strain rats, 8 of 13 Osborne-Mendel rats, and 4 of 12 Wistar rats.

Incipient or established carcinomas were found by Costa et al [83] in the livers of 10 of 30 rats that completed 7-month inhalation exposures. The concentrations of carbon tetrachloride were not given.

Liver necrosis due to carbon tetrachloride seems to be a necessary precursor to development of tumors or cancers in the liver. A positive correlation was found between the degree of liver necrosis and the incidence of hepatomas in mice given 30 oral doses at different intervals. In the chronic inhalation experiments of Smyth et al, [56] Smyth and Smyth, [57] and Adams et al, [69] there was no evidence, in any species, of liver necrosis where the carbon tetrachloride exposure concentrations were less than 200 ppm. Evidence of liver necrosis has not been found by examination of workers where the exposures were less than 25-50 ppm. [26,59,61] There have been no reports of liver cancer in humans who have been chronically exposed but without evidence of liver necrosis having occurred.

The findings in the eyes of workers exposed to carbon tetrachloride at 5-10 ppm indicate that exposures should be limited to less than 5 ppm to protect the eyes as well as the liver from chronic injury. There is no evidence from human experience to determine what level of exposure below 5 ppm is safe. However, to provide for a margin of safety it is recommended that worker exposures be limited to 2 ppm determined as a time-weighted

average exposure for up to a 10-hour workday, 40-hour workweek. The evidence indicates that the recommended standard will be sufficiently restrictive of carbon tetrachloride exposure that adverse effects will not result from the allowable environmental exposures.

Exposure to carbon tetrachloride other than by inhalation can occur in the work environment. Absorption of liquid carbon tetrachloride through the skin has been shown to occur in humans and animals. [48,66,67] Skin contact with carbon tetrachloride can also result in irritation and dermatitis. [13,25]

Stewart and Dodd [48] estimated that the amount of carbon tetrachloride absorbed during topical exposure of both hands for 30 minutes would be equivalent to vapor exposure of about 10 ppm for 3 hours.

Exposure of the skin was a definite factor which was not evaluated in a number of occupational reports, but it was evident from the type of work involved. [45,54,59,60] Farrell and Senseman [22] considered a case of polyneuritis to have been caused by absorption of carbon tetrachloride through the skin. It is recognized that many workers handle small amounts of carbon tetrachloride or work in situations where, regardless of the amount used, there is only negligible contact with the substance. Under these conditions, it should not be necessary to comply with many of the provisions of this recommended standard, which has been prepared primarily to protect worker health under more hazardous circumstances. 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 carbon tetrachloride" has been defined as exposure above half the environmental limit, thereby delineating

those work situations which do not require the expenditure of health resources for environmental and medical monitoring, and associated recordkeeping. 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 may exist. However, because of nonrespiratory hazards such as those resulting from skin absorption or eye contact, it is recommended that appropriate work practices and protective measures be required regardless of the air concentration.

# VI. WORK PRACTICES

The 2 methods currently used for manufacturing carbon tetrachloride are the chlorination of methane and the chlorination of carbon disulfide. Suitable controls for the safe use of methane, chlorine, and carbon disulfide should be used.

Information about engineering controls for the handling of chlorine and carbon disulfide is given in the respective Chemical Safety Data Sheets of the Manufacturing Chemists' Association. [139,140] The Manufacturing Chemists' Association's Safety Data Sheet, SD-3 [1] provides further information concerning specific work practices for carbon tetrachloride.

(a) Bulk Handling

All piping and valves at the unloading station should be carefully inspected prior to connection to the transport vehicle. Personal protection must be provided during both inspection and connection. Periodic inspection during unloading is also recommended to avoid the possibility of leaks. Eye wash and safety shower installations should be readily available in the immediate area. In cold climates these installations may be located just inside an easily accessible door of a building. All personnel involved in unloading must be made aware of the toxic properties of the solvent and the necessity for wearing the proper personal protection. Unloading areas must be properly posted "Danger: unloading carbon tetrachloride". The wheels of the tank trucks must be chocked. A metal rail-mounted flag and derailer must be mounted between the tank car and incoming rail traffic. Pipes, pumps, and related equipment must be labeled as containing carbon tetrachloride.

