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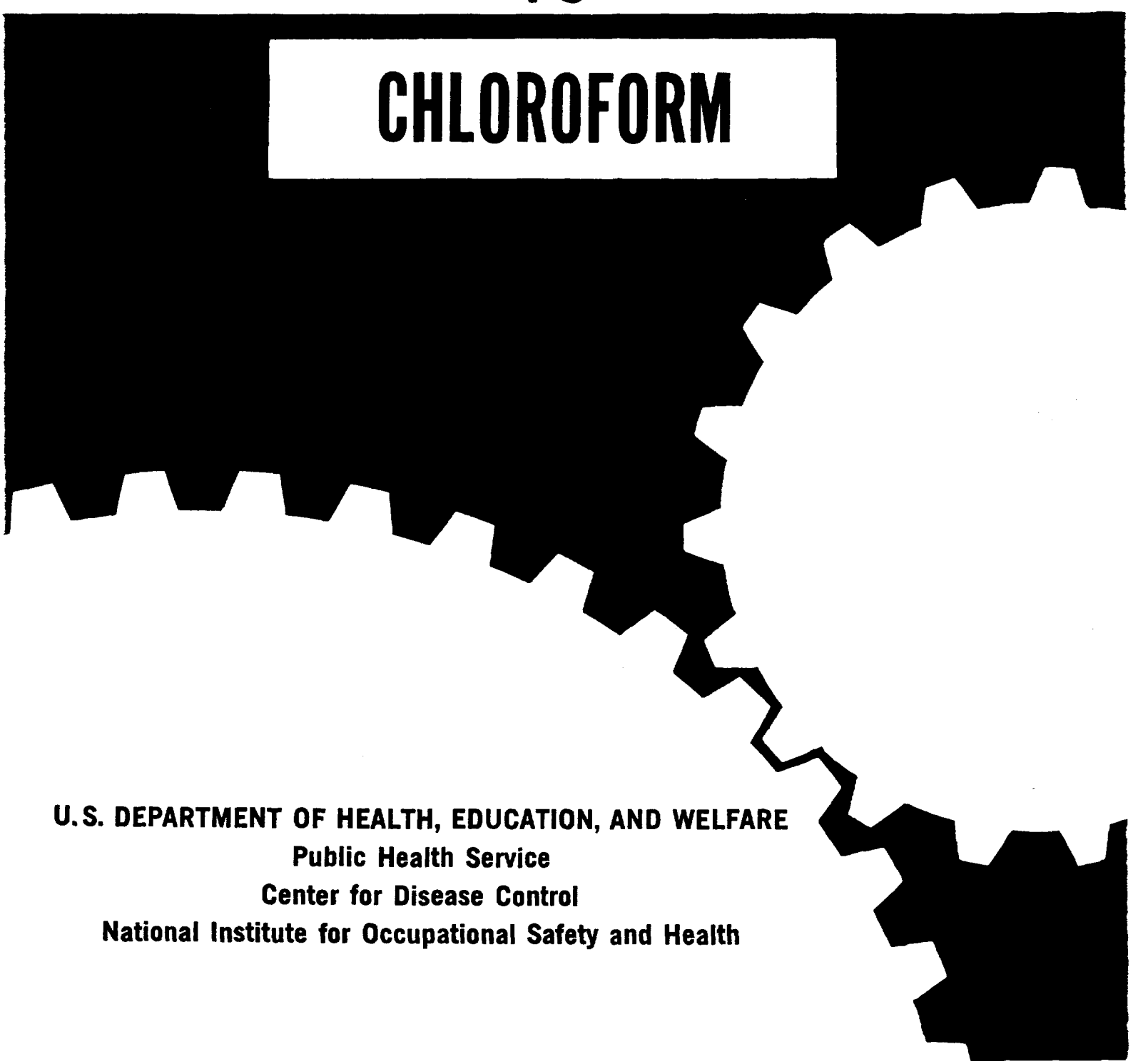
OCCUPATIONAL EXPOSURE TO CHLOROFORM



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 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 chloroform by members of my staff and the valuable constructive comments by the Review Consultants on Chloroform, by the ad hoc committee of the American Conference of Governmental Industrial Hygienists, by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, and by Edwin C. Hyatt, NIOSH consultant on respiratory protection. The NIOSH recommendations for standards are not necessarily a consensus of all the

consultants and the professional society that reviewed this criteria document on chloroform. Lists of the NIOSH Review Committee members and of the Review Consultants appear on the following pages.

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The Office of Research and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and recommended standard for chloroform. Agatha Corporation developed the basic information for consideration by NIOSH staff and consultants under contract No HSM-99-73-20. Keith H. Jacobson, Ph.D., had program responsibility and Stanley C. Mazaleski, Ph.D., served as criteria manager.

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CRITERIA DOCUMENT: RECOMMENDATIONS FOR AN OCCUPATIONAL EXPOSURE STANDARD TO CHLOROFORM

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I. RECOMMENDATIONS FOR A CHLOROFORM STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that worker exposure to chloroform ($CHCl_3$) 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 day, 40-hour week over a working lifetime; compliance with the standard should therefore prevent adverse effects of chloroform 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.

"Exposure to chloroform" is defined as exposure above half the time-weighted average (TWA) environmental limit. Exposures at lower environmental concentrations will not require adherence to the following sections, except for Sections 4 (b) and (c) and Section 6 (d).

