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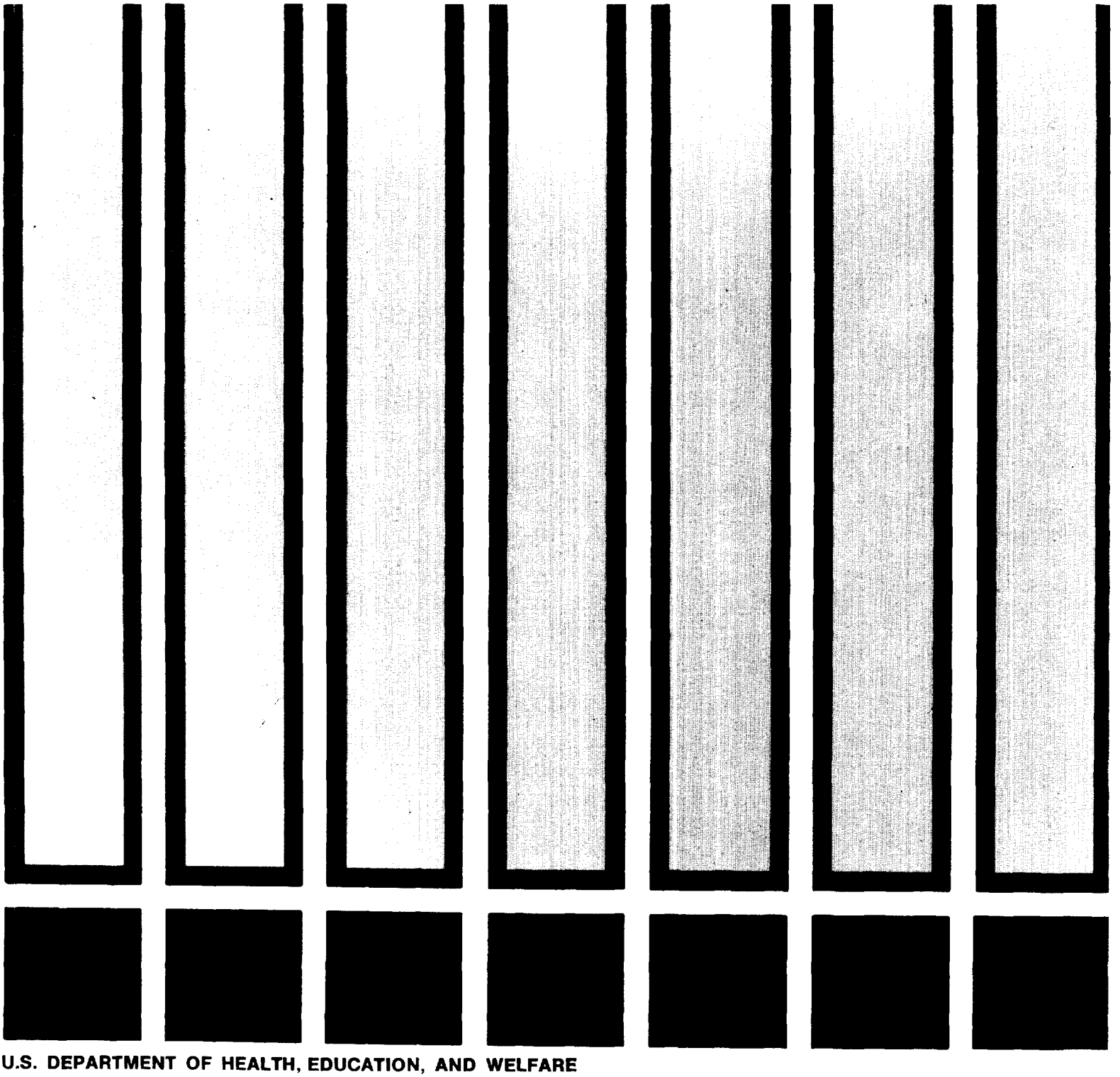
(METHYL CHLOROFORM)



U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service Center for Disease Control

National Institute for Occupational Safety and Health

criteria for a recommended standard....

OCCUPATIONAL EXPOSURE TO 1,1,1 - TRICHLOROETHANE (Methyl Chloroform)

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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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 1,1,1-trichloroethane by members of my staff and the valuable, constructive comments by the Review Consultants on 1,1,1-Trichloroethane, by the ad hoc committees of the American Industrial Hygiene Association and the American Academy of Occupational Medicine, and by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine. The NIOSH recommendations for standards are not necessarily a consensus of all the consultants and

professional societies that reviewed this criteria document on 1,1,1-trichloroethane. Lists of the NIOSH Review Committee members and of the External Reviewers appear on the following pages.

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The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and recommended standard for 1,1,1-trichloroethane. The Division Review staff for this document consisted of Keith H. Jacobson, Ph.D., Chairman; Richard A. Rhoden, Ph.D.; Paul E. Caplan; and special reviewers Hervey B. Elkins, Ph.D. and Charles C. Hassett, Ph.D.

Agatha Corporation developed the basic information for consideration by NIOSH staff and consultants under contract HSM-99-73-20. Robert W. Mason, Ph.D., had NIOSH program responsibility and John A. Wass, Ph.D., served as criteria manager.

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CRITERIA DOCUMENT: RECOMMENDATIONS FOR AN OCCUPATIONAL EXPOSURE STANDARD FOR 1,1,1-TRICHLOROETHANE (METHYL CHLOROFORM)

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CRITERIA DOCUMENT: RECOMMENDATIONS FOR AN OCCUPATIONAL EXPOSURE STANDARD FOR 1,1,1-TRICHLOROETHANE (METHYL CHLOROFORM)

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I. RECOMMENDATIONS FOR A 1,1,1-TRICHLOROETHANE STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that worker exposure to 1,1,1-trichloroethane (CH_3CCl_3), also known as methyl chloroform, 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 1,1,1-trichloroethane 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 1,1,1-trichloroethane" is defined as exposure above 200 ppm measured as a time-weighted average (TWA) for up to a 10-hour workday, 40-hour workweek.

Occupational exposure to 1,1,1-trichloroethane requires adherence to all the following sections. Exposure at lower environmental concentrations will not require adherence to Sections 1, 2, 7(b), and 4(a) except 4(a)(5).

Section 1 - Environmental (Workplace Air)

(a) Concentration

Occupational exposure shall be controlled so that workers are not exposed to 1,1,1-trichloroethane at greater than a ceiling concentration of

350 ppm (1,910 mg/cu m) as determined by a 15-minute sample.

(b) Sampling and Analysis

Procedures for sampling and analysis of workroom air shall be as provided in Appendices I and II or by any method shown to be at least equivalent.

Section 2 - Medical

(a) Preplacement initial or interim medical and work history.

(b) Preplacement physical examinations giving attention to at least the neurological, cardiovascular, and liver functions, and skin condition.

(c) A judgment should be made of the worker's ability to use positive or negative pressure respirators.

(d) Periodic examinations shall be made available on an annual basis or at some other frequency to be determined by the responsible physician.

(e) Proper medical management shall be made available to workers suffering from adverse effects of 1,1,1-trichloroethane.

(f) Initial medical examinations shall be made available to all workers within 60 days of the promulgation of the standard.

(g) Workers shall be advised that available scientific information from one experimental animal study has shown that the offspring of mice and rats exposed at high levels of 1,1,1-trichloroethane were observed to have congenital abnormalities. The relevance of this study to male or female workers or their offspring has not yet been determined. It does, however,

suggest that employers and workers attempt to minimize exposure to 1,1,1-trichloroethane whenever possible. If the physician becomes aware of any adverse reproductive effects including repeated spontaneous abortions in 1,1,1-trichloroethane exposed workers or congenital abormalities in their children, this information should be forwarded to the Director, National Institute for Occupational Safety and Health.

(h) Medical records shall be maintained for all persons employed in work involving exposure to 1,1,1-trichloroethane. All pertinent medical records with supporting documents shall be maintained for 20 years after the individual's employment is terminated. These records shall be made available to the designated 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.

Section 3 - Labeling and Posting

(a) The following warning sign shall be affixed in a readily visible location on processing or other equipment and on 1,1,1-trichloroethane storage tanks or containers:

1,1,1-TRICHLOROETHANE

BREATHING VAPOR MAY BE
HAZARDOUS TO HEALTH.

May generate toxic gases on contact
with open flame, hot surfaces, or
other heat-producing conditions.
Keep containers closed when not in use.
Use only with adequate ventilation.
Avoid breathing of vapor.
Avoid contact with skin.
Notice to physician: Sympathomimetic
amines are contraindicated.

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.

(b) This sign shall also be posted at or near entrances to areas in which there is occupational exposure to 1,1,1-trichloroethane.

Section 4 - Personal Protective Equipment and Clothing

(a) Respiratory Protection

(1) Engineering controls shall be used wherever necessary to maintain 1,1,1-trichloroethane concentrations at or below the recommended environmental exposure standard. Compliance with the permissible exposure limits may be achieved by the use of respirators only:

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

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

(C) During emergencies when air concentrations of 1,1,1-trichloroethane may exceed the recommended limits.

(2) When respirators are permitted, 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) To determine the class of respirator to be used, the employer shall measure the atmospheric concentration of 1,1,1-

trichloroethane in the workplace initially and thereafter whenever process, worksite, climate, or control changes occur which are likely to increase the 1,1,1-trichloroethane concentration. This requirement shall not apply when only self-contained or combination supplied-air and self-contained positive pressure respirators are used.

(B) The employer shall ensure that no worker is being exposed to 1,1,1-trichloroethane in excess of the exposure limit because of improper respirator selection, fit, use, or maintenance.

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

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

(E) Respirators specified for use in higher concentrations of 1,1,1-trichloroethane are permitted in atmospheres of lower concentrations.

(F) 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) Chemical cartridges and canisters shall not be used for periods of time in excess of those indicated in Table I-1. In any case chemical cartridges and canisters should be replaced after each day of use.

(5) Where an emergency may develop that could result in employee injury from overexposure to 1,1,1-trichloroethane, 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 1,1,1-trichloroethane, protective clothing shall be worn. The clothing should be resistant to 1,1,1-trichloroethane. Gloves, boots, overshoes, and bib-type aprons that cover boot tops 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. Hands placed in liquid 1,1,1-trichloroethane shall be protected by impervious gloves. Any liquid 1,1,1-trichloroethane that contacts the skin should be promptly removed.

TABLE I-1

RESPIRATORY PROTECTION
FOR 1,1,1-TRICHLOROETHANE

Condition Vapor Concentration	Respirator Type
500 ppm or less	A chemical cartridge respirator with organic vapor cartridge(s), maximum service life of 5 hours; chemical cartridges should be changed after each day of use.
	A self-contained breathing apparatus
1000 ppm or less	A chemical cartridge respirator with a full facepiece and organic vapor cartridge(s), Maximum service life of 2 hours
	A gas mask with a chin-style or a front- or back-mounted organic vapor canister
	A supplied-air respirator with a full facepiece, helmet or hood
	A self-contained breathing apparatus with a full facepiece
Greater than 1000 ppm or entry and escape from unknown concentrations	Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode
	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	A gas mask providing protection against organic vapors
	An escape self-contained breathing apparatus

(c) Eye Protection

Eye protection shall be provided for, and worn by, any employee engaged in an operation where 1,1,1-trichloroethane liquid or spray may enter the eye. Chemical-type goggles or safety glasses with splash shields made completely of 1,1,1-trichloroethane-resistant materials shall be used. Suitable eye protection shall be in accordance with 29 CFR 1910.133.

Section 5 - Informing Employees of Hazards from 1,1,1-Trichloroethane

(a) All new and present employees in any 1,1,1-trichloroethane area shall be kept informed of the hazards, relevant symptoms, effects of overexposure, and proper conditions and precautions concerning safe use and handling of 1,1,1-trichloroethane.

(b) 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. It shall include a description of the general nature of the mechanical surveillance procedures and why it is advantageous to the worker to undergo these examinations.

The information explaining the hazards of working with 1,1,1-trichloroethane shall be kept on file and readily accessible to the worker at all places of employment where 1,1,1-trichloroethane is manufactured, used, transported, or stored.

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

Section 6 - Work Practices

(a) Handling and Storage

(1) Containers delivered by closed truck or rail shall not be unloaded until the vehicle in which they arrived has been ventilated. The absence of any odor of 1,1,1-trichloroethane should not be used as a criterion of adequate ventilation.

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

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

(4) Processes and storage facilities shall not be located near open flames or high-temperature operations, unless precautions are taken to prevent fire and explosion hazards.

(b) Contaminant Controls

(1) Suitable engineering controls designed to limit exposure to 1,1,1-trichloroethane shall be utilized if needed. Ventilation systems, if used, shall be designed to prevent the accumulation or recirculation of 1,1,1-trichloroethane in the workroom and to effectively remove 1,1,1-trichloroethane from the breathing zones of workers. Adequate, uncontaminated make-up air shall be provided. 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, if necessary, to limit environmental concentrations for nonroutine operations that require the application of 1,1,1-trichloroethane.

(c) Equipment Maintenance and Emergency Procedures

(1) 1,1,1-Trichloroethane hazard areas

A hazard area that workers may enter (any space with physical characteristics and sources of 1,1,1-trichloroethane that could result in concentrations of 1,1,1-trichloroethane in excess of the environmental limits) shall have exits that are 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 two separate means of exit shall be provided from each room or building in which 1,1,1-trichloroethane 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 1,1,1-trichloroethane shall be thoroughly ventilated to assure an adequate supply of oxygen and a safe concentration of 1,1,1-trichloroethane, tested for 1,1,1-trichloroethane and inspected prior to each entry. Ventilation shall be maintained while workers are in the space.

(C) Inadvertent infiltration of 1,1,1-trichloroethane into the confined space while work is in progress inside shall be prevented by disconnecting and blanking off 1,1,1-trichloroethane

(D) 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.

(E) Written operating instructions and emergency medical procedures shall be formulated and posted in conspicuous locations where accidental exposure to concentrations of 1,1,1-trichloroethane in excess of the environmental limit may occur. These instructions and procedures shall be printed both in English and in the predominant language of non-English-speaking workers, if any. 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 1,1,1-trichloroethane is likely. If 1,1,1-trichloroethane is splashed on the worker, contaminated clothing shall be promptly removed and the skin washed with soap and water. If liquid 1,1,1-trichloroethane contacts the eyes, they shall be thoroughly irrigated with clean water, promptly followed by medical assistance. Such incidents shall be reported to the immediate supervisor by the affected employee or by a fellow worker.

Section 7 - Monitoring and Recordkeeping

(a) General

Workers are not considered to be occupationally exposed to 1,1,1-trichloroethane if environmental concentrations, as determined on the basis of an industrial hygiene survey, do not exceed the action level, or if there is no operation, storage, or handling of 1,1,1-trichloroethane in any form, or contamination of workplace air by 1,1,1-trichloroethane from other sources. These industrial hygiene surveys shall begin within 6 months after this standard is promulgated, and be repeated at least every 3 years and within 30 days after any process or operating change likely to result in increases of airborne concentrations of 1,1,1-trichloroethane. Records of these surveys, including the basis for concluding that airborne concentrations of 1,1,1-trichloroethane are at or below the action level, shall be maintained until the next survey has been completed.

The following requirements apply to occupational exposure to 1,1,1-trichloroethane, ie, to workplaces where the action level is exceeded.

(b) Personal Monitoring

A program of breathing zone or personal monitoring shall be instituted to identify and measure the exposure of all employees occupationally exposed to 1,1,1-trichloroethane. This sampling and analysis shall be conducted every 3 months on at least 25% of the workers so that each worker's exposure is measured at least every year; this frequency and percentage of employees sampled may be different if so directed by a professional industrial hygienist. Sufficient samples shall be taken and analyzed to permit construction of valid estimates of the TWA and ceiling concentration exposures. If monitoring of any worker shows

exposure in excess of the recommended environmental limit, additional monitoring shall be promptly initiated. If confirmed, control procedures shall be instituted as soon as possible; these may precede and obviate confirmatory monitoring if the employer desires. Affected employees shall be advised that exposures have been excessive and be notified of the control procedures being implemented. Monitoring of these employees shall be conducted at least as often as every 30 days and shall continue until 2 successive samplings at least a week apart confirm that exposure no longer exceeds recommended limits. Normal monitoring may then be resumed.

For each TWA concentration determination, a sufficient number of samples to characterize each worker's exposure during each workshift shall be taken and analyzed. The number of TWA and ceiling concentration determinations for an operation shall be based on such factors as the variations in location and job functions of workers in that operation.

(c) Recordkeeping

Environmental monitoring records shall be maintained for at least 20 years. These records shall include methods of sampling and analysis used, types of respiratory protection used, and TWA and ceiling concentrations found. Each employee shall be able to obtain information on his own environmental exposures.

Pertinent medical records shall be retained for 20 years after the last occupational exposure to 1,1,1-trichloroethane. Records of environmental exposures applicable to an employee should be included in that employee's medical records. These medical records shall be made available to the designated medical representatives of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, of the employer, and of the employee or former employee.

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 1,1,1-trichloroethane. 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, (NIOSH) 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. The criteria and recommended standard should enable management and labor to develop better engineering controls resulting in more healthful work environments. Simply complying with the recommended standard should not be the final goal.

These criteria for a standard for 1,1,1-trichloroethane are part of a continuing series of criteria developed by NIOSH. The proposed standard applies only to the processing, manufacture, and use of 1,1,1-trichloroethane 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, especially central nervous system (CNS) and hepatic insult, (2) be measurable by techniques that are valid, reproducible, and available to industry and governmental agencies, and (3) be attainable with existing technology.

Further research is needed to more completely characterize the effects of certain levels of 1,1,1-trichloroethane on workers, especially epidemiological, chronic and teratological studies. Animal studies are underway at the National Cancer Institute to determine if 1,1,1-trichloroethane is carcinogenic. Similar studies are being performed by the Dow Chemical Company.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

1,1,1-Trichloroethane (CH_3CCl_3) is also known as methyl chloroform and alpha-trichloroethane. [1,2]

There are two isomers of trichloroethane. The 1,1,2 isomer is also known as ethane trichloride, vinyl trichloride, beta-trichloroethane and monochloroethylenechloride. [1-3] Some reports do not clearly distinguish between the isomers, and some confusion exists in the literature because of indiscriminate use of the term trichloroethane. [4-7]

The odor threshold of 1,1,1-trichloroethane was reported by the American National Standards Institute to be around 100 ppm. [8] Stewart found a sex difference in odor "acceptance" at 350 ppm. [9] May [10] reported that the odor threshold for 1,1,1-trichloroethane of his subjects was 400 ppm, and that they perceived the odor more clearly at 700 ppm. Arthur D. Little Inc. [11] reported the odor recognition threshold, detected by four expert panel members when 1,1,1-trichloroethane was in room air, to be 16 ppm. These data reflect the variability in odor threshold values and highlight the danger of using odor as a criterion for detection of harmful levels of 1,1,1-trichloroethane. Some physical data for 1,1,1-trichloroethane are presented in Table XII-1. [1,8,12-15]

1,1,1-Trichloroethane was first marketed as an industrial cold cleaning solvent in 1951. [16] United States production of 1,1,1-trichloroethane in 1961 was 20,000,000 lbs. [17] In 1966, when the US Tariff Commission began tabulating production data separately for 1,1,1-trichloroethane, production of 242,943,000 lbs by four manufacturers was

Production has increased steadily and in 1973, production of 548,394,000 lbs was reported. [19-24]

There are many uses of 1,1,1-trichloroethane as a solvent and cleaning agent. [16,25,26] In 1969, Gleason et al [27] tabulated over 40 products, marketed by 30 companies, which contained it. Among the products were type cleaners, color film cleaners, insecticides, spot removers, cements and adhesives, and fabric cleaning solutions. [27] One of the most common industrial uses is as a degreasing agent.

Workers involved in the manufacture of 1,1,1-trichloroethane, in its formulation into the many products containing it, and in their final uses, are potentially exposed to 1,1,1-trichloroethane. In addition to job related exposures, workers may be exposed to 1,1,1-trichloroethane by home use of the many products which contain it.

Commercial 1,1,1-trichloroethane contains small amounts of stabilizing substances. Among the materials which may be used for this purpose are glycol diesters, ketones, nitriles, dialkyl sulfoxides, dialkyl sulfides, dialkyl sulfites, tetraethyl lead, nitroaliphatic hydrocarbons, 2-methyl-3-butyn-2-ol, tertiary butyl alcohol, 1,4-dioxane, dioxolane, sec-butyl alcohol, and monohydric acetylenic alcohols. [12,14] 1,1,1-Trichloroethane preparations containing these additives are called inhibited 1,1,1-trichloroethane.

NIOSH estimates that 100,000 US workers are potentially exposed to 1,1,1-trichloroethane in their places of employment.

Historical Reports

Tauber, [2] in 1880, used 1,1,1-trichloroethane as an anesthetic

agent in humans to produce unconsciousness without excitation or notable effects on respiratory or heart rates. Vomiting and fatigue were experienced, however, during recovery from anesthesia. Tauber's experiments with frogs, rabbits and dogs also showed that 1,1,1-trichloroethane did not materially affect respiratory or pulse rates during anesthesia. [2]

Blondeau [28] anesthetized frogs and guinea pigs with 1,1,1-trichloroethane saturated air and reported his experiments in 1883. He found that it took longer to produce anesthesia with 1,1,1-trichloroethane than with chloroform, and he considered that 1,1,1-trichloroethane would be more offensive as an anesthetic. [29]

Experimental studies of 1,1,1-trichlorethane as an inhalation anesthetic, with dogs as the experimental animal, were reported in 1887 by Dubois and Roux. [30] They prepared purified 1,1,1-trichloroethane and found it to have a pleasant odor which was not as penetrating and suffocating as that of chloroform. They found that dogs became completely anesthetized in 7 to 8 minutes when inhaling air saturated with 1,1,1-trichloroethane. There was a slight acceleration of respiration initially, but, with muscular relaxation, the respiration soon became calm and regular. Within 1 to 2 minutes after cessation of 1,1,1-trichloroethane inhalation, the animals were completely awake. There was no excessive salivation as with chloroform and the authors considered that, at least with dogs, 1,1,1-trichloroethane was superior to chloroform as an anesthetic agent. [30]

Exposures of an unspecified number of mice to 1,1,1-trichloroethane to determine the minimum concentrations required to produce prostration,

loss of reflexes, and death within 2 hours of exposure, were reported by Lazarew in 1929. [31] 1,1,1-Trichloroethane was 1 of 12 chlorinated hydrocarbons studied. To attain each of the end points, higher concentrations of the 1,1,1- than of the 1,1,2-isomer were required as shown in Table III-1.

TABLE III-1

EFFECTS OF TRICHLOROETHANE ISOMERS ON MICE

Isomer	Minimum Concentration For Response Within 2 Hours of Exposure (mg/l)		
	proneness	loss of reflexes	death
1,1,1-	40	45	65
1,1,2-	10	15	60

Adapted from Lazarew [31]

Lazarew assigned toxicity ratings to the 12 compounds based on the concentrations required to cause prostration. [31] Higher indices meant greater toxicity. The index for 1,1,1-trichloroethane was 3.5 compared to 14 for 1,1,2-trichloroethane, meaning that the 1,1,2- isomer was 4 times as toxic as the 1,1,1- isomer. This index was misinterpreted by Lehmann and Flury [3] who gave toxicity in the reverse order.

Effects on Humans

(a) Experimental Central Nervous System Effects

The most harmful effects of 1,1,1-trichloroethane seem to be manifested as CNS disorders. These include impairment of perceptual speed,

reaction time, manual dexterity, and equilibrium.

Anesthesia was induced smoothly by 1,1,1-trichloroethane and maintained uneventfully for 30 minutes in a 30-year-old volunteer in an experiment reported in 1959 by Krantz et al. [32] Recovery was slow but uneventful. The subject complained of being tired for several hours after the anesthesia.

In 1958 and 1959, Dornette and Jones found the concentration of 1,1,1-trichloroethane to vary from 10,000 to 26,000 ppm for induction of anesthesia, and to vary from 6,000 to 22,500 ppm for maintenance of light anesthesia in surgical patients. [33] The patients were given 0.43 mg of atropine and 11 mg of morphine by intramuscular injection 1 hour before induction of anesthesia. Nitrous oxide-oxygen (4:1) was used as the vehicle for 1,1,1-trichloroethane and as a supplemental anesthetic agent.

The investigators [33] found that, because of the lack of an irritating odor, the 1,1,1-trichloroethane could be administered concurrently with the start of the nitrous oxide and that light plane 1 anesthesia (analgesia and progressive loss of consciousness) usually occurred within 2 minutes after the onset of administration. They [33] did not attempt to assess the effect of 1,1,1-trichloroethane alone, but considered that at least one-quarter of the total narcosis could be attributed to the nitrous oxide. Recovery from light plane 1 anesthesia and recovery of reflexes usually occurred within 3-5 minutes after discontinuation of the anesthetic agent.