(b) Storage and Use

Carbon tetrachloride should be stored in cool, dry places. It is corrosive to iron and certain other metals when in contact with water, especially at elevated temperatures and reacts violently with aluminum and magnesium. Vessels and equipment which will contain carbon tetrachloride should be of tin, galvanized iron, nickel or nickel-copper alloys, or of especially resistive lined containers. [1,2]

The processes in which carbon tetrachloride is used should be in closed systems whenever feasible. Vents on tanks or vessels must be provided where large volumes of carbon tetrachloride are used or stored. A scrubber should be installed in the venting system to prevent carbon tetrachloride vapor from escaping to the outside atmosphere. All outside exhaust vents must be posted and located away from any location where people normally work. All piping and equipment should be marked as containing carbon tetrachloride. Piping should be located so that the possibility of mechanical damage to it is minimized.

Safety showers and eye wash facilities are necessary in areas where accidental exposure is likely to occur. Use of these facilities minimizes the effects of skin and eye exposure prior to medical or first aid treatment. Recording of the incident at the time of treatment is important for future reference should the incident result in adverse health effects.

(c) Equipment Maintenance

All equipment used for handling carbon tetrachloride must be emptied and purged prior to entry or disassembly. Tanks may only be entered after it has been determined that the level of carbon tetrachloride is within acceptable limits and that the oxygen content is adequate (20%). Emergency

entry may be made only if a self-contained breathing unit is provided and protective clothing is worn.

(d) Emergencies

Spills must be anticipated. Storage tanks should be diked to contain the contents of the tank. 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 exposure level has been reduced to the level prescribed by this standard. Disposal of carbon tetrachloride or carbon tetrachloride contaminated materials should be done in compliance with local, state, and federal 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.

Maintenance personnel involved in emergency rescue or cleanup must be informed of the toxic properties of the solvent and instructed on the necessity of wearing personal protective equipment.

(e) Skin and Eye Protection

Carbon tetrachloride is irritating to the skin, [13,25] and can also be absorbed by this route. [22,48] For these reasons, protective clothing that is both resistant and relatively impervious to carbon tetrachloride should be used whenever liquid carbon tetrachloride is handled. Information about penetration of carbon tetrachloride through some materials can be found in the report by Johnson and Merciez. [141] Additional information about penetration of carbon tetrachloride through various materials and also their resistance to breakdown by carbon

tetrachloride can be found in Rogers' report. [142] Carbon tetrachloride liquid and vapor can affect the eye, [13,25,27,28,56,58] and chemical type goggles made entirely of carbon tetrachloride resistant materials should be used wherever there is work with liquid carbon tetrachloride.

(f) Respiratory Protection

For adequate respiratory protection against the 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 [143] published by the AIHA and the ACGIH in 1963. The American National Standards Practices for Respiratory Protection, ANSI Z88.2-1969, [144] also classifies, describes, and gives the limitations of respirators.

There are 3 categories of respirators: atmosphere-supplying respirators, air-purifying respirators, and the combination of 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 not be used for protection above 10 times the TWA, although the majority of wearers can

obtain protection in atmospheres of higher carbon tetrachloride concentrations. On the same basis, NIOSH recommends that the full facepiece, operated with negative pressure, may be used up to 50 times the TWA.

Carbon tetrachloride, with an odor threshold above 20 ppm, [145,146] has poor warning properties and air-purifying respirators are not recommended.

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.

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## VIII. APPENDIX I

## SAMPLING PROCEDURE FOR

## COLLECTION OF CARBON TETRACHLORIDE

### General Requirements

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

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

(c) A record shall be made of:

(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 shall be collected as near as practicable to the face of workers without interfering with freedom of movement.