Section 1 - Environmental (Workplace Air)

(a) Concentration

Occupational exposure shall be controlled so that no worker will be exposed to chloroform in excess of 10 ppm (48.9 mg/cu m) determined as a time-weighted average exposure for up to a 10-hour workday, 40-hour workweek, or for any 10-minute period to more than 50 ppm (244 mg/cu m).

(b) Sampling and Analysis

The procedure for sampling and analysis of workroom air for compliance with the standard shall be as provided in Appendix I, or by any method shown to be equivalent or better in precision, sensitivity, accuracy, and specificity.

Section 2 - Medical

(a) Comprehensive preplacement medical examinations shall be made available to all workers subject to "exposure to chloroform" and yearly thereafter, unless a different frequency is indicated by professional medical judgment.

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

(1) A comprehensive or interim medical and work history giving special attention to gastrointestinal symptoms and mental status. The worker's alcohol consumption should be reviewed.

(2) A comprehensive medical examination, giving particular attention to cardiac rhythm, liver and kidney function. Liver function tests and urinalysis shall be performed.

(3) An evaluation of the advisability of the worker's using negative- or positive-pressure respirators.

(4) Proper medical management shall be provided for workers adversely affected by chloroform.

(c) The medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employee or

former employee, and of the employer shall have access to all medical records.

(d) Medical records shall be maintained for persons employed one or more years in work involving exposure to chloroform. All medical records with pertinent supporting documents shall be maintained at least 5 years after the individual's employment is terminated.

Section 3 - Labeling (Posting)

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

CHLOROFORM

DANGER: INHALATION MAY BE

HAZARDOUS TO HEALTH.

Keep containers closed when not in use.

Use only with adequate ventilation.

Avoid breathing vapor.

Avoid contact with skin.

May generate toxic phosgene gas on contact

with flame or very hot metal surface.

This warning sign shall be printed both in English and in the predominant language of non-English-speaking workers, if any, unless they are

otherwise trained and informed of the hazardous conditions. All illiterate workers shall receive such training.

If exposures to chloroform in the workroom exceed the recommended standard, and a variance permitting the use of respiratory controls has been granted, the following shall be added to the sign: No worker allowed to enter area without proper respiratory protection.

Section 4 - Personal Protective Equipment and Clothing

When the limit of exposure to chloroform prescribed in subsection (a) of Section 1 cannot be met through application of available engineering controls in the design of equipment, systems, or operating procedures, an employer must utilize, as provided in subsection (a) of this Section, a program of respiratory protection to effect the required protection of every worker exposed.

(a) Respiratory Protection

Appropriate respirators shall be provided and used when a variance has been granted to allow respirators as a means of control of exposure to routine operations and while the application is pending. Administrative controls can be used to reduce exposure. Respirators shall also be provided and used for nonroutine operations (occasional brief exposures above the standard and for emergencies); however, for these instances a variance is not required but the requirements set forth below continue to apply. Appropriate respirators as described in Table I-1 shall only be used pursuant to the following requirements:

(1) For the purpose of determining the type of respirator to be used, the employer shall measure the atmospheric concentration of

chloroform in the workplace when the initial application for variance is made and thereafter whenever process, worksite, climate, or control changes occur which are likely to increase the chloroform concentration. This requirement shall not apply when only atmosphere-supplying positive pressure respirators are used.

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

(3) A respiratory protective program meeting the general requirements outlined in Section 3.5 of American National Standard Practices for Respiratory Protection Z88.2-1969 shall be established and enforced by the employer. In addition, Sections 3.6 (Program Administration), 3.7 (Medical Limitations), and 3.8 (Approval) shall be adopted and enforced.

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

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

(6) Respirators specified for use in higher concentrations of chloroform are permitted in atmospheres of lower concentrations.

(7) Chemical cartridges and canisters shall not be used for periods of time in excess of those indicated in Table I-1.

(8) Employees shall be given instruction on the use of respirators assigned to them, cleaning of the respirators, and how to test for leakage.

(9) Wherever bulk chloroform is handled, emergency and escape-type respirators shall be made readily available for each worker. Continuous contact must be maintained with employees working in enclosed spaces where chloroform concentration may become excessive.

(b) Protective Clothing

In any operation where the worker may come into direct contact with liquid chloroform, protective clothing shall be worn. The clothing must be both impervious and resistant (such as neoprene or polyvinyl chloride) to chloroform. Bib-type aprons should be at least knee length, gloves should be lined to absorb perspiration, and boots or overshoes shall be provided when necessary. Impervious supplied air hoods or suits should be worn when entering areas with limited egress such as pits or tanks. All protective clothing should be well aired and inspected for physical defects prior to reuse.

TABLE I-1

REQUIREMENTS FOR RESPIRATOR USAGE

Concentrations of Chloroform	Respirator Type
Less than or equal to 100 ppm	1) Chemical cartridge respirator with replaceable organic vapor cartridge with half or full facepiece. Maximum service life of 3 hours. 2) Full face gas mask, chin type, with organic vapor canister. Maximum life of 4 hours. 3) Type C supplied air respirator, demand type (negative pressure), with half mask facepiece.
Less than or equal to 1000 ppm	1) Full face gas mask, chest or back mounted type, with industrial size organic vapor canister. Maximum service life of 2 hours. 2) Type C supplied air respirator, demand type (negative pressure), with full facepiece.
Less than or equal to 2000 ppm	1) Type C supplied air respirator, continuous flow or pressure-demand type (positive pressure) with full facepiece, hood or helmet.
Greater than 2000 ppm	1) Self-contained breathing apparatus with positive pressure in full facepiece. 2) Combination supplied air respirator pressure-demand type, with auxiliary self-contained air supply.
Emergency (no concentration limit)	1) Self-contained breathing apparatus with positive pressure in facepiece. 2) Combination supplied air respirator, pressure-demand type, with auxiliary self-contained air supply.
Evacuation or Escape (no concentration limit)	1) Self-contained breathing apparatus in demand or pressure-demand mode (negative or positive pressure). 2) Full-face gas mask, front or back mount type with industrial size organic vapor canister. 3) Mouthpiece respirator with escape type organic vapor canister (escape type gas mask).