Electroencephalographic patterns during 1,1,1-trichloroethane anesthesia were reported by Siebecker et al [34] to show little change before circulatory depression, and the changes were similar to those during

2-bromo-2-chloro-1,1,1-trifluoroethane (halothane) anesthesia. The investigators [34] found 1,1,1-trichloroethane to be clinically less potent than either chloroform or 2-bromo-2-chloro-1,1,1-trifluoroethane, and even less potent than trichloroethylene in supplementing nitrous oxide-oxygen for anesthesia.

In an experiment reported in 1961 by Stewart et al, [35] the exposure chamber concentration was increased continuously from 0 to 2,650 ppm for 15 minutes (total exposure). One of seven exposed subjects became very lightheaded when the concentration reached 2,600 ppm, and at 2,650 ppm, two could not stand, and three others became very lightheaded. Two of the seven subjects did not become lightheaded. One subject maintained the ability to perform a normal Romberg test (loss of proprioceptive control evidenced by unsteadiness of standing patient when eyes are closed) throughout the exposure. The other six subjects regained their equilibrium within 5 minutes after cessation of exposure. The five subjects who became lightheaded reported a feeling of malaise for 5 hours after the exposure. The inhibited 1,1,1-trichloroethane used in this experiment contained 94-97% 1,1,1-trichloroethane, 2.4-3.0% dioxane, 0.12-0.3% butanol, and small amounts of 1,2-dichloroethane, water and other materials. [35]

Equilibrium was disturbed and the Romberg test was positive in subjects exposed at 1,740-2,180 ppm of uninhibited 1,1,1-trichloroethane in experiments reported by Torkelson et al in 1958. [36] Groups of two to four individuals were exposed at each concentration. Other concentrations studied by these investigators were about 500 ppm or 1,000 ppm. Lightheadedness was experienced by three of four subjects exposed at 1,000 ppm for 70-75 minutes. Coordination and equilibrium as measured by Flanagan

tests (aptitude classification test of coordination) during exposure, and Romberg tests following exposure, were impaired. [36] Equilibrium was not disturbed by exposures at 1,000 ppm for 30 minutes and neither reflexes nor equilibrium was disturbed by exposures at 500 ppm for up to 450 minutes.

Stewart et al [35] reported responses of their subjects to three different exposures at about 900 ppm of the same inhibited 1,1,1-trichloroethane. The results are presented in Table III-2.

TABLE III-2

RESPONSE OF HUMAN SUBJECTS EXPOSED
AT 900 ppm 1,1,1-TRICHLOROETHANE

Exposure Data	Response
900 ppm (3 subjects) 20 minutes	Positive Romberg in 1 subject; greater effort required to perform normal Romberg in 2 subjects; normal heel-to-toe walking; lightheadedness in 2 subjects
910 ppm (2 subjects) 35 minutes	Increased mental effort required to perform normal Romberg test; heel-to-toe walking performed well; persistent lightheadedness in 1 subject
951 ppm (3 subjects) 73 minutes	Increased mental effort required to perform normal Romberg test after 10 minutes of exposure; consistently positive Romberg tests in 1 subject after 15 minutes of exposure; heel-to-toe walking performed well by all; no lightheadedness

Adapted from Stewart et al [35]

There were no symptoms of central nervous system response at 500 ppm of this inhibited 1,1,1-trichloroethane observed by Stewart et al [35] in two experiments in each of which six subjects were exposed for up to 3

hours. Neither balance nor coordination was affected.

Psychophysiologic performance in six students, 20-23 years of age, was studied by Salvini et al [37] during exposures to inhibited 1,1,1-trichloroethane at 350 and 450 ppm. [26] The psychophysiologic tests, including a perception test, the Wechsler memory scale, complex reaction time test, an aspiration test, and a manual dexterity test by the O'Connor method were performed during the first and last hours of 8 exposure hours. The subjects were exposed individually in a 4 x 3 x 4 meter room at 20 C and 45% relative humidity from 8:30 AM to 12:30 PM and from 2 to 6 PM. During exposure the subjects alternated their activity with a 1-hour study period followed by 20 minutes of physical exercise (3 k cal/minute). [37]

The only factor that was reported to be statistically significant with regard to 1,1,1-trichloroethane was the interaction between perception of mental strain and 1,1,1-trichloroethane exposure at 450 ppm. Under stress conditions, exposure to 1,1,1-trichloroethane at 450 ppm decreased perceptive capabilities. [37] Because of the choice of subjects (healthy students) as well as the lack of controls on intervening variables (food and drinking habits), it would seem that further work is needed to justify a dose-response relationship.

Twelve subjects were exposed at 250, 350, 450 and 550 ppm of 1,1,1-trichloroethane in inspiratory air during four continuous 30-minute periods in an experiment reported by Gamborale and Hultengren [38] in 1970. The air-gas mixture was supplied via a breathing valve and a mouthpiece with very low resistance. The effects of the introduction of the breathing tube were not assessed. In the final 20 minutes of each exposure period, five performance tests were made. Two of them were tests of perceptual speed

and the others were tests of simple reaction time, choice reaction time and manual dexterity.

The same subjects were also studied in control conditions in which inspiratory air contained no 1,1,1-trichloroethane but in which all operations and measurements were the same as during exposure to the solvent. The presence or absence of 1,1,1-trichloroethane was completely disguised for the subjects by menthol crystals in a canister, introduced through the tube to the mouthpiece. To balance the training effects between conditions, the order of conditions was reversed for half the subjects. [38]

The change in mean performance level during exposure to the increasing concentrations of 1,1,1-trichloroethane differed systematically from the change under control conditions. The level of performance in the manual dexterity test and two perceptual tests was affected by training, but the training effect was less pronounced during exposure to 1,1,1-trichloroethane. The tests of reaction time were less sensitive to training and with these there was an absolute decline in performance capability as the exposure concentration increased. [38] This study suffers from several deficiencies, as the substance used to disguise the 1,1,1-trichloroethane odor may itself have had a toxic effect and the introduction of a breathing tube may have induced stress in the subjects.

Statistically significant performance differences between experimental and control conditions were obtained for all tests with exposures at 350 ppm or more. 1,1,1-Trichloroethane had an adverse effect on subject performance capability at 350 ppm. [38]

An experiment designed to simulate occupational exposures was reported by Stewart et al [39] in 1969. Mild sleepiness occurred repeatedly in four of five subjects exposed 6.5 to 7 hours daily for 5 consecutive days at 500 ppm of a commercial 1,1,1-trichloroethane preparation. Other subjective symptoms of central nervous system response that were occasionally experienced by the subjects were lightheadedness and mild headache. The ability of two subjects to perform a modified Romberg test was impaired during the last 5-6 hours of each daily exposure. Their ability to perform the test normally was regained 5-10 minutes after removal from exposure. [39]

The 1,1,1-trichloroethane [26] used in this experiment contained (in liquid form) 4 vol% of 1,4-dioxane, 0.5 vol% butylene oxide, and 0.5 vol% of nitromethane as inhibitors. The liquid also contained traces of 1,2-dichloroethane (1,755 ppm), 1,1-dichloroethane (803 ppm), chloroform (385 ppm), carbon tetrachloride (370 ppm), trichloroethylene (245 ppm), 1,1,2-trichloroethane (147 ppm), and vinylidene chloride (176 ppm). [39]

(b) Effects on the Cardiovascular System

Depression of the circulatory system was found with 1,1,1-trichloroethane, evidenced by a drop in blood pressure and bradycardia.

Blood pressure dropped to 70% of the preanesthetic level, but no significant electrocardiographic changes were found during the anesthesia reported by Krantz et al [32] in 1959.

A drop in systolic blood pressure of 5-10 mm of mercury in about 50% of their patients during 1,1,1-trichloroethane anesthesia was reported by Dornette and Jones. [33] In three patients, there was a greater drop in systolic blood pressure, and in one of these, a drop of 60 mm of mercury

was observed. In all three, blood pressure returned to preoperative levels when the 1,1,1-trichloroethane concentration was reduced to maintenance levels. Electrocardiograms of 32 of the patients showed 6 cases of changes in nodal rhythm, 3 cases with occasional premature ventricular contractions, 2 cases with frequent premature ventricular contractions, and 2 cases with depressed S-T segments. One case of cardiac arrest during light anesthesia with 1,1,1-trichloroethane was reported, but the authors [33] considered there was no definite evidence to either incriminate or absolve 1,1,1-trichloroethane.

Depression of the circulatory system, evidenced by hypotension and bradycardia, was reported by Siebecker et al [34] to be an effect of 1,1,1-trichloroethane during anesthesia.

Stewart et al [35] did not find blood pressure changes in their subjects exposed to inhibited 1,1,1-trichloroethane when its concentration rose from 0 to 2,650 ppm for 15 minutes, or at 900-955 ppm for up to 75 minutes.

Electrocardiograms of four individuals were normal throughout exposures of 70-75 minutes duration at 900-1,000 ppm of uninhibited 1,1,1-trichloroethane in the experiment reported by Torkelson et al. [36] They found no significant changes in pulse rate or blood pressure during 450 minutes of exposure at 415-590 ppm of uninhibited 1,1,1-trichloroethane. [36]

Trochimowicz et al [40] did not find cardiac sensitization in a study of 41 dogs given 0.5% (v/v) 1,1,1-trichloroethane. An experimental group was subjected to myocardial infarction by placement of a copper wire within selected sites of the descending left coronary artery. Results

demonstrated greater potential for sensitization, evidenced by changes in the ECG and serum glutamic-oxaloacetic transaminase (SGOT) levels, in the group that recovered from infarction as compared to the normal, healthy group.

(c) Effects on other Organ Systems

Serum transaminase (unspecified) was studied by Dornette and Jones [33] in five patients before anesthesia and 2, 4, and 6 days after anesthesia. Although there were slight increases noted in two patients, the authors [33] concluded that anesthesia with 1,1,1-trichloroethane of up to 2 hours duration would not be hepatotoxic.

Positive urinary urobilinogen was found 7 hours after exposure in two of seven male subjects exposed for 15 minutes to inhibited 1,1,1-trichloroethane in a concentration increased continuously from 0-2,650 ppm during the 15-minute exposure. [35] On examination of centrifuged urine, five subjects were found to have 1-2 red blood cells per high-power field, compared to none before exposure.

Elevated urinary urobilinogen was reported by Stewart et al [35] in one of three male subjects 20 hours after removal from a 20-minute exposure at 900 ppm of inhibited 1,1,1-trichloroethane. In one experimental exposure of six male subjects at 500 ppm of inhibited 1,1,1-trichloroethane for 78 minutes, 3-6 red blood cells per high power field and a trace of albumin were found in the urine of one subject 20 hours after the exposure. Serum glutamic-oxaloacetic transaminase was not affected by any of the exposures reported by Stewart et al. [35]

In a subsequent experiment reported in 1969 by Stewart et al, [39] there were no clinical findings indicative of liver or kidney injury in

subjects exposed about 7 hours/day on 5 consecutive days at 440-560 ppm of a different inhibited 1,1,1-trichloroethane preparation. Torkelson et al [36] did not find evidence of liver or kidney injury in subjects experimentally exposed at 450-590 ppm of uninhibited 1,1,1-trichloroethane for up to 450 minutes or at 900-1,190 ppm for up to 75 minutes. McNutt et al, [41] found significant changes in the livers of mice exposed at 1,000 ppm 1,1,1-trichloroethane continuously for 14 weeks and minor changes in mice exposed at 250 ppm. Changes in the 1000 ppm group included triglyceride accumulation, necrosis of hepatocytes, and cytoplasmic alterations of centrilobular hepatocytes. Cytoplasmic alterations were described as "mild to minimal" in the 250 ppm group.

(d) Intentional, Accidental, or Suicidal Exposures

Nausea, vomiting, diarrhea, and fatigue were the overt signs of poisoning reported by Stewart and Andrews [42] in 1966 in a 47-year-old worker who drank 1 oz of inhibited 1,1,1-trichloroethane. The onset of nausea began about 30 minutes after the ingestion, gastric lavage was performed on hospitalization 2 hours later, and the vomiting and diarrhea subsided 6 hours after ingestion. During this time the patient remained oriented, coordinated and alert, and there were no abnormal findings in a detailed neurologic examination. His blood pressure was 120/80 and his heart rate was 84 beats/minute.

At the time of admission to the hospital the hematocrit was 53% and hemoglobin concentration was 18 g/100 ml. Proteinuria was 1+ and there were 8-10 red blood cells in a high-power field examination of concentrated urine. A slight elevation in serum bilirubin concentration was found 48 hours after hospitalization. Other findings, including urinalysis, SGOT,

serum glutamic-pyruvic transaminase (SGPT), blood urea nitrogen (BUN), and ECG, remained normal. [42]z

Serum bilirubin concentrations of 2-11 mg/100 ml (normal < 1.5 mg/100 ml), SGOT of 340-1,110 Karmen units (normal = 5-40), alkaline phosphatase of 7-30 Bessey-Lowry units (normal = 0.8-2.5), prothrombin time of 17/12-20/12 seconds (normal = 70-100%), and thymol turbidity of 8-15 units (normal = 0-6 units) were reported in 1969 by Litt and Cohen [43] in five teenage boys who had sniffed a spot remover containing 1,1,1-trichloroethane and trichloroethylene. These data are probably indicative of liver damage. All five were nauseated immediately after inhalation. Two of them reported nervous system symptoms including paresthesia, tinnitus, ataxia, and headache. In addition to the complications imposed on the interpretation of this report by the mixed composition of the inhalant, three of the patients had also sniffed glue, and one had "snorted" heroin. Among five other patients in whom findings of impaired liver or kidney function were not found, only one became nauseated after sniffing the spot remover. [43]

Two fatal cases in which the subjects intentionally inhaled cleaning fluids containing 1,1,1-trichloroethane were reported by Hall and Hine [44] in 1966. A 19-year-old woman was observed sniffing cleaning fluid over several days and acting irrationally. She was found dead on her bed. Pathologic findings on autopsy were confined to the respiratory system, stomach and brain. The vessels of the bronchi were congested, and the bronchi contained thick, yellowish-brown secretions. There was passive congestion throughout the lungs and the parenchyma showed considerable amounts of thick, dark red blood and thin frothy fluid in the congested

areas. The mucosa of the stomach was hyperemic. The leptomeninges were thin, glistening, transparent and markedly congested. The ventricles (brain) contained clear cerebrospinal fluid. The vascular markings were prominent, and there was acute passive congestion throughout the brain. [44]

There were indications of chronic, intentional inhalation of a cleaning fluid containing 1,1,1-trichloroethane in the other fatal case studied by Hall and Hine. [44] In this case, a 29-year-old man was found dead in bed with a washcloth over his mouth. There were several empty cleaning fluid cans in the room. On autopsy, pathologic findings were confined to the respiratory system and the kidneys. The lungs were congested and edematous, the vessels were dilated, and small hemorrhagic areas were present. The kidneys showed marked vascular congestion around the pyramids, especially on the periphery. [44]

In neither of the cases reported by Hall and Hine [44] were drugs or solvents detected in the stomach contents, and no barbiturates were found in the blood.

Twenty-nine cases of sudden death in the United States from sniffing 1,1,1-trichloroethane during 1964-69 were reported by Bass. [45] These 29 deaths were among 110 cases of sudden death from sniffing volatile hydrocarbons and halocarbons studied by the author. [45] Suffocation in plastic bags was not a factor in any of these 110 cases, and death was quick in all. In 18 of the 110 cases, death followed sniffing and some sort of exercise. No anatomical abnormalities were found from gross or microscopic post mortem examinations which would explain the sudden deaths. The author [45] discussed the possibility that the deaths resulted from

cardiac sensitization to endogenous catecholamines.

Serum enzyme studies of a patient who was hospitalized after inhaling a mixture of 1,1,1-trichloroethane and trichloroethylene were reported by Griffiths et al [46] in 1972. The man's respiration was arrested by the time that he entered the hospital, probably due to the effects of the mixture inhaled. Prothrombin activity was 60-91% of normal on days 1-4 and 100% on day 5. The SGOT measurements by the Reitman-Frankel method were 85, 160, 270, and 176 on days 1-4, respectively, (normal = 8-40 units). Lactic dehydrogenase (LDH) measurements by the Wroblewski-LaDue method were 450, 1,690 and 1,020 on days 1, 3, and 5, respectively, (normal = 200-500 units). Fractionation of LDH on day 5 showed that its major source was the heart. The patient died on day 5 without regaining consciousness. Some heart cell necrosis and early fatty metamorphosis in the liver were found on autopsy.

Twenty-one deaths from abuse or gross misuse of decongestant aerosol sprays containing 1,1,1-trichloroethane in the solvent resulted in removal of several such products from the market (Federal Register 38:21935-36, 1973).

(e) Effects of Occupational Exposures to 1,1,1-Trichloroethane

Industrial experiences with 1,1,1-trichloroethane exposed workers were discussed by Torkelson et al [36] in 1958. They reported that when it was used in confined spaces, varying degrees of anesthesia had occurred, and that two individuals had died from exposures in unventilated tanks. The authors did not give any additional information about these incidents. However, Irish [14] considered that the concentrations may have been near saturation, approximately 167,000 ppm. He gave the exposure time of one

worker as 30 minutes, and stated that the exposure time was not known in the other case.

Another death from occupational exposure to 1,1,1-trichloroethane in an open tank was reported by Stewart [47] in 1963. The vapor concentrations were reported to have "exceeded several thousand ppm." No other details were reported.

A more detailed account of a fatal occupational exposure to 1,1,1-trichloroethane was given by Kleinfeld and Feiner [48] in 1966. A man was working in a 14 x 7 x 7 foot vault cleaning grease from conduits with rags dipped into 1,1,1-trichloroethane. He left the vault, reentered to connect a circulating fan, but left before connecting the fan. He collapsed shortly after emerging, and stopped breathing. Mouth-to-mouth resuscitation and oxygen failed to revive the worker. It was estimated he spent 10 minutes in the vault and that the 1,1,1-trichloroethane concentration was "in excess of 5,000 ppm." [48]

Six fatal occupational exposures to 1,1,1-trichloroethane were reported by Stahl et al [49] in 1969. The 1,1,1-trichloroethane had been used for paint removal in one, for cleaning an air vent in another case, and for cleaning electrical equipment in the other four cases. In five cases, the work was performed in closed spaces. The circumstances of exposure in the sixth case were not as well defined. All of the workers were found dead in their exposure areas. The skin of two of these workers was reported to be cyanotic. Congestion and edema of the lungs were found in all the workers at autopsy. Varying amounts of congestion were also found in other organs. [49]

An extensive report of gross and microscopic autopsy observations of a worker who died while working with 1,1,1-trichloroethane in a confined space was given by Hatfield and Maykoski [50] in 1970. A 27-year-old worker was found in a 450-gallon aircraft tip tank which he had been cleaning with a pad saturated with 1,1,1-trichloroethane. When found by fellow workmen he was unresponsive, cyanotic and apneic. Articifical respiration was unsuccessful and the worker died. Significant autopsy findings included considerable congestion of some myocardial vessels, moderate edema and marked congestion of the lung parenchyma with focal extravasations of red blood cells into the alveoli, and acute passive congestion of the spleen, kidneys, and brain. Eighty minutes after the accident, 500 ppm of 1,1,1-trichloroethane were found in the tank. The work conditions were simulated later and concentrations of 36,000-62,000 ppm were generated. [50]

In their 1958 discussion of occupational experience with 1,1,1-trichloroethane, Torkelson et al [36] reported that they knew of four cases of illness or unconciousness from work in confined areas. In these four cases the individuals had recovered quickly after removal from exposure and aftereffects were not observed. No details of these incidents were reported.

Giddiness and lightheadedness were experienced by three coworkers of the fatal case reported by Kleinfeld and Feiner [48] in 1966. These men worked in a 14 x 7 x 7 foot underground vault removing grease from conduits with rags dipped into 1,1,1-trichloroethane. When they noticed their symptoms, they emerged from the vault into fresh air, and apparently had an uneventful recovery.

Four men experienced "minor effects," particularly giddiness, from exposure to 1,1,1-trichloroethane, but continued to work with it. [49] They were cleaning electrical equipment in two closed compartments of a ship with a spray apparatus. Neither the duration of exposure nor the exposure concentrations were reported. One man, who apparently had been unconcious, awoke and found his three coworkers dead. These three deaths were discussed previously. Aftereffects of the survivor were not reported by Stahl et al. [49]

Dizziness to the point of being unable to stand was experienced by a worker while cleaning a floor with 1,1,1-trichloroethane. [51] This case was one of four acute exposures reported by Stewart [51] in 1971. The worker poured large quantities of 1,1,1-trichloroethane on the floor and mopped up the excess with rags while on his hands and knees. The room, 15 x 15 x 8 feet, was ventilated by one door. The worker was exposed for about 1 hour with intermittent exits to fresh air for 1-2 minutes to relieve his dizziness. Fifteen minutes after exposure he was still dizzy but he was lucid and well-oriented. An abnormal Romberg's sign was found in a detailed neurologic examination. One hour later, results of a repeated detailed neurologic examination were normal. The worker felt marked fatigue for 24 hours. Other findings at the time of the incident, and for 6 days thereafter, were normal. The tests included electrocardiograms and those for liver and kidney function. [51]

Another case reported by Stewart [51] in 1971 was that of a 55-year-old man who used 1,1,1-trichloroethane to remove ceiling-tile adhesive. He worked for 1 hour in a poorly ventilated room, became dizzy, and fell from a ladder, suffering a scalp injury. Fifteen minutes later, the results of

a detailed neurologic examination with the patient supine were normal. Other tests, including those for liver and kidney injury and an ECG, were normal. Sixteen hours following exposure the patient was asymptomatic. However, on the fourth day after exposure, this worker's urinary urobilinogen rose to 9 units/24 hours and remained elevated for 4 days. Reticulocyte counts were between 0.3 and 0.45%. Results of other clinical tests, repeated over 10 days, remained normal.

The subject of a third case reported by Stewart [51] in 1971 was a 47-year-old man with coronary artery disease. The man became dizzy and nauseated when he spent 2 hours cleaning a crane with a sponge, which he continually soaked in 1,1,1-trichloroethane (contained in an open 5-gallon pail). Thirty minutes after removal from exposure he was anxious and perspiring. Results of a detailed neurologic examination, ECG, and tests for liver and kidney injury were normal.

A worker who experienced a sudden onset of nausea, vomiting, "explosive diarrhea" and dizziness 2 hours after leaving work was the subject of a fourth case reported by Stewart. [51] The previous day the man had worked in the vicinity of an engine cleaning operation where 1,1,1-trichloroethane had been used and he had been aware of its odor throughout the day. His illness, however, was not attributed by the author to the effects of 1,1,1-trichloroethane. The illness lasted for 6 hours. Results of a physical examination by the plant physician the following morning were "completely normal."

(f) Absorption and Excretion

Absorption of inhaled 1,1,1-trichloroethane from alveolar air was studied with Cl-38 labeled 1,1,1-trichloroethane by Morgan et al [52] and

reported in 1970. Approximately 5 mg of pure, labeled 1,1,1-trichloroethane diluted with air was inhaled in a single breath. The breath was held for 20 seconds to ensure maximum absorption and the subject exhaled through a trap containing 50 grams of 18/52 mesh granulated charcoal. The subject then inhaled one breath of room air and exhaled again through the same charcoal. The amount asorbed on the charcoal was subtracted from the amount inhaled to give the absorbed dose. After the admistration, the subject continued to inhale room air and to exhale through a charcoal trap. The traps were changed initially every 2 minutes and later every 10 minutes for 1 hour. In that time, 44% of the total dose of inhaled 1,1,1-trichloroethane was excreted in the exhaled breath. The Cl-38 labeled 1,1,1-trichloroethane activity was measured by gamma-ray scintillation spectrometry. [52]

Stewart et al [9] studied breath analysis in subjects exposed at 0, 100, 350 and 500 ppm 1,1,1-trichloroethane to develop a method for biologic monitoring. A total of twenty men and women were exposed at those concentrations for periods of 1, 3, and 7.5 hours in a controlled environment chamber. Chamber air was measured by a Wilks MIRAN-I monitoring device, with a gas chromatograph as a backup system. Breath samples were analyzed for 1,1,1-trichloroethane by gas chromatography. Exposures were repeated for up to 4 weeks. Breath samples were taken from 1 minute to 71 hours after exposure at each exposure level. The authors found that the rate of 1,1,1-trichloroethane excretion was a function of exposure duration. The data generated a family of postexposure breath decay curves that could be used to estimate the magnitude of exposure. 1,1,1-Trichloroethane was readily detectable 16 hours after exposure at 100

ppm for 7.5 hours. Some data are presented in Table III-3.