(b) Samples shall be collected to permit determination of TWA workday exposures for every job involving exposure to carbon tetrachloride 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 shall 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 shall be calibrated with a representative charcoal tube in line, over a normal range of flowrates (50-1000 ml/min). Calibration curves shall be established for each sampling pump and shall be used in adjusting the pump prior to and during each field use. New calibration curves shall be established for each sampling pump after making any repairs on modifications to the sampling system.

(2) The volumetric flowrate through the sampling system shall 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 with the inlet facing down.

(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 50-1,000 ml/min, depending on the pump. Total sample volumes of 5-80 liters are recommended, eg, a sample could be collected at 1,000 ml/min for 80 minutes to give a total sample volume of 80 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 collected in 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.

# IX. APPENDIX II

## ANALYTICAL PROCEDURE FOR DETERMINATION OF CARBON TETRACHLORIDE

### Principle of the Method

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

(b) The carbon tetrachloride 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 carbon tetrachloride on a gas chromatograph with a flame ionization detector is 5 μg/sample.

(b) The upper limit value for carbon tetrachloride is 1.0 mg/sample. This is the estimated amount of carbon tetrachloride 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 carbon tetrachloride, it is recommended that a smaller volume of air be sampled.

Interferences

(a) Carbon tetrachloride 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 carbon tetrachloride with the chromatographic conditions described in this method could interfere. These may be eliminated by altering operating conditions of the gas chromatograph using a different column packing or using a selective detector, ie, electron capture.

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 can be accomplished rapidly.

Disadvantages of the Method

(a) The amount of sample which can be taken is limited by the weight of carbon tetrachloride 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 organic compounds in high concentrations may displace carbon tetrachloride 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 (FFAP) stationary phase on 80/100 mesh Chromosorb W (or equivalent), acid washed and treated with dimethyldichlorosilane.

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

(d) Glass stoppered microtubes of 2.5-ml capacity or 2-ml vials that can be sealed with inert caps.

(e) Microsyringe of 10-$\mu$l 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) Carbon tetrachloride, 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 carbon tetrachloride 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 0.2μl 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 carbon tetrachloride on the charcoal that is removed in the desorption process. This desorption efficiency 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. A known amount of the compound is injected directly into the activated charcoal with a microliter syringe, and the tube is capped with inert plastic.

At least 5 tubes are prepared in this manner and allowed to stand at least overnight to ensure complete adsorption of carbon tetrachloride 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 carbon tetrachloride is added to it. The desorption samples and blanks are desorbed and analyzed in exactly the same manner as previously described.

Two or 3 desorption standards are prepared for analysis by injecting the same volume of carbon tetrachloride into 0.5 ml of carbon disulfide with the same syringe used in the preparation of the desorption samples. These are analyzed with the desorption samples.

The desorption efficiency equals the difference between the average peak area of the desorption samples and the peak area of the blank divided by the average peak area of the desorption standards, 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 carbon tetrachloride 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 carbon tetrachloride is injected into exactly 10 ml of carbon disulfide in a glass-stoppered flask. The density of carbon tetrachloride (1.59 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 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 carbon tetrachloride/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 carbon tetrachloride on the front and reserve sections of the charcoal tube.

(c) Corrections must be made to the carbon tetrachloride 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 carbon tetrachloride found on the front section of the blank charcoal tube from the weight of carbon tetrachloride found on the front section of the sample charcoal tube to give a corrected formt section weight.