(c) Eye Protection

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

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

Section 5 - Informing Employees of Hazards from Chloroform

At the beginning of employment in a chloroform area, each employee shall be informed of the hazards, relevant symptoms, effects of overexposure to and the proper conditions and precautions concerning safe use and handling of chloroform.

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

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.

Information on file and readily accessible to workers shall include that specified in Appendix II, on US Department of Labor Form OSHA-20 "Material Safety Data Sheet", or a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Handling and Storage

(1) Where employees are required to enter confined areas where containers of chloroform are stored, such as a delivery van, entry shall not be made until the space has been ventilated or checked for concentrations of chloroform.

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

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

(b) Contaminant Controls

Suitable engineering controls designed to limit exposure to chloroform to that prescribed in subsection (a) of Section 1 shall be utilized where appropriate and feasible. Where ventilation systems are used to achieve such control, they shall be designed to prevent the accumulation or recirculation of chloroform in the workroom and to effectively remove chloroform from the breathing zones of workers. Ventilation systems shall be subjected to regular preventive maintenance and cleaning to ensure maximum effectiveness, which shall be verified by periodic airflow measurements. In addition, necessary measures shall be taken to ensure that discharge outdoors will be in conformance with all appropriate environmental regulations.

(c) Equipment Maintenance and Emergency Procedures

Air saturated with chloroform is immediately dangerous to life and if a limited egress situation exists, emergency procedures must be established and followed.

(1) Chloroform hazard areas

Exits shall be plainly marked. Emergency exit doors shall be conveniently located and shall open to areas which will remain free of contamination in an emergency.

(2) Confined spaces

(A) Entry into confined spaces or in other situations of 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, etc, which have contained chloroform, shall be thoroughly ventilated, tested for chloroform, and inspected prior to entry.

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

(D) Confined spaces shall be ventilated or otherwise maintained to keep the chloroform concentration below the limit and to prevent oxygen deficiency.

(E) Personnel entering confined spaces shall be equipped with a lifeline tended by another worker outside the space who shall be equipped with approved respiratory, eye, and skin protection.

(F) Written operating instructions and emergency medical procedures shall be formulated and posted in conspicuous locations where accidental exposure to anesthetic concentrations of chloroform may occur. These instructions and procedures shall be printed both in English

and in the predominant language of non-English-speaking workers, if any, unless they are otherwise trained and informed of the hazardous areas. All illiterate workers shall receive such training.

(d) Showers and Eye Wash Fountains

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

Section 7 - Monitoring and Recordkeeping

Workroom areas where it has been determined, on the basis of a professional industrial hygiene survey or the judgment of a compliance officer, that the environmental concentrations do not result in TWA workday exposures above half the TWA environmental limit shall not be considered to have chloroform exposure. Records of these surveys, including the basis for concluding that the exposures are at or below half the limit, shall be maintained until a new survey is conducted. Surveys shall be repeated when any process change indicates a need for reevaluation or at the discretion of the compliance officer. Requirements set forth below apply to areas in which there is chloroform exposure.

Employers shall maintain records of environmental exposures to chloroform based upon the following sampling and recording schedules:

(a) In all monitoring, samples representative of the exposure in the breathing zone of employees shall be collected. An adequate number of samples shall be collected to permit construction of a TWA exposure for workers in each operation or process. The minimum number of representative TWA exposure determinations for an operation or process shall be based on the number of workers exposed as provided in Table I-2 or as otherwise indicated by a professional industrial hygiene survey.

(b) The first environmental sampling shall be completed within 6 months of the promulgation of a standard incorporating these recommendations.

(c) Environmental samples shall be taken as soon as feasible but at least within 30 days after installation of a new process or process changes likely to cause an increase in environmental concentrations.

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

(e) Where exposure levels are found to be greater than those prescribed in Section 1 (a), suitable control measures shall be initiated. Once controls are implemented, sampling should be resumed until it is established that the controls are effective.

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

TABLE I-2

SAMPLING SCHEDULE

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

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing occupational diseases arising from exposure to chloroform ($CHCl_3$). The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "... develop criteria dealing with toxic materials and harmful physical agents and substances which will describe ... exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

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

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

These criteria were developed to assure that the standard based thereon would (1) protect against development of acute and chronic effects from chloroform, (2) be measurable by techniques that are valid, reproducible, and available to industry and governmental agencies, and (3) be attainable with existing technology.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Chloroform ($CHCl_3$) is a nonflammable, clear, colorless, volatile liquid at ordinary temperature and pressure. It has a pleasant ether-like, nonirritating odor. [1] The more important physical properties are presented in Table X-1. [1-4]

Chloroform was originally made from acetone and bleaching powder and can also be made by reduction of carbon tetrachloride. The principal method of manufacture is now chlorination of methane. [1]

Prior to World War II, chloroform was used primarily as an anesthetic and a pharmaceutical. The annual production of chloroform in the United States at that time was between 2,000,000 and 3,000,000 lbs. It is now seldom used as an anesthetic, [1] but it is used by many manufacturers for pharmaceutical purposes. [5,6] The production of chloroform for the manufacture of chlorodifluoromethane has grown over the years from 40,396,000 lbs in 1955 to 230,766,000 lbs in 1971, the latest year for which data are available. [7-23]

In 1971, chloroform was manufactured by 6 chemical companies in the United States. Two of these companies and 3 others used chloroform in the manufacture of chlorodifluoromethane. [23]

NIOSH estimates that 80,000 people are potentially exposed to chloroform in their working environment.