TABLE III-3

1,1,1-TRICHLOROETHANE BREATH CONCENTRATIONS
OF MEN AND WOMEN EXPOSED AT 350 ppm

Time	Men			Women		
	No.	Mean	Range	No.	Mean	Range
	Isolated 1-Hour Exposure					
2 Minutes preexit exposure	3	150	144 - 157	3	183	173 - 193
1 Minute post exposure	3	76.4	48.6 - 108	2	120	116 - 123
23 Hours post exposure	3	1.11	0.75 -1.63	2	0.8	0.57 - 1.03
	Isolated 7.5-Hour Exposure					
2 Minutes preexit exposure	4	234	222 - 252	3	254	247 - 262
1 Minute post exposure	4	149	444 - 153	4	181	156 - 205
16 Hours post exposure	4	7.07	6.62 - 7.73	4	6.93	4.83 - 8.74

Adapted from Stewart et al [9]

Absorption of liquid 1,1,1-trichloroethane through the skin was studied by Stewart and Dodd [53] and reported in 1964. Six subjects each immersed one thumb in a beaker of 1,1,1-trichloroethane for 30 minutes. The experiment was designed to prevent contamination of the inhaled air with 1,1,1-trichloroethane. Alveolar air samples were collected when their thumbs had been submerged for 10, 20, and 30 minutes. 1,1,1-Trichloroethane concentrations in alveolar air were measured by a gas chromatograph equipped with both an electron capture detector and a hydrogen flame detector. The ranges of concentrations of 1,1,1-trichloroethane found in the alveolar air are shown in Table III-4.

TABLE III-4

1,1,1-TRICHLOROETHANE CONCENTRATIONS
FOUND IN ALVEOLAR AIR OF
EXPERIMENTAL SUBJECTS

Duration of Immersion	Alveolar Air Concentrations, ppm
10 minutes	0.10 - 0.10
20 minutes	0.14 - 0.37
30 minutes	0.19 - 1.02

Adapted from Stewart and Dodd [53]

On another occasion, one of the subjects immersed one hand in 1,1,1-trichloroethane for 30 minutes. The maximum concentration of 1,1,1-trichloroethane found in this subject's alveolar air (21.5 ppm) occurred 10 minutes after his hand was removed from the liquid. [53]

Further information on absorption of 1,1,1-trichloroethane was not found in a search of the literature. However, concentrations of 1,1,1-trichloroethane have been studied in the blood [35,54] and breath [54] of subjects during exposure and several investigators have studied concentrations of 1,1,1-trichloroethane in alveolar air of subjects after removal from experimental exposures. [35,39,52,54-57]

1,1,1-Trichloroethane in the blood was determined during and after exposure in the experiments reported by Stewart et al. [35] The concentrations are listed in Table III-5.

TABLE III-5

1,1,1-TRICHLOROETHANE
CONCENTRATIONS IN BLOOD
AFTER EXPERIMENTAL EXPOSURES

Exposure Conditions	Sampling Time, Minutes	Blood Concentrations 1,1,1-Trichloroethane, ppm
500 ppm	30	1.5
78 minutes	7.5	6.5
	25, after removal from exposure	Just detectable in 4 of 6 subjects
955 ppm	15	1
73 minutes	30	2 - 4
	65	7 - 10
	30 post exposure	Not detected
0 - 2,650 ppm	9 post exposure	5 ± 1
15 minutes total exposure time	20 post exposure	0.5 ± 1

Adapted from Stewart et al [35]

A comprehensive study of blood concentrations of 1,1,1-trichloroethane during exposure was reported by Astrand et al. [54] The data show effects of exercise, exposure time, and exposure concentration on blood levels. Some of the data are presented in Table XII-2. The simultaneous concentrations of 1,1,1-trichloroethane in the alveolar air, arterial blood, and venous blood were studied. Twelve healthy, young male subjects were exposed at 250 and 350 ppm of 1,1,1-trichloroethane during rest and during periods of exercise. A linear correlation was found between alveolar air and blood concentrations of 1,1,1-trichloroethane (within the alveolar air, a concentration range of 100-300 ppm, and in the arterial blood, a concentration range of 2-8 ppm). The concentrations in

alveolar air and the arterial blood with exposure at 350 ppm during rest were the same as with exposure at 250 ppm during light exercise. [54]

Table III-6 lists the reported concentrations of 1,1,1-trichloroethane in the blood of victims of fatal intoxication.

TABLE III-6

REPORTS OF 1,1,1-TRICHLOROETHANE CONCENTRATIONS IN THE BLOOD OF VICTIMS OF FATAL INTOXICATION

Authors		Concentrations, ppm
Hatfield and Maykoski [50]	1 case	60 ppm
Stahl et al [49]	3 cases	1.5*, 60, 62, and 120 ppm
Hall and Hine [44]	2 cases	130 and 720 ppm

* This death was attributed to suffocation

The concentration of 1,1,1-trichloroethane in the alveolar air during and after removal from exposure were found to depend on the exposure concentration, [35,54,55] the duration of exposure, [35] the time since the last exposure, [35,39,52,54-58] the breathing capacity of the subject, [54,55] previous exposure history, [39] exercise during exposure, [54] and individual factors. [55]

After exposure of six subjects at 600 ppm of 1,1,1-trichloroethane for 3 hours, Gazzaniga et al [56] found the concentrations in alveolar air shown in Table III-7.

TABLE III-7

CONCENTRATIONS OF 1,1,1-TRICHLOROETHANE
IN THE ALVEOLAR AIR OF SUBJECTS
EXPOSED AT 600 ppm FOR 3 HOURS

Time After Removal From Exposure	Concentrations, ppm	
	Average	Range
1 minute	77	65-90
4 hours	46	40-50
12 hours	21	15-25
24 hours	10	7-13
48 hours	2	1-3.5
96 hours	1	0.5-1

Adapted from Gazzaniga et al [56]

In a similar experiment reported by Stewart et al, [35] the concentrations in the exhaled air decreased at a faster rate than was reported by Gazzaniga et al. [56] After subjects were removed from 3 hours of exposure at 496 ppm of inhibited 1,1,1-trichloroethane, Stewart et al [35] reported the alveolar air concentrations in Table III-8.

TABLE III-8

CONCENTRATIONS OF 1,1,1-TRICHLOROETHANE
IN THE ALVEOLAR AIR OF SUBJECTS
EXPOSED AT 496 ppm FOR 3 HOURS

Time After Removal From Exposure	Concentrations (ppm)	
	Average	Range
30 minutes	65	35-90
1 hour	38	30-40
4 hours	20	19-21
20 hours	2.6	1.5-4

Adapted from Stewart et al [35]

With exposures of 2 hours duration at 460 and 632 ppm of 1,1,1-trichloroethane, Fukabori [55] reported average alveolar air concentrations in four subjects after removal from exposure, as shown in Table III-9.

TABLE III-9

CONCENTRATIONS OF 1,1,1-TRICHLOROETHANE
IN THE ALVEOLAR AIR OF SUBJECTS
EXPOSED AT 460 AND 632 ppm FOR 2 HOURS

Time After Removal From Exposure	Concentrations, ppm			
	460 ppm exposure		632 ppm exposure	
	Average	Range	Average	Range
Immediately	134	127-140	222	187-279
30 minutes	34	36-36	69	60-77
1 hour	23	22-25	41	34-53
4 hours	4.6	2.1-8.9	9.7	6.5-15

Adapted from Fukabori [55]

When subjects were exposed by Stewart et al [39] to inhibited 1,1,1-trichloroethane 6.5 to 7 hours/day on 5 consecutive days at an average concentration of 507 ppm (420-612 ppm), the concentrations in the alveolar air 16 hours after removal from each daily exposure increased on successive days. They [39] did not present the data, but reported that 1,1,1-trichloroethane was found in alveolar air for 1 month after the last exposure.

1,1,1-Trichloroethane and tetrachloroethylene were both still present in the breath of one individual at 0.1 ppm 1 month after removal from an exposure to the vapors of these two compounds. [57] The individual was exposed 7 hours/day for 5 days to a vapor mixture containing 370 ppm of 1,1,1-trichloroethane and 130 ppm of tetrachloroethylene. [57,58]

Application of breath analysis to evaluate occupational exposure was reported in 1972 by Prost et al. [59] They found that collection of expired air samples in bags was acceptable to the workers. They took breath samples 1 hour before the end of the workday and immediately after the workday. The study involved only 12 workers and the investigators [59] considered that it was inadequate for making formal conclusions. However, from results of analysis of the breath samples the investigators were able to differentiate the workers exposed at greater concentrations of 1,1,1-trichloroethane from those exposed at lesser concentrations. The expired air of degreasers working in a confined environment without ventilation contained 25 ppm of 1,1,1-trichloroethane compared to 3-5 ppm found in the expired air of subjects doing similar work in a larger room with ventilation. [59]

Stewart et al [35] reported that only trace amounts of 1,1,1-trichloroethane were excreted in the urine. Morgan et al, [52] using C1-38 labeled 1,1,1-trichloroethane, found that the urinary excretion rate of labeled compounds during the first hour after inhalation was less than 0.01% of the total dose/minute.

(g) Metabolism

The metabolites of 1,1,1-trichloroethane which have been found in man are carbon dioxide, trichloroethanol (TCE), and trichloroacetic acid (TCA). [39,55,59-61] The major metabolite would seem to be TCE with smaller amounts of TCA and CO2 present. [39]

In the study reported by Stewart et al [39] in 1969, the 24-hour urinary excretion of TCA and TCE by the subjects repeatedly exposed at 500 ppm of 1,1,1-trichloroethane, 7 hours/day for 5 days, was as detailed in Table III-10.

The analytical method used by Stewart et al [39] for determining TCA and TCE was not mentioned in the report.

Trichloroacetic acid in the urine of two subjects exposed to 1,1,1-trichloroethane was studied by Tada [60] and reported in 1969. The subjects were first exposed at average concentrations of 210 ppm during six 2-hour sessions; one on the first day, two on the second, two on the third, and one on the fourth day. Urine samples were collected periodically to determine the TCA concentration, adjusted to a specific gravity of 1.024, as well as the total amount excreted per day. TCA was determined by the alkali-pyridine-benzidine method. The concentration of TCA in the urine and the total amount excreted per day increased each day of exposure, then slowly decreased over the next 4 days. The maximum amount excreted per day was 3.1 mg, averaged for the two subjects.

TABLE III-10

URINARY METABOLITES OF
1,1,1-TRICHLOROETHANE IN MAN

Sample time Relative To Exposure*	Urine Concentrations Averages And Ranges, mg/24 Hours	
	TCA	TCE
Preexposure	14.2 (8.0-11.8)	1.0 or less
First exposure day	7.5 (2.6-10.5)	20.1 (7.9-49.0)
Second exposure day	10.9 (8.2-19.3)	30.1 (14.8-66.5)
Third exposure day	12.3 (5.6-27.0)	29.3 (19.1-51.0)
Fourth exposure day	14.1 (7.8-19.2)	46.6 (23.4-93.6)
5 days after last exposure	18.0 (13.0-26.0)	7.0 (1.0-14.9)
12 days after last exposure	17.0 (8.0-22.0)	less than 1.0

* Exposure at 500 ppm 1,1,1-trichloroethane
Adapted from Stewart et al [39]

In a second experiment reported by Tada, [60] the same two subjects were exposed at an average of 420 ppm 1,1,1-trichloroethane, 2 hours/day for three days. With this exposure, both the TCA concentration in the urine and the total amount excreted per day continued to increase on the 2 days following the last exposure, before beginning to decline on the third and fourth days after exposure. The maximum amount excreted per day was 7.2 mg, averaged for the two subjects.

Excretion of TCA in the urine of two subjects was studied for 8 days and reported by Fukabori [55] in 1970. These subjects were exposed 2 hours/day to 1,1,1-trichloroethane at average concentrations of 195 ppm on the first day, 376 ppm on the second, 558 ppm on the third, and 832 ppm on

the fourth day. The maximum amount of TCA (7.5 mg/day) was excreted on the day following the last exposure. Four days after the last exposure, an average of 2.5 mg TCA/liter of urine was found, compared to a normal value in Japanese men of 0-0.9 mg/liter. TCA was measured by Fukabori [55] by the alkali-pyridine-benzidine method.

Trichloroacetic acid has been studied in the urine of workers occupationally exposed to 1,1,1-trichloroethane. [59-61]

A field survey of 15 workers in a printing plant who were exposed to 1,1,1-trichloroethane every workday was reported by Tada [60] in 1969. Urine was collected for 8 hours on workdays 3 through 5. Atmospheric concentrations of 1,1,1-trichloroethane determined every day by the alkali-pyridine two-phase method at various parts of the room averaged 37 ppm for 7-hour workdays. The TCA concentrations in the urine averaged 3.4 mg/liter (3.0-3.7 mg/liter for the daily averages).

Seven of the women studied by Weitbrecht [61] had TCA concentrations of 20-60 mg/liter of urine. The atmospheric exposures of these women were reported to be 40 ppm or less as determined by methyl bromide indicator tubes. The author himself was dubious about the meaning of his air measurements.

Prost et al [59] also studied TCA excretion by workers occupationally exposed to 1,1,1-trichloroethane and concluded that it was not as reliable for evaluation of exposure as analysis of breath for 1,1,1-trichloroethane.

(h) Effects on Mucous Membranes and Skin

Passive congestion and edema were found in the lungs of workers who were found dead from over exposure to 1,1,1-trichloroethane at their places of work in reports by Stahl [49] and by Hatfield and Maykoski. [50]

Chemical analyses or other information about the inhibitors or impurities in the 1,1,1-trichloroethane to which these workers were exposed were not reported.

Marked accumulation of white, frothy, slightly bloody edema fluid was found in the lungs and a small amount of mucoid material was found in the bronchi of one of the fatalities reported by Hall and Hine. [44] The man had inhaled (and possibly aspirated) a 1,1,1-trichloroethane cleaning fluid containing dioxane. [26,39] The other fatality reported by Hall and Hine [44] had habitually inhaled another cleaning fluid containing 1,1,1-trichloroethane. In this case of chronic exposure, passive congestion was found throughout the lungs and there were considerable amounts of thick, dark red blood and thin, frothy fluid in the dependent areas. Thick, yellowish-brown secretions were found in the bronchi. Microscopic findings included some atelectasis in the lung parenchyma, edema and congestion in the lungs and desquamated epithelium in the bronchi. [44]

Slight eye irritation was experienced by one of four subjects during the experimental 30-minute exposure to uninhibited 1,1,1-trichloroethane at 900-1,000 ppm reported by Torkelson et al. [36]

Eye, nose and throat irritation have been experienced during experimental exposures to inhibited 1,1,1-trichloroethane at 400-500 ppm [37] and 420-612 ppm. [39]

Torkelson et al stated that the Dow Chemical Company had received no reports of eye irritation from industrial use of inhibited 1,1,1-trichloroethane at that time (1958), but a few cases of skin irritation associated with its use had occurred. [36]

A slight prickling and mild burning sensation on the dorsal surface of thumbs immersed for 10 minutes in 99% pure 1,1,1-trichloroethane was reported by Stewart and Dodd. [53] A mild, temporary erythema and fine scaling was observed after 30 minutes of immersion.

The subject who immersed his hand in the liquid for 30 minutes experienced a burning sensation at 4 minutes which became uncomfortable after 10 minutes of immersion. [53] At 20 minutes, his hand felt cold and the sensation persisted for 10 minutes after his hand was removed from the 30-minute immersion. A mild erythema persisted for 1 hour and a fine, chalky scale was observed. Repeated dipping of his hand into 1,1,1-trichloroethane caused an intense cold sensation, a mild erythema and a fine scale. The sensation persisted for 45 minutes after exposure and the scaliness was still observable 18 hours later. [53]

Transient irritation of the conjunctiva or the upper respiratory tract and a burning sensation of the tongue were experienced by women using pure 1,1,1-trichloroethane to clean brass frames. [61] There was no burning sensation on intact skin and an initial swelling was not observed by Weitbrecht [61] when the women wet their hands in the washing process. They did experience ice-cold fingers, however, and paleness of the skin of the hands was observed.

Epidemiologic Studies

Chronic exposures to 1,1,1-trichloroethane have not been extensively reported. Torkelson et al [36] reported in 1958 that when 500 ppm of 1,1,1-trichloroethane was used with adequate ventilation, no injuries had occurred. Stewart [47] reported in 1963 that no injury to man following

repeated occupational exposures to vapor concentrations of less than 500 ppm had been observed, and in 1966 he reiterated this. [62] These authors [36,47,62] presented no data to support their statements. Hatfield and Maykoski [50] stated in their 1970 report that 1,1,1-trichloroethane had been used to clean airplane tip tanks for several years without incident. The manner in which the tanks were customarily cleaned resulted in breathing zone concentrations of 100 to 200 ppm, with peaks inside the tanks of 800 ppm. [36] While significant details are missing from these reports, [36,47,50,62] they indicate that overt signs of adverse responses to chronic exposure to 1,1,1-trichloroethane were not apparent to the investigators.

Workers in a shop in central Italy had symptoms which apparently were attributable to substances used in the work cycle, according to a report by Binaschi et al in 1969. [63] The symptoms appeared when an inhibited 1,1,1-trichloroethane preparation began to be used in addition to the solvents already used in the shop. The concentration of 1,1,1-trichloroethane found in the work room air was 250 ppm. Additional details such as the number of workers involved, the nature of the symptoms, and the other solvents involved were not reported. [63]

Nine women washing brass frames in open containers of pure 1,1,1-trichloroethane were studied from the onset of their exposure and were the subject of a report in 1965 by Weitbrecht. [61] Air measurements were made during the summer with methyl bromide indicator tubes, the validity of which for measuring 1,1,1-trichloroethane was considered problematic. An average of 10 ppm of 1,1,1-trichloroethane was found in the general room air and 20 ppm in the worksite air. In addition to vapor exposures, the

women had their hands immersed in liquid 1,1,1-trichloroethane for varying periods of time. Breathing zone samples were not collected. It seems likely that breathing zone concentrations would have been considerably higher if the women were working directly over the solvent containers.

The women experienced transient irritation of the conjunctiva or upper respiratory passages and a characteristic burning sensation of the tongue. They also reported that their teeth felt dull (rhubarb effect). They did not experience a burning sensation or initial swelling when their hands were placed in liquid 1,1,1-trichloroethane. They did have a feeling of ice cold fingers. A sustained paleness of the fingers occurred only at the beginning of the work, otherwise it appeared only when the manipulation was carried out continuously. [61]

After the windows were closed in the fall, the women complained of loss of appetite, pressure in the stomach, vomiting, tiredness, headache, and insomnia. The author [61] considered that these complaints were neurotic chain reactions influenced in part by safety signs in the shop. He did not differentiate the effects of the 1,1,1-trichloroethane exposure from the possible suggestive effect of the safety signs, and didn't comment upon the lack of the safety sign effect in the summer.

Clinically, he found hypertension in six of the women and positive urobilinogen in two; in addition, he reported what he described as autonomic dystrophy in two, circulatory dystrophy in one, and psychasthenia in one. [61]

An epidemiologic matched pair study by Kramer et al [64] measured numerous physiologic parameters of workers in two adjacent textile plants. Detailed blood chemistry and hematology studies were conducted for 151

matched pairs of employees to compare the exposed and unexposed partners. All employees in the exposed group had 1,1,1-trichloroethane (and other solvent) exposures, in varying concentrations, for up to 6 years. The concentration range was 11-838 ppm, with a mean of 115 ppm 1,1,1-trichloroethane. Whether this period of exposure would result in toxic systoms is questionable, however. Since only healthy, active workers were selected, and the average length of exposure for the study population was less than 1 year at the stated TWA, no conclusions can be drawn about chronic effects. The control group had only minimal exposure to nonchlorinated solvents.

Pairs were matched with regard to age, race, sec, work shift, job description and socioeconomic status, and examined within a 10-week period. [64] During the study it was necessary to rematch subjects due to nonparticipation. Subject height, weight, blood pressure and pulse were obtained. Laboratory blood determinations included hematocrit, hemoglobin, red blood cell count (RBC), white blood cell count (WBC), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), alkaline phosphatase, SGOT, SGPT, gamma glutamyl transpeptidase, total bilirubin, urea nitrogen, LDH, uric acid, total protein, A/G ratio, albumin, calcium and phosphorus. Electrocardiograms also were taken. For quantitative variables, t tests and tests of homogeneity of variables were made. Multiple regression analysis was performed on paired differences with respect to environmental variables, and on the combined matched exposed and control populations with respect to demographic variables.

Breathing zone samples were collected, except in a few locations where area sampling was more practical, on charcoal tubes and analyzed on a portable gas chromatograph equipped with a flame ionization detector. Samples of expired air were analyzed immediately after collection by gas chromatography.

After dismissing some subjects' data on the basis of smoking habits, high blood pressure, or prior illness, the authors presented statistical findings but no individual data. [64] 1,1,1-Trichloroethane concentrations in the breath ranged from "less than 5 ppm" to "greater than 30 ppm," with the majority, 127/151, between 5 and 29 ppm. Comparison of the health test data between exposed and control subjects revealed no statistically significant differences except SGPT and albumin. These differences were not discussed at length and the authors concluded that no health impairment was suffered by workers exposed at an average daily concentration of 115 ppm 1,1,1-trichloroethane. The conclusion suffers statistically because many of the exposed groups were not exposed very long or at high level concentrations. The use of their biologic data in the computation of averages and ranges would preclude detection of any toxic effects occurring at the greatest concentrations and exposure times, thru "averaging down" by inclusion of data for much lower levels. Such pooling also increases error variances. For a comparison of the overall exposed and control means, the average differences and the standard deviation of the set of matched differences would have been more appropriate.

Seki and his colleagues [65] surveyed four Japanese printing factories where 1,1,1-trichloroethane, the sole organic solvent in the entire process, was used to remove excess ink. Duration of

workday/workweek and operational procedures were essentially uniform. Enclosure of vapor sources and installation of exhaust systems were, in the authors' opinion, mainly responsible for variation in vapor concentration. Subjects were men 23-53 years old and had been exposed to 1,1,1-trichloroethane vapor for at least 5 years. Laboratory tests, including peripheral hemograms, blood specific gravity and urinalysis for urobilinogen and protein, were not described, but the authors state performance by "conventional methods." A Japanese version of the Cornell Medical Index health questionnaire was answered by all subjects. A test of vibrational sense was performed as well as urinalysis for TCA and TCE. Decrease in urinary metabolite levels provided the basis for calculation of biologic half-life. The vapor concentration of 1,1,1-trichloroethane in the workroom air was determined by gas-liquid chromotography. A preliminary study revealed a fairly constant vapor concentration regardless of time and location of sampling. Data are presented in Tables III-11, III-12, and III-13.

TABLE III-11

URINARY METABOLITE CONCENTRATION IN WORKERS EXPOSED TO 1,1,1-TRICHLOROETHANE

Exposure Concentration (ppm)	Metabolite Concentration (mg/l)*		No. Examined
	TCA	TCE	
4	0.6 (0.5-1.1)	1.2 (0.5-2.6)	10
25	2.4 (1.3-4.6)	5.5 (3.6-8.6)	26
53	3.6 (2.4-5.5)	9.9 (6.8-14.5)	10

* Geometric mean with SD in parenthesis
Adapted from Seki et al [65]

TABLE III-12

RESULTS OF PHYSICAL EXAMINATIONS
OF WORKERS EXPOSED TO 1,1,1-TRICHLOROETHANE

Exposure concentration (ppm)	No. Examined	No. of Healthy Subjects*
4	66	60
25	33	30
28	55	48
53	42	36

* Exclusions listed in Table III-13
Adapted from Seki et al [65]

TABLE III-13

EXCLUSIONS FROM HEALTHY CATEGORY
BY CLASS OF DISORDER

Class of Disorder	No.
Cardiovascular	10
Hepatic	3
Gastrointestonal	4
Renal	2
Bone	1
CNS	1

Adapted from Seki et al [65]

The authors found, through regression analysis, a linear relationship between the vapor concentration of 1,1,1-trichloroethane and level of urinary metabolites (TCA and TCE), and for this reason they concluded the

urinary metabolite level was a good index of 1,1,1-trichloroethane exposure. The biologic half-life of 1,1,1-trichloroethane was found to be 8.7 $\pm$ 1.8 hours.

In a detailed study of one worker, a steady increase in urinary metabolite concentrations toward the weekend as well as significant metabolite excretion on Sunday, suggested that 1,1,1-trichloroethane accummulated in the body. Total metabolite increase was primarily attributed to TCE. No dose-dependent difference in health, as reflected by the medical questionnaire, was found in any of the workers. The authors recommended, based on accummulation of 1,1,1-trichloroethane in the body, a subtraction from the maximum "no adverse effect" level for short-term exposures to establish a threshold limit value (TLV) for repeated exposures.