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

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

(4) Divide this total weight by the determined 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 carbon tetrachloride in the sampled air can be expressed in various ways using M, the weight of carbon tetrachloride 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 = 159 M/V'

# X. 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.

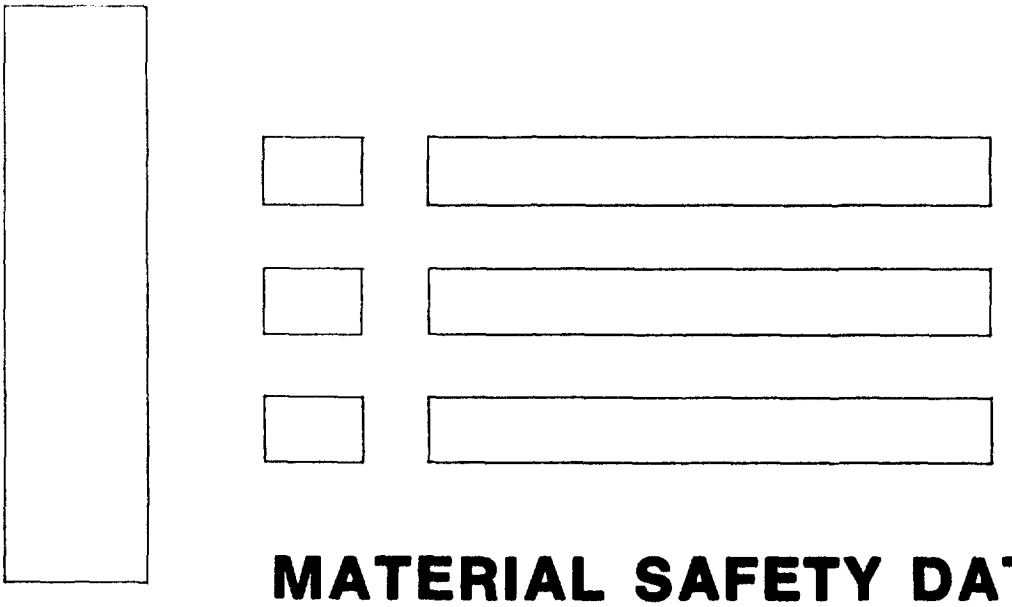
(i) Section IX. Special Precautions

"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.<br>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:

# XI. TABLES

## TABLE XI-1

## PHYSICAL PROPERTIES OF CARBON TETRACHLORIDE

| | |
|---|---|
| Chemical Abstract's serial number | 000056235 |
| Synonyms | Tetrachloromethane<br>Perchloromethane<br>Benzinoform<br>Necatorine |
| Molecular formula | CCl 4 |
| Formula weight | 153.84 |
| Boiling point | 76.75 C, 170.15 F (760 mm Hg) |
| Melting point | -23 C, -9.4 F |
| Vapor pressure | 89.5 mm Hg (20 C)<br>760.0 mm (76.7 C) |
| Specific gravity | 1.5845 (25 C),<br>(water = 1.000 at 4 C) |
| Solubility | 0.08 g/100 ml water at 25 C; miscible with alcohol, diethyl ether and benzene |
| Explosive limit | None |
| Flash point | None |
| Vapor density | 5.32 (air = 1) |
| Conversion factors (25 C; 760 mm Hg) | 1 mg/liter = 159 ppm<br>1 mg/cu m = 0.159 ppm<br>1 ppm = 6.29 mg/cu m<br>1 ppm = 6.29 µg/liter |