Historical Reports

Simpson, [24] a surgeon and obstetrician in Edinburgh, reported in an 1847 issue of Lancet on the merits of chloroform as an anesthetic agent. He advocated its use because it was pleasant to inhale, its action was more rapid and complete than that of ether, only a small amount was needed to produce narcosis, and it did not require the use of a special inhaler or instrument for its administration. He especially recommended it for use in obstetric practice because it alleviated maternal pain and recovery from anesthesia was rapid.

In 1874, Witte [25] observed that it required less chloroform to anesthetize frogs by absorption through the skin of the abdomen or thigh than by inhalation. He reported that rabbits also could be anesthetized by application of chloroform to the shaved abdomen, and he recommended that humans be anesthetized by absorption through the skin rather than by inhalation.

One of the first detailed descriptions of death from liver damage following chloroform anesthesia published in the English literature appeared in the January 26, 1894 issue of Lancet. [26] A 4-year old boy seemed to be well after an operation which lasted about 1 hour, but early the next morning he began to vomit, his pulse became weak, breathing was shallow and irregular, and he lapsed into unconsciousness. Vomiting continued (the vomitus being dark brown in color), little urine was passed, consciousness was never regained, and death occurred 30 hours after the operation. At autopsy, the liver was found to be small (14 1/2 oz), pale buff color, studded with minute purple dots, and greasy to the touch.

Microscopy revealed intense fatty infiltration with no apparent fatty degeneration.

In 1898, Desgrez and Nicloux [27] reported that carbon monoxide was formed in dogs during chloroform anesthesia. They considered that the amount of carbon monoxide in the blood after 3-5 hours of anesthesia was equivalent to that present after exposure for 30 minutes to 100 ppm of carbon monoxide in air. Carbon monoxide was measured by a "grisoumeter" and chloroform did not interfere with the analytical method.

In 1904 Schwenkenbecher [28] reported that immersion of white mice up to their necks in aqueous solutions of chloroform was lethal. The solutions ranged from 0.3%-0.7% and the immersion time from 45-165 minutes. A special collar was used to preclude inhalation, and the genital and anal openings were closed.

Moore and Roaf [29] in 1906 reported that chloroform added to hemoglobin solutions at body temperature caused a change in color and a precipitation of the hemoglobin.

In 1909, Whipple and Sperry [30] published studies of liver necrosis in dogs following anesthesia with chloroform. They compared the liver damage observed in dogs to that seen in a 19-year old woman who died 3 days after anesthesia with chloroform for 35 minutes. They concluded that in dogs chloroform anesthesia for 1-2 hours would invariably cause central liver necrosis, and that the anatomic changes in the human autopsy were identical to those observed in the experimental dogs.

Lehmann [31] was the first to mention the industrial hygiene aspects of chloroform. He stated that in Germany more than 100 tons of chloroform

was produced annually and that its manufacture in well designed factories did not create any danger to workers.

Lewin [32] in 1920 reported that the use of chloroform as a solvent for fats and resins was associated with a feeling of being "stoned", headache, dizziness, breaking of the voice, sometimes an increase in saliva flow, bronchial catarrh, pounding of the heart, and with continued exposures, disturbances of metabolism, leading to a "real change in substance in the kidney and even to albumin in the urine."

Effects on Humans

(a) Central Nervous System Effects

The most outstanding effect of chloroform on the central nervous system is narcosis. Because of this property, chloroform was extensively used as an anesthetic. Featherstone [33] concluded from a review of the literature that 20,000 ppm of chloroform was usually used to produce anesthesia and that 40,000 ppm, if continued for several minutes, could be an overdose. He suggested, for induction of anesthesia, gradually increasing the concentration of chloroform during the first 2 or 3 minutes to attain and maintain a concentration of 25,000 or 30,000 ppm until full anesthesia developed. The concentration used to produce anesthesia is usually not maintained for the duration of the operation but is replaced by a lower maintenance concentration such that the integrated exposure was actually much lower than 20,000 ppm.

In the experiments reported by Lehmann and Hasegawa [34] in 1910, dizziness and light intoxication were experienced during 20-minute exposures to chloroform concentrations of 4,300-5,100 ppm (20.8-25 mg/liter)

(Table X-2). During exposure for 15 minutes to 7,200 ppm (35.3 mg/liter) (Table X-3), these effects became so pronounced that experimental exposure of humans to more concentrated chloroform atmospheres was deemed unsafe.

Lehmann and Schmidt-Kehl [35] reported human exposures to 10 concentrations of chloroform, all lower than those used by Lehmann and Hasegawa. [34] On 6 separate days they set up fans in a 10 x 10 x 10 meter "waterproof" room to evenly distribute chloroform spray from a dispersing apparatus with an oxygen bulb attached. The chloroform concentrations were determined by alkaline hydrolysis. [35] Other than odor there were no responses until a concentration of 920 ppm was achieved; exposure at this level for 7 minutes and at all higher levels up to 3,000 ppm caused symptoms of central nervous depression. Other symptoms including "headache and heart pounding" were observed at the highest levels.