Animal Toxicity

(a) Acute Lethal Doses and Concentrations

Doses of 1,1,1-trichloroethane required to kill 50% of the animals (LD50's), when administered orally, by intraperitoneal injection (ip) or by topical application to skin, have been estimated by several investigators. [36,66-71] In the original reports, the units of measurement were either millimoles/kg, g/kg, or ml/kg. In this document, doses are normally given as ml/kg; 1 ml/kg is 1.34 g/kg.

Determinations of the LD50 of 1,1,1-trichloroethane in an oil solution (olive, peanut or corn oil) administered ip are listed in Table III-14.

TABLE III-14

LD50 AFTER IP ADMINISTRATION
OF 1,1,1-TRICHLOROETHANE

Reference Data	Characteristics of 1,1,1-Trichloroethane	Animal Species/Strain	LD50* ml/kg
Plaa et al, 1958 [66]	Commercial grade	Princeton strain male mice	12 (9.5-16.0)
Klaassen & Plaa, 1967 [67]	0.5% nitromethane 1.8% dioxane 0.2% trichloroethylene 0.2% tetrachloroethylene	Swiss-Webster male mice	3.8 (3.1-4.5)
Takeuchi, 1966 [68]	Greater than 99% pure	S-M strain mice	1.9
Klaassen & Plaa, 1967 [69]	Not described	Dogs	3.1
Gehring, 1968 [70]	Center-cut fraction less than 0.5% impurities	Swiss-Webster female mice	3.52 (3.24-3.84)
Klaassen & Plaa, 1969 [71]	Analytical grade	Sprague-Dawley male rats	3.8 (3.3-4.2)

* 95% Confidence limits in parenthesis

Environmental temperature was reported in 1971 to affect the LD50 of an inhibited 1,1,1-trichloroethane preparation studied by Horiguchi and Horiuchi. [72] At an environmental temperature of 20 C, the ip LD50 dose for NA2 mice was 3.7 ml/kg and at 30 C it was 2.6 ml/kg.

Oral doses of both inhibited and uninhibited 1,1,1-trichloroethane were administered by Torkelson et al [36] to rats, mice, rabbits, and guinea pigs for determination of the LD50 for each species. Single doses of undiluted 1,1,1-trichloroethane were administered. The determinations are listed in Table III-15.

TABLE III-15

LD50 AFTER ORAL ADMINISTRATION OF
1,1,1-TRICHLOROETHANE IN SOME LABORATORY ANIMALS

Characteristics of 1,1,1-Trichloroethane	Animal Sex/Species	LD50 (g/kg) Mean	LD50 (g/kg) 95% Confidence Limits
2.4-3.0% dioxane	35 male rats	12.3	11.0-13.7
0.12-0.3% butanol	35 female rats	10.3	8.3-12.8
Trace of ethylene dichloride	16 female mice	11.2	---
"	16 female rabbits	5.7	3.5-9.4
"	16 male guinea pigs	9.5	3.5-13.3
Uninhibited	40 male rats	14.3	12.1-17.0
Not further defined	50 female rats	11.0	9.5-13.0
"	40 female mice	9.7	---
"	40 female rabbits	10.5	9.7-11.3
"	30 male guinea pigs	8.6	6.1-12.2

Adapted from Torkelson et al [36]

Both the inhibited and uninhibited 1,1,1-trichloroethanes were applied to the skin of rabbits and covered with bandages by Torkelson et al [36] to study the effects of 24-hour absorption. Eight rabbits were used with each material. Doses of 3.98 g/kg did not kill any animals; doses of 15.8 g/kg killed less than half the animals.

The concentrations of 1,1,1-trichloroethane required to kill 50% of rats (LC50's) exposed for up to 7 hours were studied by Adams et al [73] and reported in 1950. The 1,1,1-trichloroethane used in this investigation

was a redistilled commercial product with a boiling point of 74.1 C. The total number of rats used was 326. The only impurity found by infrared analysis was 1,2-dichloroethane, in up to 1% of the liquid material. At 18,000 ppm, the exposure time required to kill one-half of the animals was 3 hours with 95% confidence limits of 2.1-4.2 hours. The concentration required to kill one-half the animals (LC50) with 7 hours of exposure was 14,250 ppm with 95% confidence limits of 12,950-15,675 ppm.

An inhibited 1,1,1-trichloroethane preparation was reported by Horiguchi and Horiuchi [74] in 1971 to have a 2-hour exposure LC50 for mice of 3,911 ppm.

(b) Central Nervous System Effects

1,1,1-Trichloroethane was administered to dogs and monkeys as an inhalation anesthetic by Krantz et al. [32] The amount of inhaled 1,1,1-trichloroethane required to induce anesthesia was 0.34 $\pm$ 0.09 ml/kg in 11 dogs and 0.28 $\pm$ 0.06 ml/kg in 10 monkeys. The period of induction was short and surgical anesthesia was uneventful. Pain reflexes were absent during surgical anesthesia and analgesia appeared to extend into the recovery period. Recovery from anesthesia of 20-30 minutes duration occurred in 2-5 minutes.

Microscopic studies of the brains and spinal cords of rats anesthetized 1 hour/day on 9 consecutive days were reported by Krantz et al [32] to be without significant findings.

Increased electroencephalographic (EEG) activity, indicative of increased vigilance in the opinion Truhaut et al, [75] was found in rabbits during 1 hour of artificial ventilation through a tracheal cannula with 6,250 ppm of 1,1,1-trichloroethane. At 16,850 ppm of 1,1,1-

trichloroethane, which killed half the animals during 2 hours of exposure, there was an initial slight increase in EEG activity. After 5-10 minutes of exposure, the EEG activity began to decrease, and the decrease continued to death or the end of exposure. [75,76]

Mice exposed at 13,500 ppm of 1,1,1-trichloroethane by Gehring [70] became anesthetized (immobilized) in 16.3 (15.4-17.2) minutes, and died after 595 (578-615) minutes (95% condidence limits in parenthesis).

Signs of central nervous system responses of rats during exposure at different concentrations of 1,1,1-trichloroethane reported by Adams et al [73] are shown in Table III-16.

TABLE III-16

NEUROLOGIC RESPONSE OF RATS TO
1,1,1-TRICHLOROETHANE

Concentration, ppm	Response
18,000	Helplessness in 5 minutes; unconsciousness in 1 hour
15,000	Unconsciousness after several hours
10,000	Decreased activity in 1-2 minutes; staggering, falling, inability to walk after 10 minutes; semiconsciousness after 3 hours
5,000	Definite but mild narcotic effect within 1 hour; decreased activity

Adapted from Adams et al [73]

Slight ataxia was observed by Adams et al [73] in a monkey after 1 hour of exposure at 5,000 ppm of 1,1,1-trichloroethane. After about 5 hours of exposure, an occasional trembling of the hands and forearms was observed.

Varying degrees of anesthesia, ranging from ataxia to semiconsciousness, were observed by Torkelson et al [36] in rats exposed at 10,000 ppm of 1,1,1-trichloroethane for 1.0, 0.5, 0.2, or 0.1 hour/day, 70 times in 90 days. The rats were reported to be more affected by the exposures at the beginning of each week than at the end.

Whether there were signs of central nervous system responses at exposures of less than 5,000 ppm 1,1,1-trichloroethane was not mentioned in the reports of Adams et al [73] or Torkelson et al. [36]

Running activity of an unspecified number of mice in rotary activity cages before, during, and after exposure to inhibited 1,1,1-trichloroethane was reported in 1971 by Horiguchi and Horiuchi. [74] The mice were exposed at 1,000 ppm of 1,1,1-trichloroethane 2 hours/day every other day for 3 weeks. Activity was measured during three consecutive 2-hour periods on 9 exposure days. The exposures occurred during the middle 2 hours. On the first and second days of exposure, activity was similar during the three periods of measurement. On all of the remaining days, there was greater activity during and after exposure than before the daily exposure. [74]

Rats and cats were exposed at 73 ppm of 1,1,1-trichloroethane 4 hours/day for up to 4 months by Tsapko and Rappoport. [77] The threshold concentration of 1,1,1-trichloroethane necessary to alter conditioned reflex activity of rats in a single 4-hour exposure was reported to be 180-900 ppm. In this chronic experiment, there were minor changes reported in the conditioned reflex activity of cats but not of rats. The differentiation reflexes were deranged in the cats.

Pathologic changes were not found in the brains of five rats examined microscopically by Tsapko and Rappoport [77] after 50 days of exposure, but

venous stasis and perivascular edema in the brains and their membranes were found on examination of five other rats after 120 days of exposure. Other findings in the brains at this time were marginal and central chromatolysis in the nerve cells of the deep layers of the cerebral cortex, the subcortical area, and the caudate nucleus; signs of neurophagia in the subcortical area and in the caudate nucleus; and vacuolization of the cytoplasm of individual cells in the serrate nucleus of the cerebellum.

Fourteen days after exposure for 120 days, only residual signs of preexisting disturbances in the circulation and signs of dystrophy, were found in five other rats. [77]

(c) Cardiovascular and Respiratory Effects

Administration of 1,1,1-trichloroethane to two dogs to induce anesthesia without premedication was reported, in an abstract by Rennick et al [78] in 1949, to have resulted in sudden death. Further experiments with five dogs under barbital anesthesia showed that ventricular extrasystoles and ventricular tachycardia were regular occurrences when epinephrine was injected after administration of repeated small doses of 1,1,1-trichloroethane. Maximum sensitization of the heart occurred after administration of 0.25-0.40 ml/kg of 1,1,1-trichloroethane; greater amounts raised the threshold dose of epinephrine, partly because of severe hypotension. [78] Epinephrine itself, however, is known to induce ventricular extrasystoles and tachycardia, and the effects noted may have been due, at least in part, to epinephrine.

Krantz et al [32] reported electrocardiograms of six dogs and two monkeys maintained under deep anesthesia by 1,1,1-trichloroethane for 1 hour. Electrocardiograms, obtained from each animal before it was

anesthetized with 1,1,1-trichloroethane by a closed technique, were used for comparison. The heart rate was increased under anesthesia and the T-wave was either flattened or inverted.

Trochimowicz et al [40] did not find cardiac sensitization in a study of 41 dogs given 0.5% (v/v) 1,1,1-trichloroethane. An experimental group was subjected to myocardial infarction by placement of a copper wire within selected sites of the descending left coronary artery. Results demonstrated greater potential for sensitization (evidenced by changes in the EEG and SGOT levels) in the group that recovered from infarction as compared to the normal, healthy group.

Respiratory failure occurred in 11 dogs when an average of 0.60 (range = 0.29-0.93) ml/kg of 1,1,1-trichloroethane had been administered and in 10 monkeys when an average of 0.59 (0.43-1.00) ml/kg had been administered. At the time of respiratory failure, the ECG patterns of six dogs and two monkeys showed depressed S-T segments and mild bradycardia, and the blood pressure was reduced to about one-half of its normal value. Oxygen consumption in three deeply anesthetized monkeys decreased 16.7-54.3%. [32]

ECG changes reported by Griffiths et al [46] in 1972 occurred in three dogs several minutes after an abrupt drop in blood pressure when 1,1,1-trichloroethane was introduced into the trachea. Before the experiment the dogs were given sodium pentobarbital (20 mg/kg). 1,1,1-Trichloroethane was administered at an average concentration of about 125,000 ppm. Duration of exposure varied from 1.5-6.0 minutes and the total amount of 1,1,1-trichloroethane administered was 10 to 40 ml. Ventribular fibrillation, followed by cardiac arrest, occurred in one dog

during its second 3-minute exposure; the first exposure had taken place 2 weeks earlier.

Cardiac arrhythmias, myocardial depression, and tachycardia were reported by Belej et al [79] to have developed in three anesthetized Rhesus monkeys exposed for 5 minutes at 25,000 ppm of 1,1,1-trichloroethane, and again 10 minutes later when they were similarly exposed at 50,000 ppm. Table III-17 lists data from cardiovascular function studies on the monkeys.

TABLE III-17

CARDIOVASCULAR EFFECTS
OF 1,1,1-TRICHLOROETHANE IN MONKEYS

Cardiovascular Function	Exposure Concentration			
	25,000 ppm		50,000 ppm	
	Control	Response	Control	Response
Heart rate (beats/min)	153.3	167.3	155.0	186.7
Myocardial force (g)	45.9	37.9	34.4	24.3
Aortic blood pressure (mm Hg)	81.7	72.3	80.3	57.0
Left atrial pressure (mm Hg)	4.2	4.3	3.8	5.1
Pulmonary arterial pressure (mm Hg)	9.1	9.2	9.0	9.8

Adapted from Belej et al [79]

The pulse rate and blood pressure component of the physiograms constructed by Truhaut et al [75,76] was decreased by 5-10 minutes of

exposure at 15,000-16,850 ppm of 1,1,1-trichloroethane in rabbits inhaling it through a tracheal cannula. At 6,250 ppm, there was a decrease in this component only during the first 10 minutes of exposure. Electroencephalograms either showed no change or increased activity at the time of the cardiac function changes. [75]

Cardiovascular function changes were associated with 1,1,1-trichloroethane inhalation in nine anesthetized dogs (pentobarbital sodium 35 mg/kg or chloralose 50 mg/kg, and 10% pentobarbital sodium) in experiments reported by Herd et al [80] in 1974. Cardiovascular function measurements included arterial pressure, left ventricular pressure, aortal blood flow, and electrocardiograms. 1,1,1-Trichloroethane purified to 99.5 vol% was administered at the desired concentrations with a positive pressure ventilation apparatus for no more than 5 minutes at a time. Recoveries from these brief exposures, judged by blood pressure and heart rate, required 10-45 minutes. Several experiments were conducted on each dog at 1-hour intervals. Concentrations of 1,1,1-trichloroethane used in the study were 8,000, 15,000, 20,000, and 25,000 ppm. [80]

A two-phase depression of blood pressure which was dependent on the inhalation concentration of 1,1,1-trichloroethane was found. [80] In the first phase, there was a sharp decrease in total peripheral resistance, a parallel decline in systolic and diastolic blood pressure, and increased myocardial contractility and cardiac output. The cardiac responses were inhibited by pretreatment with propranolol hydrochloride and they were minimal when the dogs were anesthetized by pentobarbital. [80]

The second phase of blood pressure decline was independent of the anesthetic agent and was characterized by marked decreases in stroke

volume, heart rate, and myocardial contractility. [80] Total peripheral resistance was not changed appreciably during this phase. The cardiac effects during this phase were inhibited by infusion of calcium ions. Injection of 1.2 mg of phenylephrine reversed the course of the blood pressure changes. [80]

Cardiac rhythm was studied by Reinhardt et al [81] in unanesthetized dogs during inhalation of 98.9% pure 1,1,1-trichloroethane at 2,500 (2,100-2,500), 5,000 (4,600-5,600), and 10,000 (9,700-11,600) ppm. In this study, reported in 1973, doses of epinephrine (8 μg/kg in 1 ml normal saline) were injected into a cephalic vein. A control dose of epinephrine was given after 2 minutes of breathing air and a challenge dose of epinephrine was given 8 minutes later (after 5 minutes of breathing 1,1,1-trichloroethane). Criteria indicative of cardiac sensitization were multiple consecutive ventricular beats in excess of control observations and ventricular fibrillation. [81] At the lowest concentration, cardiac sensitization was not observed in 12 dogs. Cardiac sensitization occurred in 3 of 18 dogs exposed at 5,000 ppm of 1,1,1-trichloroethane and in all 12 dogs exposed at 10,000 ppm. Ventricular fibrillation occurred in one dog exposed at the highest concentration of 1,1,1-trichloroethane, but this reverted to multiple ventricular beats within a matter of seconds and eventually to a normal cardiac rhythm with recovery. [81]

Cardiotoxicity of 1,1,1-trichloroethane also has been studied in mice [82,83], and in rats, [32,80] yielding additional information on the toxic mechanism.

1,1,1-Trichloroethane was reported by Aviado and Belej [82] in 1974 both to induce cardiac arrhythmias in mice and to sensitize the hearts of

mice to epinephrine. The investigators anesthetized 239 mice with sodium pentobarbital (0.7 mg/10 g body weight) and exposed them at either 200,000 or 400,000 ppm of 1,1,1-trichloroethane for 6 minutes. Epinephrine (6 μg/kg) was administered to 108 of the mice after the start of 1,1,1-trichloroethane inhalation. Second degree A-V blocks occurred in both groups of mice exposed at 400,000 ppm 1,1,1-trichloroethane but none occurred with 200,000 ppm. [82]

A study of the mechanism of 1,1,1-trichloroethane induced ventricular fibrillation in mice was reported in an abstract by Strosberg et al [83] in 1973. Adrenalectomized mice and mice treated with a compound (P-286), which blocks the release of adrenal catecholamines, were not protected from 1,1,1-trichloroethane induced fibrillation. The mice, whether adrenalectomized or not, were protected by reserpine and particularly by the beter-blocker propranolol.

Isometric contractions were studied by Herd et al [80] in isolated papillary muscles from rat hearts, with and without 1,1,1-trichloroethane in the aeration mixture. 1,1,1-Trichloroethane had no effect on the time taken to develop peak tension or on the duration of the contractile cycle, but the time taken to develop the maximum rate of tension generation decreased approximately 10% during the exposure. The rate of tension generation and the rate of return of developed tension returned to their normal values more rapidly when calcium ions were added to the Krebs-Ringer solution after exposure to 1,1,1-trichloroethane.

Hepatic blood flow was studied in 1967 by Rice et al [84] in isolated, perfused rat livers. The rats were given an ip injection of 1,1,1-trichloroethane (2 ml/kg) 24 hours before the livers were removed and

prepared for the measurements. Under these conditions, hepatic blood flow did not differ from the controls. A subcapsular inflammatory reaction, but no necrosis of the parenchymal cells, was found on examination of the livers after the hemodymic measurements were made. In the same experiment carbon tetrachloride did increase resistance to blood flow.

The oxygen uptake of cardiac ventricular slices from rats deeply anesthetized with 1,1,1-trichloroethane for 1 hour was found by Krantz et al [32] to be reduced from control values by one-third.

Pathologic studies of exposed dogs were reported by Griffiths et al [46] following two or three exposures 2-4 weeks apart. The dogs were killed by a lethal inhalation of 1,1,1-trichloroethane. The predominant autopsy finding was gross congestion in all tissues. Microscopic findings were slight heart cell necrosis and slight fatty infiltration of the liver. [46]

Venous hyperemia was found by Tsapko and Rappoport [77] in the liver, kidneys, heart and lungs of five rats examined after 50 days of daily 4-hour exposures to 1,1,1-trichloroethane at 73 ppm. Small foci of swelling were also found in the heart muscle. These conditions were more pronounced in five rats examined after 120 exposures.

Studies by Krantz et al [32] of blood clotting time in anesthetized animals and in vitro hemolytic action of 1,1,1-trichloroethane showed no effects.

(d) Effects on the Skin, Mucous Membranes, and Respiratory Tract

Gross or microscopic changes in the lungs which may have been attributable to exposure were not found by Prendergast et al [85] in 25 rats, 15 guinea pigs, 3 rabbits, 2 dogs, or 3 monkeys exposed 8 hours/day,

5 days/week, for 30 exposures at 2,200 ppm of 1,1,1-trichloroethane containing 8% inhibitors and having a boiling range of 73.3-78.1 C.

Lung irritation was found by Torkelson et al [36] in two groups of five female guinea pigs exposed to inhibited 1,1,1-trichloroethane at 2,000 ppm for 12 or 30 minutes, 5 days/week, for 69 exposures in 99 days. Lung irritation was not found in two other similar groups exposed for 3 or 6 minutes/day.

Lung irritation was also found by Torkelson et al [36] in two other groups of five female guinea pigs exposed at 1,000 ppm 69 times in 98 days for 3 hours or 72 minutes daily. Lung irritation was not found in two other groups exposed for 18 or 36 minutes/day.

Congestion of the lungs was found by Horiguchi and Horiuchi [74] in mice exposed on alternate days to inhibited 1,1,1-trichloroethane at 1,000 ppm for 2 hours for 9 days.

With continuous, ie 24 hours/day, 7 days/week, exposure to a 1,1,1-trichloroethane preparation at 370 ppm for 90 days, Prendergast et al [85] found gray nodules on the lower lobe of the left lung of 1 of 15 rats and nonspecific inflammatory changes in the lungs of all species tested. Varying degrees of lung congestion and pneumonitis were found in all species exposed continuously at 135 ppm for 90 days. [85]

No pathologic changes were observed in lungs of a female monkey subjected to 53 7-hour exposures at 3,000 ppm in 74 days. [73] Severe lung infections in rats dying following exposures at 5,000-18,000 ppm were found, and may reflect preexisting disease.

Moderately pronounced venous hyperemia in the lungs, emphysematous enlargement of individual groups of alveoli, and swelling of the bronchial

epithelium was found by Tsapko and Rappoport [77] in five rats exposed 4 hours daily for 50 days to 1,1,1-trichloroethane at 73 ppm. After 120 days of exposure, the emphysematous condition was much more pronounced, the interalveolar walls were thin and in some places they had broken down. The vascular walls were thickened and swollen, and around many of them there were accumulations of lymphoid and histiocyte cell elements and isolated plasma cells. The mucous membrane of the bronchi was swollen, and there were small amounts of mucus and detached epithelial cells in the lumen. The peribronchial lymphatic nodules were hyperplastic. [77] In this chronic study, even though conditioned reflex activity was not disrupted in the rats, structural changes in cortical and subcortical areas were noted. The authors did not report microscopic studies of cat brains in which changes in differential reflexes were found with chronic exposure. In the absence of other information, and because of the nature of the conditioned reflexes they were studying and the methods they used, it is difficult to assess the significance of the behavioral aspects of this study.

Chemosis and hyperemia of the conjunctivas of rabbits after instillation of 1,1,1-trichloroethane (5% in corn oil) were found by Krantz et al [32] to be similar to those produced by chloroform administered similarly and simultaneously in the other eye.

A single undiluted application of either uninhibited or inhibited 1,1,1-trichloroethane to the eyes of rabbits was reported by Torkelson et al [36] to cause slight conjunctival irritation but essentially no corneal damage.

Only a slight reddening and scaliness of the skin were reported by Torkelson et al [36] to develop when a pad of absorbent cotton saturated

with either inhibited or uninhibited 1,1,1-trichloroethane was bandaged to the shaved belly of a rabbit 10 times in 12 days. Healing was prompt when application ceased. When applied to the abraded skin, neither inhibited nor uninhibited 1,1,1-trichloroethane significantly altered the healing process. [36]

(e) Hepatic and Renal Effects

Effects on liver and kidney function and structure after acute intoxication by 1,1,1-trichloroethane have been studied extensively. [32,66,67,69-71,73,86]

Liver function of male albino Princeton strain mice was evaluated in a report by Plaa et al [66] by 30-minute sulfobromophthalein (BSP) retention and sleeping time following sodium pentobarbital ip injection (45 mg/kg). A commercial grade 1,1,1-trichloroethane preparation was administered subcutaneously, diluted in peanut oil (0.1 ml), at doses of 12, 10, 8, and 4 ml/kg. Pentobarbital sleeping time in 270 control mice was 1.5 $\pm$ 4.1 minutes (sic). Mice that slept more than 10 minutes when pentobarbital was administered 24 hours after 1,1,1-trichloroethane were considered to have slept significantly longer than control mice. BSP retention was determined only in mice with significantly elevated sleeping times. BSP retention of 1.5 mg% was considered significantly greater than control values (0.46 $\pm$ 0.50 mg%). Table III-18 summarizes significant differences from sleeping time of controls.

Significant BSP retention was found in only 7 of the 18 mice with increased sleeping, at doses of 8 and 9 ml/kg.

TABLE III-18

SLEEPING TIME IN MICE WITH
1,1,1-TRICHLOROETHANE

1,1,1-Trichloroethane Dose, ml/kg	Sleeping Time, Minutes		n/N
	Mean	Range	
12	83	14-172	10/10
10	92	10-160	8/9
8	19	17-21	2/9

(N = no. of mice tested; n = no. with significant response)
Adapted from Plaa et al [66]

Liver and kidney function studies following ip administration of analytical grade 1,1,1-trichloroethane to male Swiss-Webster mice was reported by Klaassen and Plaa [67] in 1966. The various doses of 1,1,1-trichloroethane were administered in corn oil (0.01 ml/g). Liver function was studied 24 hours after administration by 30-minute BSP retention and SGPT determinations. Kidney function was studied at the same time by phenolsulfonphthalein (PSP) excretion and by protein and glucose analyses of the urine. From determinations on control animals, the upper limit of normality was determined for BSP retention (2.1 mg%), SGPT (50 units), and PSP excretion (22% of administered dose). From the series of 1,1,1-trichloroethane doses administered, the dose which would cause one-half of the treated animals to fall above the limit (ED50) was determined for each function test. The ED50 for BSP retention was 2.75 (95% confidence limits of 2.5-3.1) ml/kg, and for SGPT, 2.5 (95% confidence limits of 2.0-3.1) ml/kg. None of the kidney function tests were abnormal. [67]

Microscopic findings in the livers consisted of enlargement of the hepatocytes, cellular infiltration and vacuolation. Slight necrosis was found when mice were given near lethal doses. [67] No microscopic changes were found in the kidneys.