Adapted from references 1,2

TABLE XI-2

CARBON TETRACHLORIDE IN EXHALED BREATH FOLLOWING INGESTION

| Collection Period after Dose (hours) | $CCl_4$ Recovered mg | | Concentration $CCl_4$ Estimated µg/liter | |
|---|---|---|---|---|
| | Exp. 1 | Exp. 2 | Exp. 1 | Exp. 2 |
| 0.15 - 0.40 | | 135.8 | | 1,810 |
| 0.43 - 0.68 | | 170.8 | | 2,372 |
| 0.72 - 0.97 | | 111.5 | | 1,328 |
| 1.0 - 1.5 | | 199.5 | | 1,177 |
| 1.55 - 2.55 | | 313.0 | | 932 |
| 2.6 - 3.6 | | 233.0 | | 754 |
| 2.9 - 4.9 | 701.5 | | 895 | |
| 4.5 - 6.5 | | 326.5 | | 406 |
| 7.3 - 9.3 | 121.5 | 241.0 | 155 | 291 |
| 11.25 - 13.25 | | 66.9 | | 89 |
| 12.5 - 14.5 | 37.9 | | 48 | 17 |
| 23.9 - 25.9 | | 13.1 | | |
| 26.9 - 28.9 | 32.8 | | 38 | |
| 31.5 - 33.5 | 9.0 | | 12 | |
| 36.5 - 38.5 | 8.9 | | 11 | |

Adapted from Wells [18]

TABLE XI-3

CARBON TETRACHLORIDE CONCENTRATIONS IN DRYCLEANING PLANTS USING CLOSED MACHINES

| Plant | Observation Time (min) | Operation | $CCl_4$ Vapor, ppm Average | Maximum |
|---|---|---|---|---|
| 1 | 120 | Usual | 20 | 65 |
| 2 | 23 | Usual | 71 | 151 |
| 2 | 3 | Spraying | 11 | 43 |
| 18 | 67 | Usual | 38 | 540 |
| 19 | 64 | Usual | 29 | 980 |
| 20 | 112 | Usual | 47 | 1,250 |
| 20 | 52 | Cleaning machines | 338 | 7,100 |
| 21 | 81 | Usual | 29 | 85 |
| 22 | 96 | Usual | 10 | 173 |
| 22 | 50 | Cleaning machine | 206 | 1,252 |
| 23 | 106 | Usual | 24 | 108 |
| 24 | 63 | Usual | 50 | 172 |

Adapted from Smyth and Smyth [57]

TABLE XI-4

CARBON TETRACHLORIDE CONCENTRATIONS IN TEN PLANTS MANUFACTURING OR USING CARBON TETRACHLORIDE

| Area or Process Sampled | Plant No. | Sampling time Minutes | Carbon Tetrachloride, ppm Ave. | Max. |
|---|---|---|---|---|
| General Room Air | 25 | 10 | 15 | 32 |
| | 27 | 58 | 22 | 195 |
| | 27 | 5 | 54 | 65 |
| | 28 | 27 | 10 | 22 |
| | 29 | 19 | 0 | 0 |
| | 30 | 23 | 26 | 170 |
| Closed System | 25 | 45 | 62 | 800 |
| | 26 | 32 | 59 | 194 |
| | 26 | 26 | 84 | 303 |
| Half-closed System | 25 | 44 | 58 | 130 |
| | 25 | 55 | 70 | 389 |
| | 25 | 12 | 508 | 2,050 |
| | 26 | 53 | 60 | 238 |
| | 26 | 13 | 152 | 216 |
| | 27 | 5 | 23 | 65 |
| | 27 | 8 | 51 | 85 |
| | 27 | 195 | 96 | 345 |
| | 27 | 54 | 158 | 1,680 |
| | 27 | 23 | 21 | 43 |
| | 28 | 57 | 63 | 282 |
| | 29 | 36 | 85 | 240 |
| | 29 | 93 | 155 | 324 |
| | 30 | 5 | 69 | 174 |
| | 31 | 60 | 650 | 1,060 |
| | 33 | 90 | 31 | 173 |
| | 33 | 76 | 92 | 396 |
| | 34 | 14 | 14 | 66 |
| | 36 | 36 | 98 | 232 |
| Cleaning tanks, etc. | 25 | 55 | 286 | 7,860 |
| | 26 | 47 | 138 | 450 |
| | 27 | 22 | 72 | 151 |
| | 30 | 14 | 216 | 1,042 |
| | 30 | 8 | 300 | 392 |
| Spraying, etc. | 25 | 45 | 41 | 300 |
| | 30 | 13 | 191 | 494 |
| | 33 | 41 | 20 | 66 |
| | 33 | 37 | 110 | 176 |
| | 34 | 20 | 62 | 108 |
| | 34 | 41 | 82 | 414 |