Heilbrunn et al [36] tabulated 31 cases of "chronic chloroform poisoning" from the literature and recounted one case of a 33-year old male who habitually had inhaled chloroform for 12 years. The psychiatric and neurologic symptoms reported in this latter case were depression, loss of appetite, hallucinations, ataxia, and dysarthria.

Other symptoms from habitual use of chloroform such as moodiness, mental and physical sluggishness, nausea, rheumatic pain, and delirium are presented in Table X-4. These effects were reported from nonoccupational exposures. [36-40]

Three days after a 19-year old patient ingested an unknown amount of chloroform, Storms [41] noted cerebellar damage characterized by an instability of gait and a slight tremor on finger-to-nose testing. These signs disappeared in 2 weeks.

Fokina [42] reported effects of chronic exposure in the work environment to mixtures of chlorinated methanes, including chloroform. Although the concentrations were not given, it was stated that the maximum permissible concentrations of individual components were exceeded at times. (There was no MAC for chloroform in Russia in 1965. [43]) The majority of workers showed signs of autonomic dysfunction, including diminution or disappearance of the corneal reflexes, dissociation between the deep (exaggerated) and superficial (sluggish) reflexes, marked persistent dermographism, general hyperhydrosis, acrohyperhydrosis, blotchiness of the skin of the hand and forearms, tenderness when pressure was applied to specific cervical points, and arterial hypotension. Autonomic dysfunction was mainly found in workers employed for less than 3 years. Workers employed for more than 5 years showed diencephalic disturbances and autonomic polyneuritis. [42]

(b) Hepatotoxic Effects

Toxic effects of chloroform on the liver have been studied most often in conjunction with its use as an anesthetic, or in a few cases where a person either accidentally or intentionally ingested chloroform. Liver damage has been evaluated by liver function tests, and by macroscopic and microscopic observations.

Cullen et al [44] studied prothrombin in 6 patients before and after light to moderate chloroform anesthesia of 60-90 minutes' duration. Concentrations of chloroform in the blood were found to be 15-18 mg%. Prothrombin, determined by a 2-stage titration technique, was normal in all cases prior to operation and decreased in all cases following operation, by

an average of 18% with a range of 11-40%. Icteric indices were markedly elevated in 2 of the patients.

Elevated serum transaminase activity and prothrombin time were observed by Storms [41] in a 19-year old patient who had accidentally ingested an unknown amount of chloroform. The patient was comatose and cyanotic, breathing was labored, diastolic pressure reduced, pulse was 108, and there were decreased deep tendon reflexes. Liver function tests performed over a period of several days following ingestion are summarized in Table X-5. The values of all tests were normal 8 weeks after ingestion.

Delayed chloroform poisoning often occurred in obstetrical cases, [45-48] and many authors have described instances of this occurring after delivery. This delayed chloroform poisoning is usually characterized by a latent period of a few hours to a day before symptoms develop; then drowsiness, restlessness, jaundice, and vomiting may occur, followed by fever, elevated pulse rate, liver enlargement, abdominal tenderness, delirium, coma, and abnormal findings in liver and kidney function tests. Death often ensues, usually from 3-10 days post partum. Autopsy reports generally describe the liver as having a bright yellowish color, and on microscopy, fatty infiltration with necrosis.

Examples of delayed chloroform poisoning following obstetrical anesthesia in which vomiting, jaundice, delirium, coma, and sometimes death occurring are presented in Table X-6. Results of urine and blood analyses of 2 cases are presented in Table X-7. Gibberd [45] studied 3 women given chloroform prior to delivery, who died from acute diffuse necrosis of the liver. Each had received prenatal care by a physician and had apparently been in normal health. Lunt [49] reported on 3 obstetrical exposures to

chloroform from which all patients recovered. Obstetrical exposures, such as reported by Gibberd [45] and Lunt, [49] were generally multiple in nature, with the first chloroform concentrations administered to reduce pain but not to produce deep narcosis. Inhalations of chloroform from capsules or bottles were given for relief of pain at various intervals during labor, often separated by several hours. Furthermore, chloroform was often used as the anesthetic agent during delivery. Obstetrical patients were exposed to chloroform intermittently over long periods of time.

Surgical exposures differ from obstetrical exposures in that in the former there is usually an initial, high concentration great enough to produce unconsciousness, [48,50-53] followed by maintenance levels for the duration of the operation, usually lasting for 1/2 hour-2 hours.

Whipple and Sperry [30] recorded a fatal case of chloroform poisoning following a minor surgical procedure lasting only 35 minutes. Vomiting began the night after the operation and cramps developed on the following day. Muscle tremors, jaundice, and restlessness also developed. Three days after the operation the patient became comatose, his pulse rate and temperature increased and he died. Autopsy showed advanced central necrosis of the liver and fatty degeneration of the kidneys and heart.

Liver damage has also been reported following ingestion of chloroform. [52,54] Schroeder [52] described an acute case in which a man ingested 4 oz of chloroform. When first observed, his pupils were dilated, he was cyanotic and perspired profusely. An electrocardiographic tracing obtained a few hours after admission showed only occasional extrasystoles and minimal S-T depression. On the following day, there was no abnormality

to be found in the tracing. He developed hepatomegaly with jaundice and vomiting. There were initial rises in serum bilirubin, alkaline phosphatase, and SGOT. Recovery began on the fifth day after ingestion.