Swelling of the proximal convoluted renal tubules was reported in 1965 by Plaa and Larson [86] in all five male Swiss mice studied after an ip dose of 2.5 ml/kg of 1,1,1-trichloroethane (otherwise not described) in olive oil (0.1 ml/10 g). No necrotic changes were found. Protein in excess of normal (100 mg%) was found in the urine of one of nine mice given 2.5 ml/kg, in none of three administered 5 ml/kg. Glucose levels were normal in the urine of mice at both dose levels. [86]

The ED50 ip dose (corn oil, 0.01 ml/g) of 99.5% pure 1,1,1-trichloroethane, eliciting a significant elevation (above 54 units) of SGPT activity in female Swiss-Webster mice, was reported by Gehring [70] to be 16.8 (95% confidence limits of 15.2-18.5) ml/kg. With similar mice, he [70] reported that with inhalation at 13,500 ppm, half the mice died in 595 (95% confidence limits of 578-615) minutes.

Analytical grade 1,1,1-trichloroethane administered ip at 2.8 ml/kg (corn oil, 1 ml/100 g) to male Sprague-Dawley rats by Klaassen and Plaa, [71] caused no changes from control values in hepatic triglycerides, hepatic glucose 6-phosphatase, or degree of liver lipoperoxidation. They did find a significant increase, in vitro during lipoperoxidation, with an intermediate amount of 1,1,1-trichloroethane added to the incubation medium of rat liver slices. Lesser amounts of 1,1,1-trichloroethane had no effect on lipoperoxidation of the incubated liver slices and greater amounts were inhibitive.

Liver and kidney findings reported by Adams et al [73] in rats subjected to various inhalation exposures to redistilled 1,1,1-trichloroethane are listed in Table III-19.

TABLE III-19

EFFECTS OF 1,1,1-TRICHLOROETHANE IN RATS

Exposure data	Findings
18,000 ppm/2 hours	Increased kidney weights; no significant pathologic changes
18,000 ppm/0.3 hours	No pathologic findings
12,000 ppm/7 hours	Increased liver weights, numerous small clear vacuoles (fat) throughout cytoplasm of hepatic cells, considerable congestion and hemorrhagic necrosis in central areas; slight increase in kidney weights; no pathologic findings
8,000 ppm/7 hours	Fatty changes in the liver; no necrosis
8,000 ppm/5 hours	No pathologic findings

Adapted from Adams et al [73]

Male and female mongrel dogs were given ip doses of 2.5 or 3.5 ml/kg of 1,1,1-trichloroethane in corn oil by Klaassen and Plaa [69] to determine the LD50 (3.1 ml/kg). Similar animals were given ip doses of 0.75 and 1.05 ml/kg for studies of SGPT activity and 30-minute PSP excretion 24 hours after injection. Fifty units of SGPT were considered as the upper limit of normality; the ED50 dose of 1,1,1-trichloroethane at 24 hours was 0.87 ml/kg. PSP excretion was not affected by the treatment. Moderate neutrophilic infiltrations in the sinusoids and portal areas were found in

the livers of the dogs surviving the LD50 study. Slight subcapsular liver necrosis was found in dogs from the ED50 study. [69]

Liver function was studied in three dogs by Krantz et al [32] before and after 1 hour of anesthesia with 1,1,1-trichloroethane. No changes in retention of BSP were found immediately, or 24 or 72 hours after the anesthesias. They [32] did find evidence of midzonal liver necrosis in one rat anesthetized for 1 hour/day on 9 consecutive days, but not in two other similarly exposed rats or in other rats anesthetized for 1 hour/day on 3 or 6 consecutive days.

Chronic administration of 1,1,1-trichloroethane has also been studied for effects on the liver and kidneys by other investigators. [36,73,74,77,84,85,87]

Increases in microsomal and cell-sap protein were found by Platt and Cockrill [87] in five rats given seven daily oral doses of 1.25 ml/kg 1,1,1-trichloroethane in liquid paraffin. Activities of two liver enzymes, NADPH2-cytochrome C reductase and glutamic dehydrogenase, were greater in the treated than in the control rats. The activities of seven other liver enzymes studied in the treated rats did not differ from control values. These seven enzymes were aminopyrine demethylase, NADH2-cytochrome C reductase, glucose-6-phosphatase and four dehydrogenases (lactic, glutamic, 6-phosphogluconate, and glucose-6-phosphate). Body and liver to body weight ratios were not changed from control values by the treatment. [87]

Congestion of the livers and inflammation around bile ducts were found by Horiguchi and Horiuchi [74] in NA2 male mice following nine 2-hour exposures to inhibited 1,1,1-trichloroethane at 1,000 ppm on alternate days over 3 weeks.

Increased liver weights were reported by Torkelson et al [36] in 5 male rats exposed 70 times in 99 days to inhibited 1,1,1-trichloroethane at 10,000 ppm 1 hour/day, 5 days/week. Liver weights did not increase in other rats exposed for 0.5, 0.2 or 0.05 hours/day in the same experiment.

Increased liver weights were found in female guinea pigs exposed 69 times in the same experiment at 2,000 ppm, for 0.5 or 0.2 hours/day, and in others exposed 69 times at 1,000 ppm, for 3.0 or 1.2 hours/day. Exposures of shorter daily duration at 2,000 or 1,000 ppm did not result in increased liver weights. In the guinea pigs with increased liver weights, fatty changes were found in the livers.

No liver or kidney effects were reported by Torkelson et al [36] in 126-130 exposures of rats, guinea pigs, rabbits or monkeys to inhibited 1,1,1-trichloroethane at 500 ppm. The exposures were 7 hours/day, 5 days/week.

Fatty degeneration of the liver was reported by Adams et al [73] for guinea pigs, but not rats or rabbits, exposed 31 times in 44 days for 7 hours/day, to redistilled 1,1,1-trichloroethane at 5,000 ppm. Fatty degeneration was also found in livers of guinea pigs exposed 20 times for 7 hours/day at 3,000 ppm. No liver or kidney effects were reported for rats or monkeys repeatedly exposed (about 50 times) 7 hours/day, 5 days/week at 3,000 ppm. Liver or kidney effects were not reported for guinea pigs similarly exposed at 1,500 ppm over 2 months or at 650 ppm over 3 months.

No evidence of liver or kidney injury was reported by Prendergast et al [85] among animals exposed to inhibited 1,1,1-trichloroethane at 2,200 ppm for 8 hours/day, 5 days/week for 6 weeks or at 370 or 135 ppm continuously for 90 days. At each exposure concentration, 15 rats, 15

guinea pigs, 3 rabbits, 2 dogs and 3 monkeys were exposed.

A continuous exposure experiment lasting 14 weeks was reported in 1974 by MacEwen and Vernot [88]. Exposure concentrations of 1,1,1-trichloroethane for which the purity was not stated were 250 and 1,000 ppm. At each concentration, 180 mice, 40 rats, 8 dogs and 4 monkeys were exposed. A similar group of animals was housed in the same type of exposure chambers for control studies. Ten mice were removed weekly from each group for gross examination, liver fat stains and liver triglyceride determinations.

Liver weights relative to body weights and liver triglyceride concentrations were significantly different from controls in all groups of mice examined after the 1,000 ppm exposure. These measurements were only slightly, or not at all altered in mice from the 250 ppm exposure. In mice examined 2 and 4 weeks after removal from exposure, relative liver weights and liver triglyceride concentrations were not significantly different from controls. Continuous exposure of mice at 1,000 ppm produced a significant increase in microglobular fat droplets in centrilobular hepatocytes. A slight increase was seen also at 250 ppm. There was no evidence by light microscopy of hepatocyte necrosis, inflammation, or fibrosis in any of the mouse livers examined. Focal hepatocyte necrosis, observed by electron microscopy, was greatest at the 12th week of exposure where it was present in 40% of the mice exposed at 1,000 ppm. This necrosis was associated with an acute inflammatory infiltrate and hypertrophy of Kupffer cells. [88]

Liver to body weight ratios were also significantly increased in rats exposed to 1,1,1-trichloroethane at 1,000 ppm, but at 250 ppm they were similar to controls. [88] Cytoplasmic alterations found by electron

microscopy were most severe in centrilobular hepatocytes of the 1,000 ppm group and were mild to minimal in the 250 ppm group. These alterations consisted of vesiculation of the rough endoplasmic reticulum with loss of attached polyribosomes, increased smooth endoplasmic reticulum, microbodies and triglyceride droplets. Some cells had swollen cisternae of the endoplasmic reticulum. [88]

The authors [88] also observed chronic respiratory disease, in 12 of 40 control rats, in 28 of 40 exposed at 250 ppm, and in 7 of 40 exposed at 1000 ppm. It appears that the respiratory disease was intercurrent rather than related to exposure.

No lesions in dogs or monkeys were ascribed to the exposure by the investigators. [88] McNutt et al, [41] however, found significant changes in the livers of mice exposed at 1000 ppm 1,1,1-trichloroethane continuously for 18 weeks and minor changes in mice exposed at 250 ppm. Changes in the 1000 ppm group included triglyceride accummulation, necrosis of hepatocytes, and cytoplasmic alterations of centrilobular hepatocytes. Cytoplasmic alterations were described as "mild to minimal" in the 250 ppm group.

Moderately pronounced venous hyperemia and swelling of individual groups of cells was found by Tsapko and Rappoport [77] in rats examined after 50 days of daily 4-hour exposures to 1,1,1-trichloroethane at 73 ppm. In the rats examined after 120 days of exposure, these effects were more prominent, and protein dystrophy of the liver parenchymal cells was found. [77]

No adverse effects were reported by Eben and Kimmerle [89] in rats exposed at 220 and 440 ppm of 1,1,1-trichloroethane. Two groups of 20

rats each were exposed for 4 hours, at 220 and 440 ppm during the acute experiment, and another group of 20 rats at 200 ppm 1,1,1-trichloroethane for 14 weeks, 8 hours/day, 5 days/week. Analysis demonstrated no significant changes in the standard hematology (Hgb, RBC, WBC, HCT, MCV and differential white count) and chemistry tests, SGOT, SGPT, sorbital dehydrogenase, total bilirubin, urea, creatinine and glucose. On microscopic examination, no pathologic changes were found.

Quast et el [90] reported chronic inhalation by rats in a 1975 interim report. Two groups of rats, each consisting of 96 males and 96 females, were exposed at 875 and 1,750 ppm 1,1,1-trichloroethane, respectively, for 6 hrs/day, 5 days/wk for 52 weeks. The 1,1,1-trichloroethane formulation was analyzed for composition by gas chromatography and introduced into a 3.7 cu m stainless steel chamber. The vapor concentration of 1,1,1-trichloroethane in the chamber was calculated from the ratio of material delivery rate and total chamber air flow rate. The concentration was verified at regular intervals by infrared spectrophotometry.

Food and water were withheld during the exposure period. A control group of 192 male and 192 female rats was not subjected to lower exposures but was deprived of food and water on the same schedule as the experimental group. The portion of the diurnal cycle during which the animals were expozed was not stated. The investigators measured body weight, RBC count, Hgb concentration, packed cell volume, differential white count, and urinalysis for pH, specific gravity, sugar and albumin concentrations, presence of Ketone bodies, and bilirubin. After the experimental period, animals were observed until moribund or dead. Representative specimens of

all major organs and glands were taken for microscopic examination. Behavioral signs indicative of CNS depression, such as hyperactivity, were sought. The authors reported no signs or indices attributable to 1,1,1-trichloroethane exposure. Several "spontaneous lesions" were found, but on comparison of frequencies between control and experimental groups were not associated with exposure. The portion of the diurnal cycle during which the animals were exposed was not stated. These findings were reported after 24 months and 18-23% of the males and 32-37% of the females were still alive at that time.

(f) Absorption, Excretion, Metabolism

Only limited information on absorption of 1,1,1-trichloroethane was found. Concentrations of 1,1,1-trichloroethane were measured by MacEwen and Vernot [88] in the blood of dogs and monkeys during 14 weeks of continuous exposure at 250 and 1,000 ppm. Table III-20 lists the concentrations found.

Excretion by rats of 1,1,1-trichloroethane labeled with carbon 14 at the 1 position was reported by Hake et al [91] in 1960. The doses administered to three rats were 727, 642 and 705 g/kg (approximately 0.5 ml/kg). For two rats in which it could be measured, an average of 97.6% of the administered dose was excreted unchanged in the exhaled air during 25 hours, and in three rats an average of 0.85% (0.55, 0.86, and 1.14%) of the administered radioactivity was found in the urine.

TABLE III-20

CONCENTRATION OF 1,1,1-TRICHLOROETHANE
IN BLOOD OF DOGS AND MONKEYS, μg/g

Week	Dogs		Monkeys	
	250 ppm	1,000 ppm	250 ppm	1,000 ppm
3	11	75	4	33
5	16	46	14	48
9	9	38	3	17
13	17	75	4	30

Adapted from MacEwen and Vernot [88]

Concentrations of 1,1,1-trichloroethane were studied by Boettner and Muranko [92] in the breath of rats after removal from exposures at various concentrations and durations. With 3-hour exposures, concentrations of 100, 200, 500 and 1,000 ppm of 1,1,1-trichloroethane were used. At 350 ppm, exposure times were 1, 2, 5, 10 and 20 hours. Breath samples were collected at 1, 2, 4 and 8 hours after removal from exposure and analyzed by gas chromatography. The logarithm of the concentrations found in the breath at 1 and 8 hours after removal from the 3-hour exposures was plotted against the logaritham of exposure concentrations and linear relationships were found. The exposures at 350 ppm demonstrated an approach to equilibrium at 5 hours of exposure. [92]

Metabolites of labeled 1,1,1-trichloroethane identified by Hake et al [91] were carbon dioxide in the exhaled air (0.5% of the administered dose) and the glucuronide of 2,2,2 tetrachloroethanol in the urine. From 10 to

25% of the activity in the urine was removed with toluene and was volatilized by air drying. From 25 to 30% of the activity remaining in the urine was also volatilized by air drying. The investigators [91] did not find chlorinated acetic acids in the urine.

Urine of male and female Wistar rats was analyzed by Ikeda and Ohtsuji [93] for total trichloro compounds (TTC), trichloroacetic acid (TCA), and trichloroethanol (TCE) following 8 hours of exposure to 1,1,1-trichloroethane at 200 ppm. Urine was collected for 48 hours from the beginning of the exposure and analyzed colorimetrically using the Fujiwara reaction. The optical extinction after oxidation of the urine sample was attributed to TTC; that without oxidation to TCA, as well as the difference between the two, was attributed to TCE. Average 48-hour excretions (mg/kg body weight) from eight rats were: TTC 3.6 $\pm$ 1.0; TCA 0.5 $\pm$ 0.2; and TCA 3.1 $\pm$ 1.0. Similar data were obtained with seven rats after ip injections of 1,1,1-trichloroethane (6.9/ml/kg). Urine collected [93] for two consecutive 48-hour periods after injection yielded the data in Table III-21.

The "behavior" of 1,1,1-trichloroethane and its metabolites was investigated in the expired air, blood and urine of male Wistar rats by Eben and Kimmerle. [89] To quantitate concentrations of 1,1,1-trichloroethane and its metabolites, a gas chromatograph, equipped with an Ni-63 electron capture detector, was used. The major metabolites studied were TCE and TCA in the urine, 24 hours after exposure, for 3-4 days in the acute group, and 16 hours after exposure, daily, in the subchronic group. Chloral hydrate concentrations were also determined in the blood and 1,1,1-trichloroethane was determined in the blood and breath.

TABLE III-21

URINARY METABOLITES OF
1,1,1-TRICHLOROETHANE IN RATS
AFTER IP INJECTION

Collection Period	Urinary Metabolites, mg/kg body weight (mean +SD)		
	TTC	TCA	TCE
0-48 hours	4.0 ± 1.5	0.5 ± 0.2	3.5 ± 0.4
48-96 hours	0.3 ± 0.1	0.3 ± 0.1	not measurable
Controls	0.3 ± 0.1	not measurable	0.3 ± 0.1

Adapted from Ikeda and Ohtsuji [93]

All animals in the acute experiment (220 and 440 ppm) excreted most of the TCE in the urine within 24 hours. Both TCA and TCE concentrations in the urine reflected a dose-dependent increase. 1,1,1-trichloroethane concentrations in the breath were also found to be dose-dependent, but decreased exponentially with time, after exposure.

In the subacute experiment, at 200 ppm, TCE concentrations in the urine increased continuously, reaching a maximum between the 55th and 65th days, and then decreased. Within the first few days, TCA concentrations rose to about 20 mg, then remained constant. 1,1,1-Trichloroethane and TCE concentrations in the blood were almost constant throughout the exposure period, and chloral hydrate was not detected. 1,1,1-Trichloroethane was not detected in the following tissue: adipose, brain, hepatic, renal, cardiac or splenic.

Enzymatic dechlorination of 1,1,1-trichloroethane by rat liver microsomes in vitro was found to be minimal (less than 0.5% of Cl 36 removed) by Van Dyke and Wineman. [94] Exposure of rats for 5 days, 7 hours/day, to 500 ppm of 1,1,1-trichloroethane, had no effect on the

dechlorinating system, and dechlorination of 1,1,1-trichloroethane was not enhanced by exposure to the enzyme inducer, methoxyflurane.

Herd and Martin [95] investigated the effects of 1,1,1-trichloroethane on mitochondrial metabolism. Biochemical characteristics of metabolism were studied by polarography; calcium uptake, respiratory rates and mitochondrial ATP activity were measured in albino rat liver and heart mitochondria. The investigators found a marked decline in ADP respiration with pyridine nucleotide linked substrates, an unaffected rate of succinate-linked ADP respiration, and an alteration of the passive permeability characteristics of the mitochondria to calcium and hydrogen ions. It was concluded that the results gave an explanation for 1,1,1-trichloroethane-induced depression of myocardial respiration. [95]

(g) Drug Interactions and Potentiation of 1,1,1-Trichloroethane Toxicity

1,1,1-Trichloroethane was found by Van Dyke and Rikans [96] to stimulate aniline hydroxylase activity when added to the incubation medium of rat liver microsomes. In the same experiment, it had no effect on aminopyrine demethylase.

Metabolism of hexobarbital, meprobamate, and zoxazolamine, based on loss of righting reflex, was studied by Fuller et al [97] in male rats and mice, 24 hours after removal from 24 hours of continuous exposures to reagent grade 1,1,1-trichloroethane at 3,000 ppm. The sleeping times induced by all three drugs were also reduced in rats and mice exposed to 1,1,1-trichloroethane. This indicates that 1,1,1-trichloroethane stimulates the activity of hepatic microsomal enzymes used to metabolize these drugs.

Other studies were conducted with hexobarbital to determine the mechanism by which 1,1,1-trichloroethane reduced the sleeping time. [97] To functionally block the hypophysis, rats were treated with morphine sulfate (20 mg/kg ip) for 4 days before exposure. This treatment did not alter the effect of 1,1,1-trichloroethane on hexobarbital sleeping time. In another experiment, adrenalectomized rats retained the 1,1,1-trichloroethane effect on hexobarbital sleeping time. [97]

Other groups of rats were treated with either cycloheximide or actinomycin D to block protein synthesis before they were exposed to 1,1,1-trichloroethane. [97] Both these drugs blocked the effect of 1,1,1-trichloroethane inhalation on hexobarbital sleeping time by preventing reduction of hexobarbital narcosis and an increase in hexobarbital metabolism.

In vitro studies showed that both hexobarbital and zoxazolamine metabolism by rat livers were increased by exposure of the donor rat to 1,1,1-trichloroethane. Aminopyrine demethylase, NADPH cytochrome C reductase activity, and cytochrome P-450 activity were also increased by exposure. [97]

Sleeping time induced by ip administration of hexobarbital sodium (80 mg/kg) in random-bred male and female Swiss albino mice was reported, in 1970 by Lal and Shah, [98] to be decreased if the mice were exposed to reagent grade 1,1,1-trichloroethane. Most of the experiments were conducted with only male mice. Groups of males were exposed for 24 consecutive hours to approximately 600, 1,500, 3,000 and 6,000 ppm and sleeping time was determined 24 hours after exposure. Maximum reduction in sleeping time (50-60%) occurred after exposures at 3,000-6,000 ppm. Higher

exposure concentrations were less effective.

Other experiments were conducted at the 3,000 ppm exposure level. When 24 hours of total exposure time were completed in three to six exposure periods, each separated by 18-21 hours, a cumulative effect was shown by progressive decreases in sleeping time. [98]

The cause of the decreased hexobarbital sleeping times following 1,1,1-trichloroethane exposures was studied. [98] It was found that neither barbital nor chloral hydrate induced sleeping times were affected by exposure to 1,1,1-trichloroethane. Oxidation of hexobarbital by 9,000 G supernatant fractions from livers of exposed mice was increased. Reduction of p-nitro-benzoic acid by the same liver fractions was not affected by exposure of the mice to 1,1,1-trichloroethane.

Treatment of mice with atropine, chlorpromazine or tolazoline immediately before and after 12 hours of exposure to 1,1,1-trichloroethane, did not block the effect of exposure on hexobarbital sleeping time. [98]

Administration of two doses of phenobarbital (50 mg/kg ip) by Cornish et al [99] 1 and 2 days before injection of reagent grade 1,1,1-trichloroethane at doses of 0.3, 0.5, 1.0 and 2.0 ml/kg, did not enhance the hepatoxicity of 1,1,1-trichloroethane, evaluated by SGOT determinations. Similar increases in SGOT levels were found in control (no phenobarbital treatment) and treated animals at each 1,1,1-trichloroethane dose level. The SGOT levels were significantly increased by 1,1,1-trichloroethane with or without phenobarbital pretreatment.

Enhancement of 1,1,1-trichloroethane hepatotoxicity by phenobarbital was reported in 1973 by Carlson. [100] In this experiment, the male rats were pretreated with phenobarbital (50 mg/kg/day) for 4 days before an

exposure for 2 hours to 1,1,1-trichloroethane at 11,600 ppm. This exposure without pretreatment, and phenobarbital without exposure, had no effect on relative liver weights, liver glucose-6-phosphatase, or the serum enzymes SGPT and SGOT. The combination of pretreatment and exposure to 1,1,1-trichloroethane increased liver weights and serum enzyme activities, and decreased the liver glucose-6-phosphatase activity. Pretreatment of rats with 3-methylcholanthrene (40 mg/kg/day) for 2 days, before a 2-hour exposure to 1,1,1-trichloroethane at 13,000 ppm, did not cause any of these measurements to change from control values. [100]

Ingestion of ethanol was reported by Klaassen and Plaa [67] in 1966 to increase the hepatotoxicity of analytical grade 1,1,1-trichloroethane. Ethanol (60%) was administered by gavage (stomach tube) at doses of 5 g/kg. In one experiment, a dose of ethanol was given on each of 3 days before ip administration of 1,1,1-trichloroethane in corn oil (0.01 ml/g) at doses of 2.5-2.75 ml/kg. In another experiment, a single dose of ethanol was given 12 hours before the 1,1,1-trichloroethane. In both experiments, BSP retention was significantly higher in the ethanol pretreated rats than in control rats given only 1,1,1-trichloroethane. SGPT activity was not affected in this experiment by 1,1,1-trichloroethane at a dose of 2.5 ml/kg with or without alcohol pretreatment, and kidney function as measured by PSP excretion was similarly not affected by 1,1,1-trichloroethane doses of 2.0 ml/kg. [67] SGPT activity was also not different from controls in dogs given 1,1,1-trichloroethane doses of 0.85 ml/kg, with or without ethanol pretreatment, by Klaassen and Plaa. [69]

Exposures of rats to redistilled reagent grade 1,1,1-trichloroethane for 2 hours at 10,000 or 15,000 ppm or for 6 hours at 5,000 or 10,000 ppm

did not increase serum enzyme levels whether or not there had been ethanol pretreatment. [101] The serum enzymes studied in this 1966 report by Cornish and Adefuin [101] were SGOT, SGPT, and isocitric dehydrogenase. The ethanol (50%) was administered by stomach tube at 5 g/kg, 16-18 hours before the vapor exposures.