Derived from references 56, 57

TABLE XI-5

WORKERS WITH SLIGHTLY RESTRICTED VISUAL FIELDS (+), DEFINITELY RESTRICTED VISUAL FIELDS (++), AND ELEVATED ICTERIC INDICES

| Plant | Type of Job | $CCl_4$, ppm Ave. | $CCl_4$, ppm Max. | No. of Workers Studied | No. of Workers with: Restricted Visual Fields + | Restricted Visual Fields ++ | Elevated Icteric Index |
|---|---|---|---|---|---|---|---|
| 25 | $CCl_4$ manufacture | 15 | 32 | 4 | 1 | | |
| | Filling containers | 35 | 389 | 3 | 2 | | |
| | Supervision, sales | 5 | 389 | 1 | 1 | | |
| | Cleaning drums | 57 | 1,252 | 1 | | | |
| 26 | $CCl_4$ manufacture | 39 | 450 | 9 | 1 | | 3 |
| | Filling containers | 75 | 238 | 4 | | | |
| | Supervision, sales | 10 | 450 | 1 | | | |
| 27 | $CCl_4$ manufacture | 26 | 195 | 6 | 4 | | 1 |
| | Filling containers | 97 | 1,680 | 1 | | | |
| | Cleaning drums | 26 | 450 | 2 | | | |
| | Supervision, sales | 12 | 151 | 1 | | | |
| 28 | $CCl_4$ manufacture | 10 | 22 | 3 | 1 | 1 | |
| | Supervision, sales | 5 | 282 | 1 | | | |
| 29 | $CCl_4$ manufacture | 30 | 240 | 4 | 2 | | 3 |
| | Filling containers | 117 | 324 | 5 | 1 | 2 | |
| | Supervision, sales | 30 | 324 | 1 | 1 | | |
| 30 | $CCl_4$ manufacture | 54 | 1,042 | 7 | 1 | 2 | 1 |
| | Supervision, sales | 26 | 494 | 1 | | | 1 |
| | Demonstration | 50 | 1,042 | 1 | | | |
| 33 | Filling extinguishers | 54 | 396 | 3 | | 1 | 1 |
| | Supervision, sales | 27 | 396 | 3 | 2 | | 1 |
| | Extinguisher testing | 37 | 110 | 3 | 2 | | 2 |
| | Demonstration | 27 | 396 | 1 | | | |
| | $CCl_4$ analysis | 54 | 396 | 1 | | | |
| | Extinguisher inspection | 54 | 396 | 1 | | | |
| 34 | Filling extinguishers | 7 | 66 | 1 | | 1 | |
| | Supervision, sales | 5 | 108 | 1 | 1 | | |
| | Extinguisher testing | 16 | 414 | 2 | 2 | | |
| | Grease removal | 8 | 108 | 1 | 1 | | |
| 22 | Drycleaning | 10 | 173 | 2 | | 1 | |
| 36 | Filling containers | 24 | 232 | 2 | | 1 | |

Adapted from Smyth and Smyth [57]