Bomski et al [55] reported enlarged livers in 17 of 68 workers exposed to chloroform in concentrations ranging up to 205 ppm. In 3 of the 17 workers with enlargement of the liver, toxic hepatitis was diagnosed on the basis of elevated serum enzyme activities and elevated serum gamma globulin. In the remaining 14 cases of liver enlargement fatty liver was diagnosed, but not confirmed by liver biopsy.

(c) Renal Effects

Although the cause of death in most cases of chloroform poisoning has been attributed to necrosis of the liver, there has also been evidence at autopsy of renal damage, including albumin and red blood cells in urine, elevated blood urea, necrosis, and fatty degeneration. [30,45,49]

In the case of delayed chloroform poisoning reported by Whipple and Sperry, [30] urine specimens contained a trace of albumin, a few hyaline casts, and considerable quantities of leucine and tyrosine. At autopsy, the convoluted tubules of the kidneys showed a definite fatty degeneration with some of the epithelial cells having undergone necrosis. The capillaries were also found to be congested.

In the studies by Gibberd [45] and Lunt [49] laboratory findings indicated renal dysfunction; there were albumin, red blood cells, and pus in the urine, congestion of cortical vessels, fatty deposits, and necrosis.

(d) Cardiovascular Effects

Cardiac irregularities were found frequently by Kurtz et al [56] in 1936 during electrocardiographic (ECG) surveillance of 113 surgical

procedures. Arrhythmias were reported in all 6 cases in which chloroform was used for anesthesia and in 83 of 107 operations in which other anesthetics were used, including ethyl ether, cyclopropane, nitrous oxide, tribromoethanol, procaine, vinyl ether, and ethylene. The authors [56] did not report the durations of anesthesia.

In 1951, Orth et al [57] reported results of ECG surveillance during surgery on 52 patients given chloroform for anesthesia. Among the 52 patients, many developed more than one type of cardiac irregularity during anesthesia and 7 patients were symptom free. There were 4 instances of sinoauricular block, 11 of sinoauricular extrasystoles, 4 of auricular fibrillation, 22 of auriculoventricular block, 14 of auriculoventricular extrasystoles, 32 of auriculoventricular rhythm, 36 of ventricular extrasystoles, 6 of slow ventricular rhythm, 2 of bundle branch block, 20 of ventricular tachycardia, and 4 cases of cardiac arrest. The authors [57] stated that "this is a higher incidence of irregularities than is observed clinically with any other anesthetic agent except trichloroethylene". The irregularities were attributed to both reflex effects on cardiac automaticity and a direct depressant effect on the myocardium. In view of the high incidence of ECG abnormalities with all studied anesthetics, [56] the possibility of all other factors in the etiology of the abnormalities needs to be considered in drawing conclusions from this study. For example Orth et al [57] did not report the durations of anesthesia while Whitaker and Jones [58] considered this to be important.

Whitaker and Jones [58] in 1965 found less frequent cardiovascular effects among 1,502 cases where chloroform was administered by a precision vaporizer in concentrations not exceeding 22,500 ppm. There were 9 cases

of arrhythmia in the 1,164 operations in which anesthesia lasted 30 minutes or less and there were 10 cases of arrhythmia in 338 operations in which the duration of anesthesia was greater than 30 minutes.

(e) Hemolysis

Belfiore and Zimmerman [59] found that chloroform could affect the fragility of the red blood cell membrane without first being metabolized in the liver. Erythrocytes from 12 healthy adults were suspended in saline solution with chloroform ranging from 0.0125-0.10 mole/liter. The control was erythrocytes in a saline solution. At concentrations of 0.0125, 0.02, and 0.025 mole/liter there was no demonstrable effect. In concentrations of 0.05 mole/liter, erythrocyte leakage of hemoglobin, lactic dehydrogenase (LDH), and malic dehydrogenase began at 7 minutes and reached a maximum at 20 minutes for hemoglobin and at 10 minutes for the enzymes.

Belfiore and Zimmerman [59] found that incubation of cells with reduced glutathione (GSH) and oxidized glutathione (GSSG) inhibited hemolysis as measured by a loss of hemoglobin. They found that inhibition increased as the concentration of GSSG increased, but did not increase as the concentration of GSH increased. It has been suggested more recently, however, that it is only the GSSG that enters the intact red blood cell; the effect of GSH is due to its oxidation to GSSG. [60]

(f) Effects on the Skin

Malten et al [61] measured injury and regeneration of forearm skin exposed to liquid industrial solvents, including chloroform. The solvents were contained in glass cylinders 2 cm in diameter which were fixed to the skin by agar-agar for 15 minutes a day for 6 consecutive days. An unspecified number of sites served as controls. The rate of water evaporation

from these sites was determined daily to evaluate the degree of skin damage and regeneration. Exposure to chloroform was reported to be similar in effect to ethanol and to cause an increase in the rate of water evaporation with repeated exposures. Recovery of normal water retention, indicative of the formation of a new horny layer, occurred slowly during the 30 days after the last exposure.

Hoffman [62] suggested that chloroform could be used on skin to combat mosquitoes and other biting insects. It seems doubtful that present-day dermatologists would recommend this use of such an irritating substance. Hoffman cautioned against getting chloroform into eyes and mucous membranes because of irritating effects.