Isopropyl alcohol or acetone administered by gavage to male Swiss-Webster mice 18 hours before ip injection of 1,1,1-trichloroethane did not alter the response of SGPT activity to the administered 1,1,1-trichloroethane. [102] The doses of 1,1,1-trichloroethane used in this experiment, by Traiger and Plaa [102] in 1974, were 1.0, 2.0 and 2.5 ml/kg. The latter dose caused increases in SGPT activity, but the increases were not affected by isopropyl alcohol or acetone pretreatment.

(h) Teratogenicity, Carcinogenicity, Mutagenicity

Sprague-Dawley rats and Swiss-Webster mice were exposed to 1,1,1-trichloroethane 7 hours/day on days 6-15 of gestation in an experiment reported by Schwetz et al in 1975 . [103] A commercial grade 1,1,1-trichloroethane preparation [16] containing 5.5% inhibitors and impurities was used. The exposure concentration of 1,1,1-trichloroethane was about 875 ppm, and the exposure concentration of the inhibitors and impurities was about 50 ppm. The numbers of bred animals subjected to this exposure were not explicitly stated in the report. The findings of the study are presented in Tables XII-3 to XII-5. An increase in liver weight was reported to be the only significant maternal, fetal or embryonal toxic effect in rats at 875 ppm. There were no significant findings reported in mice.

Although the authors [103] concluded that there were not teratogenic effects in either rats or mice, certain soft tissue and skeletal abnormalities occurred in litters of exposed rats and mice that did not occur in litters of control mothers. These abnormalities in mice included one litter with short tail, and one with cleft palate. In rats, two litters were found with supernumerary vertebra. In concluding that the abnormalities were not statistically significant, the authors compared the exposed to the control group, but in comparing the appearances of abnormalities in the 1,1,1-trichloroethane exposed group, with no appearances during exposure to other chemicals, the findings take on added significance. The experiment needs to be repeated to confirm that these are not significant effects of 1,1,1-trichloroethane.

Other studies with 1,1,1-trichloroethane involving reproduction and studies of mutagenicity were not found by a search of the literature.

A study of 1,1,1-trichloroethane exposure in rats [90] revealed two tumors in each group studied; controls, exposed males and exposed females. The tumors are only described as hyperplastic proliferations of liver cells, and they were dismissed by the authors due to appearance in the control group. Another tumor, appearing in one female rat exposed at 1,750 ppm, was variously diagnosed, by different pathologists, as a hemangiosarcoma, undifferentiated hepatic cell carcinoma or hepatoblastoma with areas of sarcoma. A second study involving carcinogenesis is currently underway at the National Cancer Institute.

Correlation of Exposure and Effect

Summaries of inhalation exposures and effects are presented in Tables XII-6 to XII-10. The most significant findings concerning the effects of 1,1,1-trichloroethane in man and animals are the depression of the CNS, cardisvoscular toxicity and hepatic toxicity. Irritation of the lungs and mucous membranes also has been reported. Information on experimental exposures of more than 6 months duration, or at 1,1,1-trichlorethane concentrations below about 75 ppm, was not found in the literature. Both experimental studies and occupational experiences indicate that 1,1,1-trichloroethane is irritating to the skin and mucous membranes and that the nervous system, cardiovascular system, and the liver are affected by exposures.

(a) Central Nervous System Effects

The first reported biologic study of 1,1,1-trichloroethane, by Tauber [2] in 1880, established that it had anesthetic properties. Clinical trials in 1958-1960 established that it was not very effective as a surgical anesthetic, and its use for this purpose was discontinued. [32-34] The anesthetic properties of 1,1,1-trichloroethane have had occupational significance, [36,49] and will continue to be of significance to work practices and requirements for respiratory protective devices.

Concentrations of 1,1,1-trichloroethane required to induce anesthesia under working conditions have not been determined. [36,49] The clinical studies are difficult to extrapolate to occupational situations because the patients were usually given sedatives before administration of anesthetic gas, and nitrous oxide was used in the 1,1,1-trichloroethane carrier gas. [33,34] Under the conditions of the clinical trials, light plane 1 anes-

thesia developed within 2 minutes when 1,1,1-trichloroethane was administered at 10,000-26,000 ppm and could be maintained by 6,000-22,500 ppm. [33]

Subjects became unable to stand when exposed experimentally to 1,1,1-trichloroethane for 15 minutes, with the concentration rising from 0 to 2,650 ppm. [35] Loss of ability to stand also has been experienced in occupational exposures [51]; however, the concentrations of 1,1,1-trichloroethane were not reported. Both these reports demonstrate the need for adherence to good work practices, and the use of proper ventilation and protective equipment when working with 1,1,1-trichloroethane.

Other central nervous system effects which could impair judgment and increase accident risk have been found with human exposure conditions which would not be anesthetic. [35,36,38]

Lightheadedness and impaired coordination and equilibrium have been experienced by subjects exposed at 900-1000 ppm for 20 minutes or more. [35,36] Other tests have shown impaired perceptual speed, reaction times, and manual dexterity during 1 hour of exposure to 1,1,1-trichloroethane at 350 ppm but not at 250 ppm. [38] Similar responses have been found with occupational exposure to 1,1,1-trichloroethane with at least one reported case of sufficient intoxication to cause a fall. [51]

Animal experiments have shown central nervous system responses and behavioral changes with exposure to 1,1,1-trichloroethane. [74,75,77] Increased EEG activity was found in rabbits during 1 hour of 1,1,1-trichloroethane inhalation at 6,250 ppm. [75] Increased running activity was found in mice exposed at 1,000 ppm 2 hours/day on alternate days. [74] In this experiment the activity did not alter until the third exposure.

Pathologic vascular changes were found in the brains of rats after 50 exposures. [77] After 120 exposures, pathologic changes in the nerve cells were found. Whether these anatomic changes reflect adverse effects of 1,1,1-trichloroethane or are histologic artifacts, is not clear since data from control rats are not presented.

(b) Cardiovascular Effects

During anesthesia, a drop in blood pressure was observed in most patients, and ECG changes in some of them. [33-35] The changes found by ECG analysis included premature ventricular contractions, depressed S-T segments, and one case of cardiac arrest. [33] The cause of the cardiac arrest was unknown.

Sudden death was reported in 1949 to have occurred in unanesthetized dogs inhaling 1,1,1-trichloroethane, and in subsequent experiments with anesthetized dogs it was demonstrated that 1,1,1-trichloroethane sensitizes the heart to epinephrine. [78] Experiments by other investigators [46,81,82] have shown that exposure to 1,1,1-trichloroethane sensitizes the hearts of dogs, monkeys, and mice. Sensitization occurred in unanesthetized dogs with 5 minutes of exposure at 5,000 ppm, but not at 2,500 ppm. [81]

Sudden death has occurred in humans from both use and misuse of 1,1,1-trichloroethane. [45,80] At least some of the 11 reported occupational fatalities may have been sudden deaths. [14,36,47,50] The occupational cases described by Kleinfeld and Feiner [48] had many similarities to cases of sudden death from inhalation of 1,1,1-trichloroethane described by Bass. [45]

Changes in cardiovascular function found in dogs exposed to 1,1,1-trichloroethane at 8,000 ppm for no more than 5 minutes included an abrupt drop in total peripheral resistance with compensatory cardiac responses. [80] Within seconds, the compensatory cardiac responses were dissipated and stroke volume, heart rate, and myocardial contractility decreased. [80] A decrease in heart rate and blood pressure was found in rabbits during the first 10 minutes of exposure at 6,250 ppm. [75] Studies of this kind have not been reported at lower concentrations of 1,1,1-trichloroethane, but similar results have been found at higher concentrations in dogs, [46,80] rabbits, [75] and monkeys. [79]

Studies with animal tissues have shown decreased oxygen consumption of heart muscle excised from rats anesthetized with 1,1,1-trichloroethane. [32] Another in vitro study showed that addition of 1,1,1-trichloroethane to the aeration mixture affected the contractile mechanics of isolated papillary muscles from rat hearts. [80]

Autopsy findings in animals exposed to 1,1,1-trichloroethane reflected the cardiovascular effects mentioned above. The predominant findings in dogs autopsied after two to three exposures in a study of cardiac rhythm, were slight heart cell necrosis and gross congestion in all tissues. [46] Congestion has been a common finding in animal tissues at autopsy after administration of 1,1,1-trichloroethane. [73,74,77,84]

Hypertension was found in six of nine women occupationally exposed to 1,1,1-trichloroethane for several months. [61] Neither blood pressure nor ECG changes were found in human subjects experimentally exposed to 1,1,1-trichloroethane at 0 to 2,650 ppm during 15 minutes, [35] or about 1,000 ppm for 70 to 75 minutes, or 400 to 600 ppm for 7.5 hours. [36] No

reports of other cases have found hypertension.

Autopsy findings in human fatalities resulting from exposure to 1,1,1-trichloroethane are indicative of a state of decreased peripheral resistance and cardiac insufficiency. [44,49,50] Fractional analysis of LDH in a patient who died 5 days after inhaling 1,1,1-trichloroethane showed the heart was the major source of the increased serum concentration of this enzyme. [46] Heart cell necrosis and liver fatty metamorphosis were also found on autopsy. [46]

(c) Liver and Kidney Effects

Slight increases in serum transaminase (unspecified) were found in two of five patients on the days following surgery under 1,1,1-trichloroethane anesthesia. [33]

Positive urinary urobilinogen was found in two of seven subjects 7 hours after an exposure of 15 minutes to 1,1,1-trichloroethane at 0 to 2,650 ppm. A few red blood cells were found in the urine of five of the subjects. [35]

Elevated urinary urobilinogen was also found in one subject following a 20-minute exposure at 900 ppm, and some evidence of possible kidney injury was found in six subjects after exposure at 500 ppm for 78 minutes. Serum enzymes were not elevated. [35]

Evidence of kidney injury (red blood cells and protein in the urine) and elevated serum bilirubin were also found in a man following ingestion of 1,1,1-trichloroethane. [35]

Autopsy findings in a woman with a history of chronically sniffing 1,1,1-trichloroethane were limited to the respiratory system, stomach, and brain. [44]

Elevated urinary urobilinogen was found in one worker after he had worked with 1,1,1-trichloroethane for 1 hour in a closed room, [51] and in two of nine women after they had worked with 1,1,1-trichloroethane for several months.

These reports [33,35,42,51] indicate a potential for both kidney injury and liver injury by 1,1,1-trichloroethane in exposed workers. Animal experiments generally do not confirm kidney injury. [66,67,69,71,73,74,85-87] The tests for liver and kidney function that have been used are not the same in animals and man and in neither animals nor man have the tests most sensitive to 1,1,1-trichloroethane effects been widely used. Stewart et al [35] reported microscopic hematuria in men experimentally exposed at 500 ppm or higher concentrations. Whether this reflects effects of the dioxane inhibitor, an incidental and unrelated effect, or a toxic effect of 1,1,1-trichloroethane, is not clear. Research to clearify this is needed.

Accumulation of triglycerides in the liver has been found in rats only with prolonged exposures at 1,000 ppm or more. [36,73,84] Necrotic changes have not generally been found but focal hepatocyte necrosis was found by electron microscopy in mice exposed continuously for 90 days at 1,000 ppm. [88] Mild to minimal changes were also found by electron microscopy in the livers of rats exposed at 250 ppm continuously for 90 days. The necrotic changes were associated with an acute inflammatory infiltration and hypertrophy of Kupffer cells. [88]

Congestion of the livers and inflammation around biliary ducts were found in mice following nine 2-hour exposures on alternate days to 1,1,1-trichloroethane at 1,000 ppm. [74]

Swelling of individual cells and moderately pronounced venous hyperemia was found in the livers of rats exposed 4 hours daily, 50 or 120 times, to 1,1,1-trichloroethane at 73 ppm. [77]

(d) Effects on Skin and Mucous Membranes

1,1,1-Trichloroethane is irritating to the skin and mucous membranes. [32,36,44,49,50,61,73,74,77,85,88]

Congestion of bronchial vessels and passive congestion throughout the lungs were found at autopsy of a woman who had chronically sniffed 1,1,1-trichloroethane. [44] Autopsy findings in another case where chronic inhalation of 1,1,1-trichloroethane may have been involved were congestion, edema, dilated vessels and small hemorrhages in the lungs. [44] Lung congestion and edema were found on autopsy of seven workers who were found dead at their site of work with 1,1,1-trichloroethane. [49,50]

Lung irritation was found by Torkelson et al [36] in guinea pigs repeatedly exposed to 1,1,1-trichloroethane at 1,000 ppm or more. Congestion of the lungs was found in mice exposed 2 hours/day, on 9 alternate days, at 1,000 ppm of 1,1,1-trichloroethane.

Chronic respiratory disease was found in rats exposed continuously at 1,000 ppm or 250 ppm for 91 days, [88] but it is not clear that endemic respiratory disease was not present prior to the exposures. Lung congestion and pneumonitis were found in all tested species exposed continuously at 135 ppm for 90 days. [85]

Transient irritation of the conjunctiva or the upper respiratory tract and a burning sensation of the tongue were experienced by women exposed at concentrations of 1,1,1-trichloroethane reported to be 10 to 40 ppm. [61] However, excretion of TCA by these workers indicated exposures of 500 ppm or above.

Skin irritation has also been reported with experimental exposures to liquid 1,1,1-trichloroethane [53] and from occupational use. [36,61] In addition to skin irritation, liquid 1,1,1-trichloroethane can be absorbed to a moderate degree through the skin.

IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION

Environmental Concentrations and Engineering Controls

There is little information available about the concentrations of 1,1,1-trichloroethane to which workers have been routinely exposed.

Concentrations of 1,1,1-trichloroethane developed in cleaning electrical equipment were reported by Burkatskaya et al [104] in 1973. The sampling and analytical method were not described. The greasy parts were sprayed with or dipped into the solvent. Parts were sprayed for 4-5 minutes and dried with a jet of air for 2-3 minutes. The room had an exhaust fan and a general two-way exhaust that provided 35-40 air changes (time interval not given).

Concentrations of 1,1,1-trichloroethane in the shop area during the spraying period were 27-70 ppm. These concentrations declined rapidly when the spraying and drying process was completed and, after 30 minutes, the room air concentration was not measureable.

Concentrations found in different parts of the room when the dipping tanks opened were 25-55 ppm. When the parts were taken from the bath, about 250 ppm of 1,1,1-trichloroethane were found in the workroom air. [104]

An average breathing zone concentration of 410 ppm 1,1,1-trichloroethane was found in a degreasing operation study reported by Hervin and Reifschneider [105] in 1973. A 3 x 3 x 3 foot metal hood vented to the outside air was provided for operations involving the use of 1,1,1-trichloroethane. The bottom of the hood was a basin which contained 5 gallons of solution. The basin was covered when not in use. The operation

involved dipping the metal parts in the solution and then standing them upright for visual inspection. The operator then shook the parts and handed them to the packer who placed them in a wooden box. This operation normally was performed intermittently for a few hours each day.

Eight breathing zone and general area samples were collected with charcoal tubes during the survey and analyzed by gas chromatography. The operations were noted for about 2 hours by the investigators. [105]

Concentrations of 1,1,1-trichloroethane in the workroom of a printing plant were studied by Tada. [60] The samples were collected from various parts of the room on the third to fifth day of the week and the 1,1,1-trichloroethane concentrations were determined by the alkali-pyridine-benzidine method. The survey showed that the workers were exposed to 1,1,1-trichloroethane at 37 ppm on the average for 7 hours/day.

Colorimetric indicator tubes (designed for methyl bromide) were used by Weitbrecht [61] to estimate air concentrations of 1,1,1-trichloroethane in a room where it was used by nine women for washing brass frames in open containers. The average concentrations found by this method were 10 ppm in the general room air and 20 ppm at the worksite. The average exposure concentrations of two of the women were estimated at 40 ppm by another non-specific colorimetric indicator method.

Kay et al [106] reported on atmospheric sampling in the vicinity of vapor degreasing operations in 21 factories. Workers wore personal samplers to measure their average exposure over most of a working day and other atmospheric samples were taken at selected points around the degreasing tanks. Some of the factories used 1,1,1-trichloroethane and others used trichloroethylene. Of 71 workers using trichloroethylene, 18

were exposed in excess of the TLV (100 ppm) throughout their working day. During the survey, concentrations of 1,1,1-trichloroethane were "well below toxic levels" (apparently meaning 350 ppm) during normal vapor degreasing.

In this same study, [106] methods of operation and ventilation were highlighted as important safeguards. The authors reported samples taken near vapor degreasing plants at 21 factories in England. They found that lip exhaust ventilation was provided at three-fourths of the open top tanks surveyed. Extraction rates varied (tank to tank) from 0 to > 100 cu ft/min. Lips slots were commonly found to be closed, by dropage of heavy objects or deposits of dirt. Conditions were found to be poorest at tanks without lip exhausts, and over half of the operators were receiving concentrations above the TLV. This was aggrevated in some conditions by poor general ventilation. Also, downward drafts caused solvent vapor to be blown out of the tanks and into the workers' breathing zone. The authors suggested that this effect could be limited by the use of covers and screens at the tank. The authors [106] found that manual unloading of tanks as well as preparation of work for the tanks, caused a sharp increase of 1,1,1-trichloroethane in the workers' breathing zones.

The following recommendations were made: (1) Degreasing tanks should be sited in well ventilated areas giving particular attention to tanks in confined areas, (2) vapor degreasing tanks should be provided with efficient lip exhaust systems (35 cu ft/min was suggested as an adequate extraction rate) and covered by protective screens to prevent escape of 1,1,1-trichloroethane vapor, (3) work should be arranged so that it can be contained in the freeboard zone of the tank during the removal of excess solvent and stacked to ensure complete drainage of the degreasing solvent,

(4) operations which require high temperature, such as welding, should not be carried out in areas where 1,1,1-trichloroethane may be present, due to breakdown to toxic products. [106]

Recent sampling by Kramer et al, [64] as part of a matched pair study of two textile plants, found that workers were exposed to an average daily concentration of 115 ppm 1,1,1-trichloroethane. During cleaning operations at noon, this level rose to about 350 ppm. Air samples were analyzed by gas chromatography.

1,1,1-Trichloroethane exposures during vapor degreasing were reported by Skory et al [107] as average concentrations and average peak concentrations. Exposures found during different phases of the work were: idling degreaser, 76 ppm (average peak concentration 187 ppm); racking and loading, 73 ppm (average peak concentration 164 ppm); cleaning parts, 95 ppm (average peak concentration 182 ppm); unloading parts, 131 ppm (average peak concentration 268 ppm).

To minimize exposure to 1,1,1-trichlorethane during these operations, the authors suggested that parts should be withdrawn slowly from the degreaser so as not to pull solvent out, heating input and condensing capacity should be properly balanced, the nozzle of the sprayer should be kept below the vapor-air interface during spraying applications, air flow in the degreasing area should be controlled so drafts do not sweep across the top of the vapor degreaser or toward the operator, and lip exhausts should be properly operated. [107]

Environmental Sampling and Analytical Methods

(a) Collection Methods

Most analytical methods are dependent upon the effectiveness and reproducibility of the uptake of 1,1,1-trichloroethane 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, [108-110] is a polar adsorbent and shows pronounced selectivity in adsorbing polar molecules, particularly water. [111] A laboratory study with 1-inch silica gel tubes indicated that the silica gel could become saturated with water and lose its collection efficiency when sampling 3 liters of air. [111]

Activated charcoal has been used as a collection medium followed by 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 method, the same column was used for sample collection and gas chromatographic analysis. This method consolidates collection and analysis into one operation, but only one analysis can be made on each sample. This method has not been developed for field use.

When solid collection media are used, it is necessary to desorb the collected contaminant from the medium. Desorbtion from charcoal was studied by Otterson and Guy [114] who 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 1,1,1-trichloroethane collected in charcoal tubes. [114]

Liquids have been used to collect chlorinated hydrocarbons from contaminated atmospheres. Midget impingers containing m-xylene or tetrachloroethylene have been used for collection in conjunction with gas chromatographic analysis, [114,115] and bubble bottles containing a pyridine solution have been used for collection in conjunction with colorimetric analysis. [60] The successful use of impingers for collection of breathing zone samples requires careful handling of glassware during collection and shipment of samples to the laboratory to avoid spillage.

Other investigators have collected grab samples of contaminated atmospheres directly in a variety of containers ranging from plastic bags to hypodermic syringes. [55,59,114]

(b) Analysis

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

The three 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) [60,116]; (2) colorimetric measurement of the reaction products of tetrachloroethane and pyridine heated in alkali solution (Fujiwara reaction) [60,117]; and (3) direct reading colorimetric indicators. [55,61,118]

The dechlorination method (alkaline hydrolysis) requires collection of the 1,1,1-trichloroethane contaminated atmosphere by a suitable collection medium followed by alkaline hydrolysis in isopropyl alcohol, and titration of the liberated chloride with silver nitrate. [116] The percentage of chlorine hydrolyzed is determined by comparison between samples and known controls. A disadvantage of this method is that chlorine is not easily removed from 1,1,1-trichloroethane and the amount removed depends on the duration of the dechlorination process. Another disadvantage is that it is not specific for 1,1,1-trichloroethane.

In the colorimetric analytical method based on the Fujiwara reaction, a stream of air containing 1,1,1-trichloroethane is passed through a bottle containing pyridine. [60] Potassium hydroxide is then added to a portion of the sample, and this mixture is heated in a boiling water bath and cooled during a fixed time period. A portion of the potassium hyroxide solution, to serve as a blank, is similarly heated and cooled. Absorption coefficients of the pyridine layer are 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. [60,61,118] These are glass tubes packed with chemicals that change color when a measured and controlled flow of air containing 1,1,1-trichloroethane passes through the chemical. 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 1,1,1-trichloroethane since liberated halide ions produce the stain and any

halogen or halogenated compounds will interfere. Federal regulations on detector tubes provide that measurements with colorimetric indicator tubes shall be correct ±25% of the values read (42 CFR 84.50).

Photodetection (halide meters), [119] infrared spectrometry, [120] and gas chromatography [115] are among the analytical methods that are based on the physicochemical properties of 1,1,1-trichloroethane.

Halide meters are made to detect the increased brightness of an arc across metal electrodes when they are enveloped by an atmosphere contaminated with halogens and halogenated compounds. These instruments are sensitive to all halogens and halogenated compounds and consequently they are not specific for 1,1,1-trichloroethane. Halide meters are suitable for continuous monitoring if 1,1,1-trichloroethane is the only halogenated contaminant present in the sampled air. [119]

An infrared spectrophotometer in conjunction with a suitable recorder can be used to document instantaneous concentrations or to record 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 hydrocarbons. [120] The atmosphere of relevant working stations must be sampled and must correspond to the breathing zone of the workers at the working stations. Infrared analysis is subject to interferences from other air contamiants 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. [112] Every

compound has a specific retention time in a given chromatography column, but several compounds in a mixture may have similar retention times. [121] This problem can be overcome by altering the stationary phase of the chromatography column or by changing the column temperature or other analytical parameters. Altering conditions usually will change the retention times and separate the components.

A mass spectrometer can be used subsequent to gas chromatography to identify the substance present in a gas chromatographic peak more positively. 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 are available. [122]

A comparative study of a colorimetric method, a gas chromatographic method, and colorimetric detection tubes for analysis of 1,1,1-trichloroethane was reported in 1970 by Fukabori. [55] The data are presented in Table XII-11. They suggest that the detector tubes give higher values than the other two methods used.

(c) Conclusions and Recommendations

(1) Compliance Method

Based on this review of air sampling and analytical methods, it is recommended that 1,1,1-trichloroethane in air samples be collected with activated coconut shell charcoal, desorbed with carbon disulfide, and analyzed by gas chromatography. Although the indirect system of measurement which requires collection and desorption prior to analysis is a disadvantage, this sampling and analytic method 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. However, unusual care is required in the handling of carbon disulfide, to prevent inhalation and skin contact, and ignition by sources such as steam pipes.

(D) 1,1,1-Trichloroethane can be identified in combination with many other compounds.

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

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

(2) Monitoring Methods

Exposure to 1,1,1-trichloroethane associated with its continuous and constant use can be monitored by infrared spectrophotometry, portable gas chromatography 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 TWA exposures to 1,1,1-trichloroethane.

Direct reading colorimetric tubes (gas detection tubes) can be used as an inexpensive way to monitor 1,1,1-trichloroethane concentrations. The tubes must be used as instructed by the manufacturer. They are not

suitable for determining compliance with the standard, as variability is larger here than with chemical and GC methods.

Biologic Evaluation of Exposure

Three studies were reported of occupational exposure evaluation by analysis of breath for 1,1,1-trichloroethane or urine for trichlorinated compounds. [59-61]

Prost et al [59] collected alveolar air samples at the end of the work day from 12 workers involved in a degreasing operation. The investigators [59] considered that their study was adequate to make formal conclusions. They were able to differentiate a group of workers with higher exposure from another group with lower exposure.