TABLE XI-6

COMPARISON OF BIOCHEMICAL VARIABLES IN 51 WORKERS EXPOSED TO CARBON TETRACHLORIDE AND 27 UNEXPOSED WORKERS

| Biochemical Variable | Units | Exposed Group | Unexposed Group | Probability % |
|---|---|---|---|---|
| Erythrocyte sedimentation | mm/hr (range) | 6-14 | 8-17 | |
| Conjugated bilirubin | mg/100ml | 0.09 | 0.05 | |
| Unconjugated bilirubin | mg/100ml | 0.60 | 0.42 | 0.05 |
| Total bilirubin | mg/100ml | 0.69 | 0.47 | 0.01 |
| Takata-Ara | mg/100ml | 92.5 | 89.6 | 0.005 |
| Glutamic-oxaloacetic transaminase | IU | 9.3 | 8.1 | |
| Glutamic-pyruvic transaminase | IU | 6.6 | 4.4 | |
| Lactic dehydrogenase | ml/ml (sic) | 130.7 | 116.8 | |
| Cholesterol | mg/100ml | 195.2 | 211.7 | |
| Serum iron | μg/100ml | 138.9 | 110.6 | 0.001 |
| Alkaline phosphastase | MME (sic) | 1.92 | 1.92 | |
| Leucineaminodipeptidase | mU/ml (sic) | 1.85 | 1.73 | |
| Sorbitol dehydrogenase | mU/ml (sic) | 1.14 | 1.45 | |
| Glutamic dehydrogenase | mU/ml (sic) | 1.27 | 0.50 | 0.001 |

Adapted from Rabes [61]

TABLE XI-7

SERUM ORNITHINE CARBAMOYL TRANSAMINASE LEVELS IN RATS (UNITS/100 ml) AFTER A DOSE OF 0.125 ml CARBON TETRACHLORIDE

| Hours after Injury | No. of Animals | Range (units x 100) | Average (units x 100) |
|---|---|---|---|
| Control | 13 | 8-25 | 19 |
| 4 | 6 | 15-31 | 23 |
| 8 | 6 | 31-43 | 38 |
| 12 | 9 | 19-43 | 28 |
| 16 | 7 | 28-55 | 43 |
| 20 | 7 | 55-66 | 59 |
| 24 | 7 | 43-88 | 64 |
| 48 | 7 | 60-120 | 78 |
| 72 | 6 | 19-59 | 38 |
| 96 | 8 | 20-59 | 39 |
| 120 | 6 | 18-31 | 25 |
| 23 days | 2 | 15-25 | 20 |

Adapted from Musser and Spooner [64]

TABLE XI-8

DISTRIBUTION OF DEATHS OF TWO SETS OF GUINEA PIGS EXPOSED TO CARBON TETRACHLORIDE

| Exposure Concentration, ppm | Diet | Cause of Death: Killed No. | Killed Age days | Unexplained No. | Unexplained Age days | Infection No. | Infection Age days |
|---|---|---|---|---|---|---|---|
| 0 | Normal | 8 | (60-130) | 0 | | 11 | (73-232) |
| 50 | Normal | 7 | (82-205) | 9 | (57-243) | 8 | (59-205) |
| 100 | Normal | 0 | | 16 | (51-84) | 7 | (59-76) |
| 200 | Normal | 0 | | 13 | (51-79) | 9 | (51-88) |
| 400 | Normal | 0 | | 19 | (50-94) | 5 | (52-58) |
| 0 | Calcium | 7 | (92-221) | 0 | | 0 | |
| 25 | Calcium | 3 | (118-199) | 5 | (133-185) | 7 | (146-192) |
| 50 | Calcium | 7 | (79-200) | 4 | (130-169) | 5 | (118-224) |
| 100 | Calcium | 5 | (79-225) | 8 | (71-162) | 3 | (79-102) |
| 200 | Calcium | 4 | (79-200) | 7 | (79-163) | 4 | (90-151) |

Adapted from Smyth and Smyth [57]

TABLE XI-9

EXPOSURE OF MONKEYS TO CARBON TETRACHLORIDE AT DIFFERENT CONCENTRATIONS

| Monkey and Sex | Exposure Concentration ppm | Number of Exposures | Duration of the Experiment days | Interval, Final Exposure to Examination days |
|---|---|---|---|---|
| 506 (F) | 50 | 62 | 93 | 0 |
| 506 (F) | 50 | 188 | 275 | 1 |
| 507 (M) | 50 | 225 | 321 | 4 |
| 508 (M) | 50 | 225 | 321 | 28 |
| 509 (F) | 200 | 62 | 93 | 0 |
| 510 (F) | 200 | 186 | 275 | 1 |
| 512 (M) | 200 | 223 | 321 | 23 |