Oettel [63] carried out systematic experiments with chloroform administered to the skin by way of a small glass vessel, 1 cm in diameter, one end of which was open, with glass hooks fused into it. Vessels were filled with chloroform and tied onto the arms of 5 subjects. Pure chloroform was used for various exposure times. Three minutes after application of chloroform, there was a sensation of burning and stinging. When exposure time was increased to 6 minutes, the pain became more intense and then subsided quickly. When the chloroform was removed, the pain increased again, only to be replaced by a loss of feeling. Erythema was noted and the hyperemia which also occurred after 3 minutes of exposure was somewhat stronger, more cherry red with a light yellow undertone. In a 30-minute period after removal of the chloroform, there was a fading away of the erythema and hyperemia, and 5 hours later, little blisters formed at the edge of the area of application. Erythema and pigmentation disappeared 7 days after the exposure.

From these studies, [61-63] it can be concluded that exposure of the skin to liquid chloroform will cause irritation, erythema, hyperemia, and destruction of the epithelium. Much of this information on skin irritation from chloroform is based on prolonged contact. However, it should be noted that repeated, brief contact can cause skin defatting.

(g) Respiratory Absorption

Absorption of inhaled chloroform was studied by Lehmann and Hasegawa [34] in 1910. In a series of 3 experiments they computed the amount of chloroform absorbed as indicated by the difference between the concentrations in the inhaled and exhaled air. Each subject inhaled chloroform vapor through the mouth and exhaled air was collected in alcohol and subsequently analyzed for chloroform by hydrolysis with alkali. In the first experiment one subject inhaled 3 different concentrations of chloroform from a vessel containing a weighed amount of chloroform and the other inhaled 4 different concentrations. Each trial was performed at intervals of at least 3 hours. At exposure concentrations ranging from 2,700-6,500 ppm and exposure times of 3-10 minutes, the percent absorption ranged from 54-73.

In the second experiment 2 subjects each inhaled chloroform for 20 minutes on 3 separate days. The exposure concentrations were between 4,300 and 5,000 ppm (20.8 and 25 mg/liter). The percentages of chloroform absorbed which ranged between 49.4 and 77 are presented in Table X-2.

In the third experiment one subject inhaled chloroform on 2 different occasions. The percentages of chloroform absorbed which ranged from 73.8-80.7 are presented in Table X-3.

(h) Breath and Tissue Concentrations

Several investigators have measured the concentration of chloroform in exhaled air, blood, and other tissues, after inhalation or ingestion of chloroform. [34,41,44,50,64-66]

The concentrations of chloroform found in exhaled air by Lehmann and Hasegawa [34] after exposure were a function of the amount inhaled and the elapsed time after exposure (Table X-3).

In 1951, Morris [50] studied chloroform in exhaled air and peripheral venous blood of patients undergoing surgery. Exhaled breath samples from 11 patients maintained for various times in the third stage (surgical level) of chloroform anesthesia were collected in alcohol and evaluated by a modified Fujiwara reaction. The data are presented in Table X-8. The concentrations found were greater in plane 3 (deep surgical anesthesia) than in plane 1 or 2 (light or moderate surgical anesthesia) and they were greater at the beginning of anesthesia than at later times during anesthesia. Since chloroform is administered intermittently during surgery, the exhaled breath concentrations probably reflected time-weighted average exposure.

Peripheral venous blood was also collected from 58 patients when blood concentrations of chloroform necessary to maintain anesthesia were thought to have been achieved. Analysis was by ether extraction and a modified Fujiwara method. Chloroform concentrations of 2.0-23.2 mg % were found. Thirty to 50% of chloroform in the blood at the end of exposure was removed in the first 15 minutes following cessation of exposure. Thereafter, the rate of elimination decreased, and "small amounts" were reported to have been detected in the blood 8 hours after exposure.

Concentrations of chloroform in the blood were also measured by Cullen et al [44] in 1940 in 3 persons undergoing surgery. Two patients were anesthetized by the absorption technique, with the inhaled gas containing at least 50% oxygen. In one subject, 60 minutes after induction of anesthesia, chloroform was 16 mg %; in the other subject it was 18 mg % 70 minutes after induction of anesthesia. In the third patient, anesthesia was induced by the open drop technique and then maintained by pharyngeal insufflation. In this patient, at 75 minutes of anesthesia, 15 mg % chloroform was found in the blood.

Storms [41] reported a case in which a 19-year old boy accidentally ingested an unknown amount of chloroform and was found to have 20 mg % of chloroform in the blood 10 hours after the ingestion. This case is reported in more detail in the section on hepatotoxicity.

Breath concentrations of chloroform in a worker after an industrial exposure to a mixture of solvents including chloroform, carbon tetrachloride, trichloroethylene, and perchlorethylene were measured by Stewart et al [64] in 1965. The exposure was defined as a "few minutes" without a gas mask followed by an unspecified time with a general purpose chemical respirator, to unknown concentrations with "strong" odors. The exposed worker experienced dizziness, weakness, nausea, and finally unconsciousness. The duration of unconsciousness is not known, but "10 minutes later" he was coherent, though uncoordinated and nauseated. Thirty minutes after his collapse, infrared analysis of his expired breath contained: perchlorethylene, 11 ppm; carbon tetrachloride, 9.5 ppm; chloroform, 7 ppm; and trichloroethylene, 11 ppm. Three days later, 0.1

ppm chloroform was found in the exhaled breath; 12 days after exposure, there was no chloroform found in the exhaled breath.

Several authors have reported on the concentration of chloroform in tissues following suicide, homicide, or death during or after an operation. Gettler [65] measured brain concentrations of chloroform from 390-480 mg/kg in 4 cases of suicide by inhalation, 372-384 mg/kg in 3 cases of homicide by inhalation, and 70-182 mg/kg in 10 cases of death during or after surgery.