Trichloroacetic acid concentrations in the urine of 15 workers were determined in a printing plant where the average daily exposure to 1,1,1-trichloroethane was 35 ppm. The average concentration of TCA found in the urine on the 3 days were 3.0-3.7 mg/liter.

Weitbrecht [61] found TCA concentrations of 20-60 mg/liter in the urine of seven women with 1,1,1-trichloroethane exposures estimated at 10-20 ppm, In this study, the atmospheric measurements were questionable and also the women were subjected to exposure through the skin.

Prost et al [59] also studied TCA excretion by workers and concluded it was not as reliable for evaluation of exposure as analysis of breath for 1,1,1-trichloroethane.

Experimental studies have shown considerable variation in results of breath analyses among investigators. [35,55,56] The concentrations in the breath depend upon past exposure history, exposure concentrations, exposure

times, time since last exposure, physical activity during and after exposure, and individual factors. [35,39,52,54-58]

Although considerable data have been collected, they have not been synthesized into useable form to be able to quantitatively evaluate exposure to 1,1,1-trichloroethane by either breath or urine analysis.

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

The first Threshold Limit Value (TLV) for 1,1,1-trichoroethane was published by the American Conference of Governmental Industrial Hygienists (ACGIH) in 1953. [123] The value set was a time-weighted average TWA of 500 ppm. The basis for this standard was not reported but most likely it was the work of Adams et al, [73] published in 1950. In 1959, Elkins [116] suggested a maximum allowable concentration (MAC) of 250 ppm, and cited the paper by Adams et al. [73]

The ACGIH published its first documentation for the TLV of 500 ppm for 1,1,1-trichloroethane in 1962. [124] This value was based on the studies of Torkelson et al [36] and Stewart et al. [35] The ACGIH report concluded that to prevent lightheadedness, the 500 ppm limit should not be exceeded for "appreciable periods."

A reduction of the TLV to 350 ppm was recommended by the ACGIH in 1963 on basis of odor, complaints of other forms of irritation, and concern for undue exposure to chlorinated hydrocarbons. [125,126]

The American Industrial Hygiene Association (AIHA) published Emergency Exposure Limits for 1,1,1-trichloroethane in 1964. [127] These limits were 2,500 ppm for 5 minutes, 2,000 ppm for 15 and 30 minutes, and 1,000 ppm for 60 minutes. Exposures for the stated times at these concentrations "will cause definite anesthetic effects and incoordination but no organic injury is expected and recovery should occur within minutes after a subject is withdrawn from exposure." [127] The data from which the emergency limits were derived came from studies on the anesthetic

trichloroethane [3,31-35] and the reports of Stewart et al, [35] Torkelson et al, [36] Stewart, [47] Rowe et al, [58] Plaa et al, [66] Adams et al, [73] and Rennick et al. [78]

The American National Standard Acceptable Concentrations of Methyl Chloroform (1,1,1-trichloroethane) (ANSI Z37.26-1970), [8] published in 1970, gave an acceptable TWA of 400 ppm for protection of health, assuming an 8-hour workday, an acceptable ceiling concentration of 500 ppm if the TWA was below 400 ppm, and a maximum peak above the ceiling of 800 ppm for not more than 5 minutes and not more than once in 2 hours. This standard was based on the reports of Stewart et al, [35] Torkelson et al, [36] Stewart, [47] Stewart and Dodd, [53] Adams et al, [73] Rennick et al, [78] and Prendergast et al. [85]

"Permissible Levels of Toxic Substances in the Working Environment" for many countries was published by the International Labour Office in 1970. [128] The standards for five countries are shown in Table V-1.

TABLE V-1

PERMISSIBLE LEVELS OF
1,1,1-TRICHLOROETHANE IN
THE WORKING ENVIRONMENT OF FIVE COUNTRIES

Country	Standard		Qualifications
	mg/cu m	ppm	
Finland	2,700	500	8 hours continuous exposure
Germany (Fed Rep)	1,080	200	MAC
Japan	1,900	350	None stated
Yugoslavia	1,080	200	None stated
Rumania	1,000	185	None stated

Adapted from reference 128

The documentation of the TLV of 350 ppm, originally given in 1966, [126] was updated in 1971. [129] Additional references cited in this documentation were Irish, [14] Stewart et al, [39] Stewart, [47] Hatfield and Maykowski, [50] Rowe et al, [58] and Hake et al. [91]

The German Research Society MAK Commission published the criteria for its MAC standard for 1,1,1-trichloroethane in 1972. [130] The standard was 200 ppm (1,080 mg/cu m) and it was reported to be an average, presumably a TWA for an 8-hour workday. This standard was based on experimental studies [35-37,39] of humans where subnarcotic effects were observed which could reduce a person's ability to work after repeated exposures lasting several hours. The studies cited included Stewart et al, [35,39] Torkelson et al, [36] and Salvini et al. [37]

The USSR MAC is 3.66 ppm (20.0 mg/cu m). [104]

The present US federal standard was adopted from "Threshold Limit Values of Airborne Contaminants for 1968." [131] It is an 8-hour time-weighted average of 350 ppm (1,910 mg/cu m) (29 CFR 1910.1000).

Basis for Recommended Environmental Standard

The recommended environmental action limit is based upon CNS responses to acute exposures [37, 38, 39] in man, cardiovascular and respiratory effects associated with chronic exposures [85, 88] in several species, the similarity of pathologic changes in man and several animal species, and the absence of reported effects in man at concentrations below the proposed limit. [65, 64]

Impairment of the CNS, to the extent that escape would be impossible, has occurred experimentally in human subjects when the exposure

concentration of 1,1,1-trichloroethane was increased from 0-2,650 ppm during 15 minutes. [35] Impaired coordination and balance have also been demonstrated in experimental exposures of human subjects to 1,1,1-trichloroethane at 900-1,000 ppm for 20 minutes or more. [35, 36]

Exposure at 250 ppm for 30 minutes followed immediately by exposure at 350 ppm for another 30 minutes resulted in impaired perceptual speed, reaction times, and manual dexterity. [38] These later findings [38] did not develop during the first 30 minutes of exposure at 250 ppm but exposure at this concentration for a longer period of time was not made. The study was also not conducted with repetitive exposures, and the effects of breathing the vapor through a mouthpiece and the use of menthol to disguise the odor of 1,1,1-trichloroethane were not assessed. The experiment with mice [74] indicated accumulative effects on the CNS of 1,1,1-trichloroethane exposure.

With exposures at 500 ppm, 7 hours/day for 5 days, CNS effects such as sleeplessness, lightheadedness, headache and an abnormal Romberg test were reported. [39]

Based on a case report of a fall resulting in injury associated with 1,1,1-trichloroethane exposure [51] and the experimental evidence that nervous system responses that might be manifested as accident proneness can occur with exposures at 450 ppm, [37] it is recommended that a ceiling exposure be established below this concentration.

1,1,1-Trichloroethane has been shown to have a direct effect on the cardiovascular system. [32, 46, 75, 76, 79, 80] The first response that has been detected upon administration of 1,1,1-trichloroethane was decreased peripheral resistance to blood flow. [80] The blood pressure

fell within seconds and continued to fall as the heart lost its contractile strength. [79, 80] These effects have been found experimentally with concentrations of 8,000 ppm or more during exposures of no more than 5 minutes.

Heart muscle from rats which had been anesthetized for 1 hour with 1,1,1-trichloroethane had impaired oxygen consumption, [32] and heart muscle from unexposed rats developed impaired contractility when exposed to 1,1,1-trichloroethane in the aeration mixture. [80] Fractional analysis of LDH from a patient poisoned with 1,1,1-trichloroethane showed that the heart was the major source of the increased amounts of this enzyme in the patient's blood. [46]

Autopsy findings of gross congestion and pulmonary edema in workers overcome by 1,1,1-trichloroethane exposures [49, 50] are evidence of cardiovascular effects of the type observed experimentally, [79, 80] or clinically. [46] Neither blood pressure changes nor ECG changes were found in humans experimentally exposed to 1,1,1-trichloroethane at concentrations of 2,650 ppm or less. [35, 36] In other experimental human exposures, blood pressure and ECG changes were not reported. [37, 38, 39] There were no significant ECG findings in the four reported cases of acute occupational exposures [51] or the one reported case of 1,1,1-trichloroethance ingestion. [42]

Changes that may be attributable to cardiovascular insufficiency have been reported in chronic animal experiments. [74, 77] Congestion of the liver and lungs was found in mice after nine 2-hour/day exposures on alternate days to 1,1,1-trichloroethane at 1,000 ppm, [74] but these authors did not adequately describe their control techniques. A more

recent study, repeating this work, has found neither congestion of the lungs nor liver, nor traces of inflammation around the biliary duct area. [132] Nonspecific inflammatory changes have been reported in several species exposed at 370 ppm continuously for 90 days. [85]

Human exposures at an average TWA concentration of 115 ppm 1,1,1-trichloroethane have been reported by Kramer et al [64] in workers exposed for 8 hours/day, 5 days/week for up to 5 years. Upon laboratory testing (hematology, blood chemistry, urinalysis and ECG) as well as medical interviews, no adverse effects were reported.

Exposures of humans at 4 to 53 ppm in four Japanese printing plants have been reported by Seki et al. [65] The investigators reported tests of vibrational sense, routine laboratory examinations in hematology and urinalysis, and medical interviews. No adverse effects were reported at these concentrations.

No adverse health effects were reported in the study by Kramer et al [64] when workers were exposed at 1-175 ppm 1,1,1-trichloroethane. Some of these workers had, for 1-2 years, previously been exposed at concentrations as high as 838 ppm, and if there had been any effects at the time, recovery had occurred because the subjects were reported to be healthy when the study began. To some extent, animal studies support these observations in exposed workers. Significant findings were not demonstrated in rats, mice, dogs and monkeys exposed at 250 ppm continuously for 90 days [84] and only minimal findings at 370 ppm continuously for 90 days. [85] In another study, minimal effects were reported in hepatic function of mice exposed continuously for 14 weeks at 250 ppm. [41] Other investigators have not reported any significant effects at similar levels in man and animals. [35,36,38,132]

Respiratory irritation has been reported in man and several other species. At 400 ppm eye, nose and throat irritation have been experienced by subjects during exposure to 1,1,1-trichloroethane. [35,37] Varying degrees of lung congestion were found in all species exposed continuously for 90 days to 1,1,1-trichloroethane at 135 ppm. [85] The authors stated, however, in view of pneumonitis in the surviving animals and in the control group, that no positive conclusions could be drawn connecting the 1,1,1-trichloroethane exposure to the effects. Irritation of the upper respiratory tract was reported among women during occupational exposure to 1,1,1-trichloroethane. [61] No other studies of respiratory disease associated with chronic occupational exposure to 1,1,1-trichloroethane have been reported. The recommended ceiling limit should protect workers from acute irritation effects, but it is not known if it will protect them from chronic respiratory effects.

From the data presented above, it is evident that a ceiling should be placed on occupational exposure to 1,1,1-trichloroethane. Evidence of CNS response at 450 ppm [37] and minimal to no response at 250 to 350 ppm [38] leads to the conclusion that 350 ppm is a reasonable ceiling concentration. This ceiling will assure a safe TWA as excursions above the action level will not lead to the chronic effects described in humans and animals. Although information on workers exposed to 1,1,1-trichloroethane for over 6 years is scarce, workers who had experienced TWA's of 217 ppm for up to 6 years showed no adverse effects, and thus it is unnecessary to recommend a TWA limit below 350 ppm to prevent chronic effects. To provide some assurance that the environmental limit is not exceeded, an action level of 200 ppm is recommended.

It is recognized that many workers handle small amounts of 1,1,1-trichloroethane or work in situations where, regardless of the amounts used, there is only negligible contact with the substance. Under these conditions, it should not be necessary to comply with all the provisions of this recommended standard. However, concern for worker health requires that protective measures be instituted below the enforcable limit to ensure that exposures stay below that limit. Therefore, environmental monitoring and recordkeeping is recommended for those work situations which involve exposure above the recommended action level of 200 ppm determined as a TWA for a 10 hour-day, 40 hour-week, to delineate work areas that do not require control of inhalation hazards. The environmental action level has been chosen on the basis of professional judgment rather than on quantitative data that delineate nonhazardous areas from areas in which a hazard definitely exists.

In view of individual variation in human response to noxious substances, as well as the variation in worker exposure to 1,1,1-trichloroethane, NIOSH recommends comprehensive preplacement and annual examinations be made available to all workers exposed to 1,1,1-trichloroethane. In certain cases, a given individual may exhibit symptoms warranting a more frequent examination schedule. Recognition of the selective hazard to the nervous, hepatic and cardiovascular systems leads to emphasis of these factors for any physical examination.

For the medical program to be effective, it is important that the worker recognize the signs and symptoms as well as hazards of working with 1,1,1-trichloroethane. At the onset of specific symptoms attributable to exposure, the physician should be consulted. Thus, NIOSH recommends that

employees be informed of health hazards and that warning signs be posted in appropriate locations in plants where 1,1,1-trichloroethane is manufactured, used or stored. Further information should be transmitted through a continuing educational program instituted by the employer.

During day-to-day work, where the occurrence of spills, sprays and splashes, as well as the generation of high concentrations of 1,1,1-trichloroethane in accidental and emergency situations, is likely to occur, appropriate control measures need to be taken. To prevent the escape of hazardous quantities of 1,1,1-trichloroethane, various engineering control procedures are recommended to contain the chemical and ensure safe working habits in the vicinity of its use, manufacture and storage. These work practices include handling, storage, ventilation, maintenance of equipment, personal hygiene and emergency procedures. Due to the hazard of a buildup of 1,1,1-trichloroethane concentration above the environmental ceiling in small work areas, special instructions are given for working in confined spaces.

To monitor the concentration of 1,1,1-trichloroethane, it is necessary to periodically sample the employees' breathing zone air. NIOSH has reviewed the literature on sampling and analytical methods in chapter IV and has recommended the sampling and analytical method presented in Appendices I and II.

Although it is known that many potentially harmful substances used in industry enter the maternal bloodstream and are capable of crossing the placenta, there is insufficient evidence at this time to exclude women of childbearing age from working in areas where 1,1,1-trichloroethane is manufactured, stored, or used. Data are available from only one study in

rats and mice, and although cleft palate, supernumerary vertebra, and split sternebra occurred, the lack of new data, ie number of animals per litter, and confirmation from other studies, precludes a firm statement of teratogenicity. The incidence of these abnormalities in large samples of these strains of rats and mice is not known. The observation of these abnormalities in this small sample experiment is not sufficient to warrant special restriction of women of child bearing age. Based on the insufficiency of the experiment, it is not recommended that pregnant females be advised of any potential hazard unless a repetition of the experiment provides confirmation of the results.

VI. WORK PRACTICES

Information concerning work practices for 1,1,1-trichloroethane can be found in the Manufacturing Chemists Association Safety Data Sheet SD-90. [15] Information on work practices for some specific uses is also available. [106,133]

(a) Transport, Handling, and Use

1,1,1-Trichloroethane may be stored in mild steel containers or, if there is excess moisture in the ambient air, in stainless steel or resin-lined containers. It can be decomposed to toxic and corrosive compounds including phosgene and hydrochloric acid by contact of liquid or vapor with open flame or red-hot surface, so it should be appropriately stored and handled to prevent such contact. [134,135] Damaged drums or other storage or transporting containers should not be welded until thoroughly purged with steam, flushed with water, and air dried. [136]

All piping and valves at the loading or unloading station should be of material resistant to 1,1,1-trichloroethane and should be carefully inspected prior to connection to the transport vehicle and periodically during the operation. Personal protective clothing must be provided during both inspection and connection. Information on imperviousness of some materials to 1,1,1-trichloroethane is available. [137] Eye wash and safety shower installations should be readily available in the immediate area. Signs indicating the location of safety showers and eye wash facilities should be prominently displayed throughout the work area. Unloading areas must be posted "DANGER: LOADING OR UNLOADING 1,1,1-TRICHLOROETHANE."

Due to the toxicity of 1,1,1-trichloroethane, processes in which it is used in large quantities should be carried out in closed systems. Well designed hoods and ventilation systems should be used to maintain exposures at or below concentrations specified by this recommended standard. Further protective measures include the use of personal protective equipment and clothing and purging of equipment prior to and during servicing and maintenance.

Safety showers are desirable and eye wash facilities are necessary in areas where 1,1,1-trichloroethane is handled. In locations where such facilities are not available, a container of water for emergency use must be kept with the first aid supplies.

(b) Equipment Maintenance

All equipment used for handling 1,1,1-trichloroethane must be emptied and purged prior to entry or disassembly. Steaming followed by washing with water is recommended for purging tanks and other containers which have held 1,1,1-trichloroethane. Pipe lines should be disconnected and capped. Under conditions where it is necessary to enter highly contaminated areas or otherwise work with 1,1,1-trichloroethane contaminated equipment, maintenance personnel must use either a self-contained breathing apparatus of the pressure demand mode, with an impervious protective suit, or a combination supplied air suit with auxiliary self-contained air supply. Ventilation should be continued during this time by blowing or drawing fresh air through the system. Safety precautions for emergency rescue require that all maintenance personnel be informed of the toxic properties of 1,1,1-trichloroethane and be instructed on the necessity of wearing personal protective equipment. Constant observation of anyone entering a

tank should be maintained in case rescue work is necessary.

(c) Emergencies

Spills must be anticipated. Storage tanks should be diked to contain the contents of the tank. Drum storage areas must also be diked to contain the volume of 1,1,1-trichloroethane present in the drums to prevent release to other areas. Areas where major spills are likely to occur should be constructed so that they may be closed until properly protected personnel can ventilate, enter, and clear the area. Warning signs must be posted so that unauthorized personnel will not enter the area. Normal work should not be continued until the concentration of 1,1,1-trichloroethane has been reduced to the recommended workplace environmental limit. Any combustion operations must be stopped until the spill is cleared. Disposal of 1,1,1-trichloroethane must be performed in compliance with local, state, and federal waste disposal regulations. Consideration should be given to pumping the diked spill to another tank. In addition, it is advisable to have facilities for transfer of the contents of a leaking tank to another suitable tank.

Areas in which small spills have occurred should be evacuated and well-ventilated. Small, portable fans may be used in confined areas where local exhaust ventilation is not feasible. Workers should not return to any work area if the odor of 1,1,1-trichloroethane is still perceptible without the concentration being determined first.

(d) Respiratory Protection

For adequate respiratory protection against the many conditions which may be encountered in individual operations, many types of respirators have been developed and approved. Each has a particular 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 Protection Devices Manual [138] published by the AIHA and the ACGIH in 1963. The American National Standards Practices for Resporatory Protection, ANSI Z88.2-1969, [139] also classifies, describes, and gives the limitations of respirators.

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

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

For 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 environmental limit, although the majority of wearers can obtain protection in atmospheres of higher 1,1,1-trichloroethane concentrations. On the same basis, NIOSH recommends that the full facepiece, operated with negative pressure, may be used up to 50 times the TWA concentration limit. As eye irritation has been reported at concentrations of 500 ppm 1,1,1-trichloroethane, it is recommended that full facepiece respirators be used above this level. Due to the adequate warning nature of 1,1,1-trichloroethane, air-purifying respirators, such as the chemical cartridge type, may be used at concentrations less than 500

ppm. When significant and nonreversible health effects may occur, at 1,000 ppm and above, self-contained breathing apparatus or supplied-air respirators with a full facepiece must be used.

The maximum use concentration guides do not take into account the service life of the filters or absorbent canisters which also affect the performance of air-purifying respirators. The approval tests (under 30 CFR 11) for these two devices specify only carbon tetrachloride for the service life test. Based on recent tests by Nelson and Harder, [140] who tested standard respirator cartridges against many types of industrial organic solvents, it is now possible to estimate the service life of approved organic vapor canisters or cartridges against 1,1,1-trichloroethane. With a test concentration of 1,000 ppm of 1,1,1-trichloroethane, they reported that the standard organic vapor cartridge has a service life of 59 minutes before a breakthrough 100 ppm of 1,1,1-trichloroethane. Under the same test conditions, a service life of 90 minutes for carbon tetrachloride was obtained. The standard industrial size gas mask canister is tested against 20,000 ppm of carbon tetrachloride and it must have a service life of 12 minutes before a breakthrough of 5 ppm. Since it has been shown that charcoal can absorb 1.5 times as much carbon tetrachloride as 1,1,1-trichloroethane, it can be estimated that the service life for an industrial size canister is 150 minutes in an atmosphere of 1,000 ppm 1,1,1-trichloroethane.

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 sertified by the Testing and Certification Laboratory of NIOSH are listed

in separate publications. These are available from the Testing and Certification Laboratory, NIOSH, Morgantown, West Virginia, 26505.

VII. RESEARCH NEEDS

Epidemiologic Studies

The evidence from epidemiologic studies is somewhat contradictory. Several studies [36,47,50,62,64] reported no adverse effects in man at concentrations of 100-800 ppm of 1,1,1-trichloroethane. Unfortunately, individual data is lacking in some, and experimental details are lacking in all of these studies.

Interpretation is further complicated by other studies [61,63] which report symptoms attributable to "substances used in the work environment," not necessarily 1,1,1-trichloroethane, at 10-250 ppm. These studies suffer from (1) exposure to vapors in addition to those of 1,1,1-trichloroethane (2) inadequate characterization of exposure concentrations and (3) intervening variables such as skin exposure and psychological effects. Therefore, carefully controlled, cross-sectional studies, which report individual data, adequately characterize the environment and control for exposure to airborne contaminants other than 1,1,1-trichloroethane, should be conducted.

Chronic Animal Studies

Although a number of animal studies have indicated chronic changes in the heart, [77] nervous reflex activity, [77] respiratory function, [77,85,88] and hepatic anatomy [41,77,88] resulting from "long term" exposure to 1,1,1-trichloroethane, most of these studies have used continuous exposures, which are not typical of the occupational setting.

Therefore, studies investigating the chronic effects of long term exposure to 1,1,1-trichloroethane should be conducted that utilize exposure schedules similar to those observed in industry, ie, an 8 to 10-hour day, 5 days per week.

Mutagenicity, Teratogenicity, Carcinogenicity

As only one study was available on teratogenicity [103], further studies are needed concerning the influence of 1,1,1-trichloroethane upon the mother and fetus. While it has not been determined if 1,1,1-trichloroethane is teratogenic, mutagenic, or carcinogenic in man, and it is not known what the tolerated dose of 1,1,1-trichloroethane is in the embryo or fetus, there is little doubt that many detrimental substances in the maternal bloodstream can readily reach the embryo or fetus via the placenta. As 1,1,1-trichloroethane concentrations in the occupational environment will lead to small but measurable concentrations of this substance in the bloodstream, additional information is needed.

A study by Dow Chemical Company in rats was inconclusive, as spontaneous neoplastic lesions occurred in both control and experimental groups. [90] A carcinogenesis study, as yet incomplete, by the National Cancer Institute may provide more data.

Synergistic Effects

From a review of the literature, it is evident that research must be initiated to answer important questions concerned with exposure to 1,1,1-trichloroethane and that a concerted effort must be directed toward

determining the possible additive, synergystic, or inhibitory effects of 1,1,1-trichloroethane, in combination with other hydrocarbons and organic solvents, on dose-response relationships.

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IX. APPENDIX I

SAMPLING PROCEDURES FOR COLLECTION OF 1,1,1-TRICHLOROETHANE

General Requirements

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

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

(c) Suggested records:

(1) The date and time of sample collection.

(2) Sampling rate and duration.

(3) Total sample volume.

(4) Location of sampling.

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

(6) Other pertinent information.

Sampling

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

(b) Samples should be collected to permit determination of TWA workday and ceiling exposures for every job involving exposure to 1,1,1-trichloroethane in sufficient numbers to express the variability of the exposures for the work situation.

(c) Apparatus for Charcoal Tube Sampling

(1) Pump, battery-operated, complete with clip for attachment to the worker.

(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 two sections of 20/40 mesh activated coconut-shell charcoal, fired at 600 C, 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 silated glass wool is placed in front of the adsorbing section. The pressure drop across the tube when in use must be less than 1 inch of mercury at a flowrate of 1 liter/min.

(d) Calibration of Sampling Instruments

(1) Air sampling instruments should be calibrated with a representative charcoal tube in line, over a normal range of flowrates (25-1000 ml/min). Calibration curves must be established for each sampling pump and be used in adjusting the pump prior to and during each field use. Airflow through the pump should be within $\pm$5% the desired rate. New calibration curves should be established for each sampling pump after making any repairs or modifications to the sampling system.

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

(e) Collection and Handling of Samples

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

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

(3) The charcoal tube should be placed in a vertical position during sampling, to prevent channeling which would result in sample loss.