Adapted from Smyth and Smyth [57]

TABLE XI-10

CARBON TETRACHLORIDE INHALATION EXPOSURES AND EFFECTS

| Author | Exposure Variables | Exposure Time | Effects |
|---|---|---|---|
| Prendergast et al [68] | Monkeys, rats, guinea pigs, rabbits, 1 ppm | Continuous 90 days | No pathological findings |
| Adams et al [69] | Guinea pigs, 5ppm | 7 hrs/day, 5 days/wk, 184 days | Increased liver weights |
| Rabes [61] | Humans, 6.3-9.5 ppm occupational | 2-3 times/yr, 14 days each time, 5 years | 23% increase in serum iron, 92% increase in GDH |
| Moeller [58] | Humans, 6.4-9.5 ppm occupational | 1 hr/day to 1 hr/week | Reduced corneal sensitivity, restricted visual fields |
| Smyth and Smyth [57] | Humans, 5-117 ppm occupational | 8-hr TWA | Restricted visual fields |
| Prendergast et al [68] | Monkeys, rats, guinea pigs, rabbits, 10 ppm | Continuous 90 days | Enlarged livers, fatty infiltration |
| Dellian and Wittgens [37] | Humans, 10-100 ppm occupational | Intermittent | CNS and gastrointestinal effects, fatty degeneration of the liver |
| Adams et al [69] | Rats, 10 ppm | 7 hrs/day 5 days/wk, 184 days | Increased liver weights |
| | Rabbits, 25 ppm | 7 hrs/day, 178 days | Fatty degeneration of the liver, cirrhosis |
| Smyth and Smyth [57] | Guinea pigs, 25 ppm | 8 hrs/day | High mortality |
| | Rats, 50 ppm | 8 hrs/day, 189 days | Cirrhosis of the liver, microscopic nerve changes |

TABLE XI-10 (CONTINUED)

CARBON TETRACHLORIDE INHALATION EXPOSURES AND EFFECTS

| Author | Exposure Variables | Exposure Time | Effects |
|---|---|---|---|
| Smyth and Smyth [57] | Monkeys, 50 ppm | 8 hrs/day, 62 days | Fatty infiltration of the liver |
| | Humans, 26-54 ppm occupational | 8-hr TWA | Elevated icteric indices |
| Stewart et al [26] | Humans, 49 ppm experimental | 70 min | Reduced serum iron |
| Elkins [54] | Humans, 10-80 ppm occupational | Several days | Nausea, vomiting, lassitude |
| | Humans, 85 ppm (40-375 ppm) occupational | Once every 2-3 weeks | Nausea, anorexia, weight loss |
| Heimann and Ford [21] | Humans, 79 ppm (33-124 ppm) occupational | Few hours daily | Fatigue, nausea, vomiting |
| Prendergast et al [68] | Rats, monkeys, guinea pigs, rabbits, 82 ppm | 8 hrs/day 5 days/week 30 weeks | Interstitial inflammation of lungs |
| Kazantzis and Bomford [59] | Humans, 45-97 ppm occupational | Daily | CNS and gastrointestinal symptoms |
| Smyth and Smyth [57] | Rats, 200 ppm | 8 hrs/day | Reduced fertility indices |
| Schwetz et al [84] | Rats, 300 ppm | 7 hrs/day, 10 days | Decreased fetal weights and crown to rump lengths, subcutaneous edema, reduced maternal body weights |
| Lehmann and Schmidt-Kehl [24] | Humans, 600 ppm | 10 min | Vertigo, headache |
| | Humans, 600 ppm | 30 min | Dizziness |
| | Humans, 14,000 ppm | 50 sec | Unconsciousness |



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