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

(5) The sample can be taken at flowrates of 25-1000 ml/min, depending on the pump. Total sample volumes of less than 35 liters are recommended, eg, a sample could be collected at 200 ml/min for 15 minutes to give a total sample of 3 liters, or at 25 ml/min for 24 hours to give a total sample volume of 36 liters. However, for determining the action level, it is also recommended that each sample be collected in 4 hours or less.

(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 passed through this tube.

X. APPENDIX II - ANALYTICAL PROCEDURES FOR DETERMINATION OF 1,1,1-TRICHLOROETHANE

Principle of the Method

(a) A known volume of air is drawn through a charcoal tube to trap the 1,1,1-trichloroethane vapor.

(b) The 1,1,1-trichloroethane 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 1,1,1-trichloroethane on a gas chromatograph with a flame ionization detector is 300 ng/sample.

(b) The upper limit value for 1,1,1-trichloroethane is 36.0 mg/sample. This is the estimated amount of 1,1,1-trichloroethane 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 high concentration of 1,1,1-trichloroethane, it is recommended that a smaller volume of air be sampled.

Interferences

(a) 1,1,1-Trichloroethane 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 1,1,1-trichloroethane with the chromatographic conditions described in this method could interfere. Such interferences may be eliminated by altering operating conditions of the gas chromatograph using a different column packing or using a selective detector.

Advantages of the Method

(a) This method provides one basic procedure 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 1,1,1-trichloroethane 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 1,1,1-trichloroethane 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 (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-μl capacity, and convenient sizes for making standards.

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

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

Reagents

(a) "Spectroquality" carbon disulfide.

(b) 1,1,1-Trichloroethane, preferably "chromatoquality" grade.

(c) Bureau of Mines Grade A helium or nitrogen.

(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 vial. The separating foam is removed and discarded; the second section is transferred to another similar test tube. These two sections are analyzed separately. Prior to analysis, 0.5 ml of carbon disulfide is pipetted (not by mouth) into each test tube to desorb 1,1,1-trichloroethane from the charcoal. A desorbtion time of 30 minutes, with occasional stirring, is recommended.

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.

(c) 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.

(d) 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 microliters of carbon disulfide are drawn into the syringe to increase the accuracy and reproducibility of the injected sample volume. The needle is removed from the carbon disulfide solvent, and the plunger is pulled back about 0.2 μl to separate the solvent flush from the sample with a pocket of air to be used as a marker. The needle is then immersed in the sample, and a 5-μl portion 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.

(e) 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 1,1,1-trichloroethane 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 I.D. 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 five tubes are prepared in this manner and allowed to stand at least overnight to ensure complete adsorption of 1,1,1-trichloroethane onto the charcoal. These five tubes will be referred to as the "desorption samples." A parallel blank tube should be treated in the same manner except that no 1,1,1-trichloroethane is added to it. The desorption samples and blanks are desorbed and analyzed in exactly the same manner as previously described.

Two or three desorption standards are prepared for analysis by injecting the same volume of 1,1,1-trichloroethane 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

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

Calibration and Standards

It is convenient to prepare standards in terms of mg 1,1,1-

trichloroethane/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 1,1,1-trichloroethane is injected into exactly 10 ml of carbon disulfide in a glass-stoppered flask. The density of 1,1,1-trichloroethane (1.2528 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 1,1,1-trichloroethane/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 1,1,1-trichloroethane on the front and reserve sections of the charcoal tube.

(c) Corrections must be made to the 1,1,1-trichloroethane 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 1,1,1-trichloroethane found on the front section of the blank charcoal tube from the weight of 1,1,1-

trichloroethane found on the front section of the sample charcoal tube to give a corrected front section weight.

(2) Subtract the weight of 1,1,1-trichloroethane found on the reserve section of the blank charcoal tube from the weight of 1,1,1-trichloroethane found on the reserve section of the sample charcoal tube to give a corrected reserve section weight.

(3) Add the corrected amounts of 1,1,1-trichloroethane present on the front and reserve sections of the sample tube to determine the total measured 1,1,1-trichloroethane 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:

$$V' = \frac{298VP}{760(T+273)} = \frac{0.392VP}{(T+273)}$$

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 1,1,1-trichloroethane in the sampled air can be expressed in various ways using M, the weight of 1,1,1-trichloroethane 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 = 247 M/V'

XI. APPENDIX III
MATERIAL SAFETY DATA SHEET

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

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

(a) Section I. Product Identification

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

competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

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

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

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

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, ie, "100 ppm LC50 rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute Inc. Flammable or reactive data

could be flash point, shock sensitivity, or other brief data indicating nature of the hazard.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicate 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.

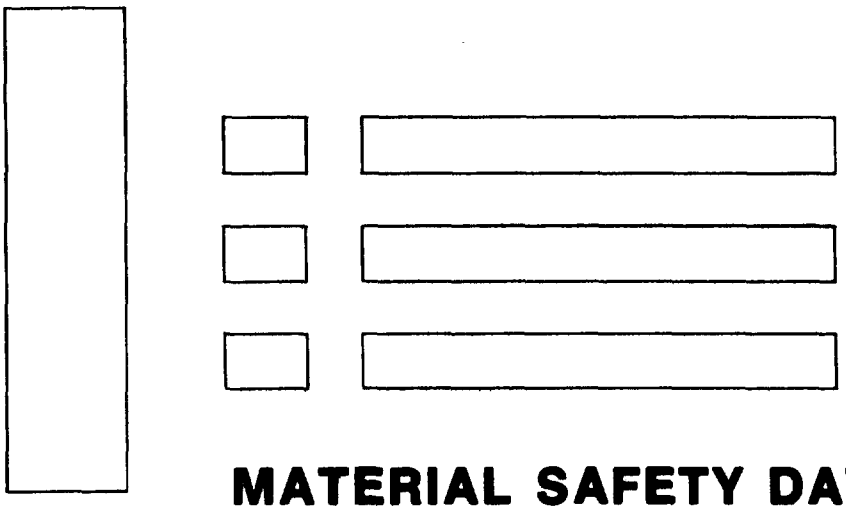
(i) Section IX. Special Precautions

"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 in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.



MATERIAL SAFETY DATA SHEET

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

II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

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

IV FIRE AND EXPLOSION DATA

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

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN

INHALATION

INGESTION

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY STATEMENTS

OTHER HANDLING AND STORAGE REQUIREMENTS

PREPARED BY

ADDRESS

DATE

XII. TABLES

TABLE XII-1

PHYSICAL PROPERTIES OF 1,1,1-TRICHLOROETHANE

Chemical Abstract's serial number			000071556
Synonyms			1,1,1-Trichloroethane Methyl chloroform Alpha-trichloroethane
Molecular formula			CH3 CCl 3
Formula weight			133.41
Boiling point			74.0 C (165.2 F) (760 mm Hg)
Melting point			-32.62 C (-26.7 F)
Vapor density			4.6 (air = 1)
Specific gravity			1.339 (20 C), (water = 1.000 at 4 C)
Solubility			0.44g/100g water at 25 C; soluble in ethyl ether, ethyl alcohol
Density of saturated air			1.6 (air = 1)
Concentration of saturated air			16.7% by volume at 25 C
Flammable (explosive) limits			10-15% in air with hot wire ignition
Flash point			None
Autoignition temperature			500 C (932 F)
Vapor pressure	Temp F	Temp C	mm Hg
	50	10	62
	68	20	100
	77	25	127
	86	30	150
	104	40	240

TABLE XII-1 (CONTINUED)

PHYSICAL PROPERTIES OF 1,1,1-TRICHLOROETHANE

Conversion factors,	1 mg/liter = 1 g/cu m = 183 ppm
(25C 760 mm Hg)	1 ppm = 5.46 mg/cu m = 5.46 μg/liter

Adapted from references 1,5,6,8,12-15

TABLE XII-2

CONCENTRATIONS OF 1,1,1-TRICHLOROETHANE
IN BLOOD OF EXPOSED SUBJECTS

	Arterial Blood, ppm Mean SD	Venous Blood, ppm Mean SD	No. of Subjects
250 ppm			
rest 36.5 ft-lbs/sec	3.0 ± 0.2	1.4 ± 0.2	12
exercise,	4.5 ± 0.2	3.1 ± 0.4	9
73.0 ft-lbs/sec	5.2 ± 0.1	3.5 ± 0.8	4
exercise			
109.5 ft-lbs/sec	5.5 ± 0.3	4.4 ± 0.4	4
350 ppm			
rest	5.0 ± 0.5	3.0 ± 0.6	5
exercise			
36.5 ft-lbs/sec	7.2 ± 0.4	4.0 ± 6.6	5
250 ppm			
rest	1.9 - 2.5*	0.5 - 1.2*	3
rest + 4% CO2	3.0 - 3.9*	0.9 - 1.3*	3
exercise + 4% CO2	3.2 - 4.5*	1.4 - 2.3*	3

* Range is presented by authors when n<3.
Adapted from Astrand et al [54]

TABLE XII-3

EFFECTS OF 1,1,1-TRICHLOROETHANE EXPOSURE* AT 875 ppm
ON REPRODUCTION DATA OF RATS AND MICE

	Rats		Mice	
	Control	Exposed	Control	Exposed
Number of litters	30	23	26	13
Corpora lutea/dam	15 ± 2	14 ± 2	--	--
Implantation sites/ litter	13 ± 2	11 ± 4	14 ± 2	14 ± 2
Live fetuses/litter	12 ± 3	10 ± 4	12 ± 2	12 ± 2
%, resorptions/ implantation sites	4 (16/378)	7 (19/255)	10 (39/369)	8 (14/175)
%, litters with resorptions	40 (12/30)	56 (13/23)	69 (18/26)	77 (10/13)
Litters totally resorbed	0/30	0/23	0/26	1/13
Resorptions/litters with resorptions	1.3 (16/12)	1.5 (19/13)	2.2 (39/18)	4.3 (26/6)
Sex ratio, M:F	54:46	53:47	54:46	47:53
Fetal body weight, g	5.42 ± 0.45	5.86 ± 0.32	1.30 ± 0.08	1.27 ± 0.13
Fetal crown-rump length, mm	43.5 + 1.4	44.0 + 0.7	26.2 + 0.8	25.6 + 1.0

* Also includes 50 ppm impurities and inhibitors

Adapted from Schwetz et al [103]

TABLE XII-4

FETAL ANOMALIES FOUND IN MICE AFTER MATERNAL EXPOSURE TO 1,1,1-TRICHLOROETHANE AT 875 ppm

Anomalies	Control %	Control No.	Exposed %	Exposed No.
GROSS				
Short tail		(0)	8	(1)
Runts (wt. less than means X - 3 S.D.)	38	(10)	31	(4)
SOFT TISSUE				
Cleft palate		(0)	8	(1)
Subcutaneous edema	27	(7)	38	(5)
SKELETAL				
Delayed ossification - skull bones	69	(18)	62	(8)
Lumbar ribs or spurs	31	(8)	38	(5)
Delayed ossification - sternebrae	4	(1)	23	(3)
Split sternebrae		(0)	15	(2)
Extra sternebrae		(0)	8	(1)
Malaligned sternebrae		(0)	15	(2)
Number of litters examined		26		13

Adapted from Schwetz et al [103]

TABLE XII-5

FETAL ANOMALIES FOUND IN RATS AFTER MATERNAL EXPOSURE TO 1,1,1-TRICHLOROETHANE AT 875 ppm

	Control		Exposed	
SOFT TISSUE	%	No.	%	No.
Dilated renal pelvis		(0)	4	(1)
Subcutaneous edema	17	(5)	17	(4)
SKELETAL				
Delayed ossification - skull bones	33	(10)	30	(7)
Lumbar ribs or spurs	13	(4)	22	(5)
Delayed ossification - sternebrae	30	(9)	16	(3)
Split sternebrae		(0)	4	(1)
Supernumerary vertebra (one, thoracic)		(0)	4	(2)
Number of litters examined		30		23

Adapted from Schwetz et al [103]

TABLE XII-6

INHALATION EXPOSURES AND EFFECTS IN HUMANS

Reference	Exposure Data	Effects
Dornette and Jones [33]	10,000-26,000 ppm 6,000-22,500 ppm	Induction of anesthesia usually within 2 minutes Maintenance of anesthesia ECG changes
Kleinfeld and Feiner [48]	More than 5,000 ppm 10 minutes	Occupational fatality
Siebecker et al [34]	Anesthesia	Circulatory depression before EEG changes
Stewart et al [35]	0-2,650 ppm 15 minutes	2 of 7 exposed subjects unable to stand; feeling of malaise for 5 hours; positive urinary urobilinogen
Torkelson et al [36]	1,740-2,180 ppm 1,000 ppm 70-75 minutes	Disturbed equilibrium Positive Romberg test ECG's normal Impaired coordination and equilibrium
Stewart et al [35]	900-950 ppm 20-73 minutes	Impaired Romberg tests, elevated urinary urobilinogen
Torkelson et al [36]	500 ppm 450 minutes	Reflexes, equilibrium, blood pressure, and pulse rate not disturbed
Stewart et al [39]	500 ppm 7 hours/day 5 days	Mild sleepiness; light-headedness; headache; impaired Romberg tests; eye nose and throat irritation; no evidence of liver or kidney injury
Stewart et al [35]	500 ppm 3 hours	Balance and coordination not affected

TABLE XII-6 (CONTINUED)

INHALATION EXPOSURES AND EFFECTS IN HUMANS

Reference	Exposure	Species and Effects
Salvini et al [37]	450 ppm 8 hours	Decreased perceptive capabilities under stress conditions; eye, nose and throat irritation
Gamberale and Hultengren [38]	350 ppm 2 hours	Perceptual speed, reaction times, and manual dexterity impaired
	250 ppm 2 hours	Perceptual speed, reaction times, and manual dexterity not impaired
Binaschi [63]	250 ppm Occupational	Unspecified symptoms
Kramer et al [64]	115 ppm Occupational	No significant distrubrances of hematology or blood chemistry
Weitbrecht [61]	Occupational exposure with skin exposure several months	Conjunctival and respiratory irritation; headache; tiredness; insomnia; gastrointestinal complaints; positive urobilinogen; autonomic and circulatory dystrophy; psychasthenia

TABLE XII-7

INHALATION EXPOSURES AND CENTRAL NERVOUS SYSTEM EFFECTS IN ANIMALS

Reference	Exposure	Species and Effects
Adams et al [73]	18,000 ppm, 5 minutes	Rats, helpless
	3 hours	Rats, unconscious
	3 hours	Rats, LC50
	14,250 ppm 7 hours	Rats, LC50
Truhaut et al [75]	16,850 ppm, 5 minutes	Rabbits, increased EEG activity
	More than 5 minutes	Decreased EEG activity
Gehring [70]	13,500 ppm, 16 minutes	Mice, anesthesia
Adams et al [73]	10,000 ppm, 1-2 minutes	Rats, decreased activity
	10 minutes	Rats, helpless
	3 hours	Rats, semiconscious
Truhaut et al [76]	6,250 ppm, 1 hour	Rabbits, sustained increase in EEG activity
Adams et al [73]	5,000 ppm, 1 hour	Rats, mild narcotic effect
	1 hour	Monkey, slight ataxia
	5 hours	Monkey, trembling of hands and forearms
Horiguchi and Horiuchi [74]	1,000 ppm, 2 hours/day 9 exposures on alternate days	Mice, increased running activity
Tsapko and Rappoport [77]	180-900 ppm, 4 hours	Rats and cats, threshold for altering conditioned reflex activity
	73 ppm, 4 hours/day up to 120 days	Cats, differentiation reflexes deranged
	50 days	
	120 days	Rats, more extreme pathologic changes in nervous tissue

TABLE XII-8

INHALATION EXPOSURES AND CARDIOVASCULAR EFFECTS IN ANIMALS

Reference	Exposure	Species and Effects
Griffiths et al [46]	125,000 ppm 1.5-6 minutes	Dogs, abrupt drop in blood pressure; ventricular fibrillation in 1 dog on second exposure; gross congestion in all tissues; heart cell necrosis
Belej et al [79]	25,000 ppm, 5 minutes	Rhesus monkeys, cardiac arrythmias; myocardial depression; tachycardia
Herd et al [80]	8,000 ppm, 5 minutes	Dogs, sharp decrease in peripheral resistance followed by decreased stroke volume, heart rate and myocardial-contractility
Truhaut et al [75]	6,250 ppm, 10 minutes	Rabbits, cardiovascular depression
Reinhardt et al [81]	5,000 ppm, 5 minutes	Dogs, cardiac sensitization to epinephrine
	2,500 ppm, 5 minutes	Dogs, no cardiac sensitization to epinephrine
Tsapko and Rappoport [77]	73 ppm, 4 hours/day 50 days 120 days	Rats, venous hyperemia and small foci of swelling in heart muscle, more severe at 120 days

TABLE XII-9

INHALATION EXPOSURES AND PULMONARY EFFECTS IN ANIMALS

Reference	Exposure Data	Species and Effects
Torkelson et al [36]	2,000 ppm, 12 minutes/day 5 days/week 69 exposures	Guinea pigs, lung irritation
	1,000 ppm, 72 minutes/day 5 days/week 69 exposures	Guinea pigs, lung irritation
Horiguchi and Horiuchi [74]	1,000 ppm, 2 hours/day 9 exposures on alternate days	Mice, lung congestion
Prendergast et al [85]	370 ppm, continuously for 90 days	Several species, nonspecific inflammation changes
MacEwan and Vernot [88]	250 ppm, continuously for 90 days	Rats, chronic respiration disease
Prendergast et al [85]	135 ppm, continuous for 90 days	Several species, varying degrees of lung congestion and pneumonitis
Tsapko and Rappoport [77]	73 ppm, 4 hours/day 50 or 120 days	Rats, emphysematous changes; swelling of bronchial membranes; hyperplastic peribronchial lymphatic nodules

TABLE XII-10

INHALATION EXPOSURES AND LIVER AND KIDNEY EFFECTS IN ANIMALS

Reference	Exposure	Species and Effects
Adams et al [73]	18,000 ppm, 2 hours	Rats, increased kidney weights
	12,000 ppm, 7 hours	Rats, increased liver weights, fatty liver changes, congestion and hemorrhagic necrosis; increased kidney weights
	8,000 ppm, 7 hours	Rats, fatty changes in liver
Torkelson et al [36]	10,000 ppm, 1 hour/day 5 days/week/70 times	Rats, increased liver weights and fatty changes
	0.5, 0.2, 0.05 hours/day 5 days/week/70 times	Rats, liver weights not increased
Adams et al [73]	3,000 ppm, 7 hours/day 5 days/week 20 exposures	Guinea pigs, fatty degeneration of the liver; no kidney or liver effects in rats or monkeys
	1,500 ppm, 7 hours/day 5 days/week for 2 mo	Rats and monkeys, no kidney or liver no effects
	650 ppm, 7 hours/day 5 days/week for 3 months	Guinea pigs, no kidney or liver effects
Pendergrast et al [85]	2,200 ppm, 8 hours/day 5 days/week for 6 weeks	Rats, guinea pigs, rabbits, dogs, monkeys, no evidence of kidney or liver injury
Torkelson et al [36]	2,000 ppm, 12 minutes/ day, 5 days/week 69 exposures	Guinea pigs, increased liver weights with fatty changes
	2,000 and 1,000 ppm < 0.2 hours/day 69 exposures	Guinea pigs, liver weights not increased

TABLE XII-10 (CONTINUED)

INHALATION EXPOSURES AND LIVER AND KIDNEY EFFECTS IN ANIMALS

Reference	Exposure	Species and Effects
Torkelson et al [36] (continued)	500 ppm, 7 hours/day 5 days/week, 126-130 exposures	Rats, guinea pigs, rabbits, and monkeys, no liver or kidney effects
Horiguchi and Horiuchi [74]	1,000 ppm, 2 hours/day 9 exposures on alternate days	Mice, liver congestion, inflammation around biliary ducts
MacEwen and Vernot [88]	1,000 ppm, continuously for 90 days	Mice, increased liver weights; increased liver triglycerides; focal hepatocyte necrosis; acute inflammatory infiltrate and hypertrophy of Kupffer cells Rats, increased liver weights; vesiculation of the endoplasmic reticulum of hepatocytes with loss of polyribosomes; increased smooth endoplasmic reticulum Monkeys and dogs, no lesions observed.

TABLE XII-10 (CONTINUED)

INHALATION EXPOSURES AND LIVER AND KIDNEY EFFECTS IN ANIMALS

Reference	Exposure	Species and Effects
MacEwen and Vernot [88] continued	250 ppm, continuously for 100 days	Rats, above changes mild to minimal; mice, no change in liver weight nor in triglycerides; monkeys and dogs, no lesions observed
Prendergrast et al [85]	135 ppm, continuously for 90 days	Rats, guinea pigs, rabbits, dogs, monkeys, no evidence of liver or kidney injury
McNutt et al [41]	1000 ppm, continuously for 14 weeks	Mice, significant changes in centrilobular hepatocytes; moderate triglyceride accumulation; necrosis of hepatocytes
	250 ppm, continuously for 14 weeks	Mice, mild to minimal cytoplasmic alterations of centrilobular hepatocytes
Tsapko and Rappoport [77]	73 ppm, 4 hours/day 50 days	Rats, venous hyperemia and swelling of individual groups of cells
	120 days	Rats, above findings exaggerated; protein dystrophy of the liver parenchymal cells

TABLE XII-11

COMPARISON OF THREE ANALYTICAL METHODS FOR DETERMINING 1,1,1-TRICHLOROETHANE CONCENTRATIONS

Sampling time, minutes	1,1,1-Trichloroethane, ppm		
	Colorimetry	Gas chromatography	Detector tube
Exp. 1 0	117.5	(90.0)*	175
15	137.5	-	220
30	227.5	140.6	220
45	222.5	-	350
60	192.5	236.3	220
75	165.0	-	280
90	210.0	236.3	250
105	237.5	-	340
120	247.5	162.9	-
Average	195.2	194.0	256.9
Exp. 2 0	277.5	(187.6)*	300
15	297.5	-	500
30	297.5	258.3	350
45	415.0	-	550
60	387.5	302.2	420
75	-	-	300
90	500.0	374.7	650
105	362.5	-	580
120	471.9	320.1	-
Average	376.2	313.8	456.2

TABLE XII-11 (CONTINUED)

COMPARISON OF THREE ANALYTICAL METHODS
FOR DETERMINING 1,1,1-TRICHLOROETHANE
CONCENTRATIONS

Sampling time, minutes	1,1,1-Trichloroethane, ppm		
	Colorimetry	Gas chromatography	Detector tube
Exp. 3 0	485.0	(339.0)*	650
15	445.0	-	580
30	695.0	551.2	650
45	605.0	-	620
60	520.0	495.0	620
75	542.5	-	550
90	662.5	601.1	600
105	605.0	-	790
120	465.0	545.0	-
Average	558.3	548.0	632.5
Exp. 4 0	760.0	(372.3)*	780
15	792.5	-	810
30	830.0	538.7	760
45	870.0	-	730
60	830.0	603.8	800
75	870.0	-	810
90	792.5	619.8	720
105	870.0	-	750
120	870.0	603.8	-
Average	831.6	591.4	770.0

* Numbers in parenthesis are not used in the calculation of the mean
Adapted from Fukabori [55]

TABLE XII-12

1,1,1-TRICHLOROETHANE EXPOSURE CONCENTRATIONS

Type of Operation and Reference	Environmental Level (ppm)	Toxic Effects Reported	Basis for Medical Evaluation	Total No. of Subjects	No. of Subjects Reporting Symptoms
Solvent Testing [146]	407*	Headaches	Medical Interview	12	"some"
Painting [141]	350	Dermatitis**	Medical interview, review of medical records	25	3
Grinding degreasing [146]	350	(Headache, cough, dizziness)**	Medical interview	12	2
Hose braiding [142]	17.5-179	(Respiratory, eye, and neural symptomatology, urticaria)**	Medical interview	19	19
Degreasing [143]	12-118	Dry nose	Physical examination (eye, ear, nose and throat) and medical interview	250	1
Visi-trol [141]	5.5-77	Dermatitis**	Medical interview	25	3

TABLE XII-12 (CONTINUED)

1,1,1-TRICHLOROETHANE EXPOSURE CONCENTRATIONS

Type of Operation and Reference	Environmental Level (ppm)	Toxic Effects Reported	Basis for Medical Evaluation	Total No. of Subjects Interviewed	No. of Subjects Reporting Symptoms
Grease spraying, paint repair [144]	39	No adverse effects	None	40	0
Gasket machine operations [145]	1-31	No adverse effects	Medical interview, urine hippuric acid determinations	13	0
Injection molding [144]	<1	No adverse effects	Medical interview	8	0

* Exposure for several hours daily, not a TWA

** Not attributed to 1,1,1-trichloroethane by author of report

Adapted from NIOSH Health Hazard Evaluation Reports [141-146]

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