Gettler and Blume [66] used a modified Fujiwara method to estimate chloroform content of tissues following death during or after an operation, or by suicide or homicide. In 7 cases where death was reported to be due solely to excessive amounts of administered chloroform, concentrations in mg/kg tissue were: brain, 372-480; lungs, 355-485; and liver, 190-275. In 9 cases of death from shock, concentrations in mg/kg were: brain, 60-182 (most were between 120 and 182); lungs, 95-145; and liver, 65-88.

Epidemiologic Studies

There are very few reports of industrial workers exposed to chloroform. The studies of Challen et al [67] and Bomski et al [55] are the only studies that contain exposure concentration measurements, descriptions of symptoms and diagnoses, and comparisons with control groups.

In 1958, Challen et al [67] reported a study of a confectionery firm in England that manufactured medicinal lozenges. In 1950, the operators began to complain of the chloroform vapor given off during the production of the lozenges. A system of part-time work was initiated to alleviate

complaints of lassitude, flatulence, water brash (British term indicative of symptoms of dyspepsia), dry mouth, thirst, depression, irritability, and frequent and "scalding" micturition, but this was not successful, and finally the operators refused to work on that particular process. In 1954, a new team of operators was engaged and in 1955 a system of exhaust ventilation was installed, after which the work proceeded without interruption.

In order to confirm the effectiveness of the ventilation system, Challen and his associates [67] were asked to ascertain the concentrations of chloroform. Additionally, clinical investigations were performed and an attempt was made to simulate the original conditions in order to compare the chloroform concentrations before and after remedial measures were introduced. The original conditions were simulated by closing the doors and windows and shutting off the ventilation system.

A single air sample was taken continously in the breathing zone of the operator of the ingredient mixing process during a period of 20 minutes coinciding with the duration of the process. Sampling at the rate of 2 liters/min was done by drawing air through 2 U tubes containing dried silica gel. Additionally, at a point in the operation where a peak concentration was expected, a 6-liter "grab" sample was taken. Air samples of 30-minute durations each were also taken in the breathing zones of cutting room operators. The samples were taken during 2 periods of production for 3 different operations on the same day (under current conditions) and during 3 periods on another day (during the simulated conditions). The samples were analyzed by alkaline hydrolysis. Results in ppm of chloroform were as follows [67]:

Operation	Period 1	Period 2	Period 3
Mixing room during normal operation:			
Continuous sampling during mixing period	128	---	---
Grab sampling during emptying period	1,163	---	---
Cutting room during normal operating conditions:			
Feeding operation	71	57	---
Dusting operation	35	31	---
Removing trays	23	29	---
Cutting room during simulation of original conditions:			
Feeding operation	219	237	161
Dusting operation	110	158	155
Removing trays	77	92	---
General atmosphere at center of room	82	98	---

Clinical investigations of 3 different groups of workers were performed by Challen et al. [67] One group of 8 employees was termed the "long service operators". These were people who refused to continue in the lozenge department after they experienced the previously described symptoms. This group of workers, when exposed to chloroform vapor in probable concentrations ranging from 77 to 237 ppm, had been observed staggering about the work area. After terminating work in the lozenge department the "long service operators" reported experiencing nausea and stomach upset after even short exposures to the smell of chloroform.

A second group of 9 employees in this study, [67] termed the "short service operators", were the replacements of the "long service operators". Two of these 9 employees did not report unpleasant experiences from chloroform exposure. Among the other 7, 5 reported dryness of the mouth

and throat at work; 2 were subject to lassitude in the evening; 1 complained of lassitude and flatulence at work, and the experiences of 2 others were similar to those of the "long service operators". The "short service operators" worked in locations where the chloroform concentrations ranged from 23-71 ppm.

A third group of 5 employees in this study [67] who worked in other departments of the firm served as controls and exhibited no symptoms. Neither tests of liver function (thymol turbidity, thymol flocculation, direct van den Bergh, and serum bilirubin), clinical examinations, nor urinary urobilinogen showed significant differences among the 3 groups of workers.

In 1967, Bomski et al [55] reported on liver injury from chloroform among workers in a pharmaceutical factory in Poland. The study included the entire group of 294 workers who used chloroform in the course of production; of these, 68 were exposed to chloroform for 1-4 years and still had contact with chloroform, 39 had chloroform contact at one time, 23 had viral hepatitis with icterus 2-3 years earlier and were designated as posticterus controls and were working in a germ-free area, and 165 worked in a germ-free area with no history of viral hepatitis. Blood pressure, blood morphology, urinalysis, blood albumin, serum protein, thymol turbidity, zinc sulfate turbidity, the "Takata-Ara" sulfate (colorimetric) test, urobilinogen, SGOT, and SGPT were measured in all. A complete medical history was taken. Sixty of the people were hospitalized for determination of BSP clearance and urinary urobilinogen.

The air in the production room was sampled and chloroform concentrations were determined using the Grabowicz [68] method. The concentration

of chloroform ranged from 2-205 ppm. No other concentration measurements were reported nor was there any mention of the frequency of sampling.

The authors [55] compared the frequency of viral hepatitis and jaundice among a group of inhabitants of the city, 18 years and older, with that of the same 68 pharmaceutical workers who used chloroform. The results showed that in 1960, 0.35% of city inhabitants had viral hepatitis, while 16.67% of the chloroform exposed workers had viral hepatitis. In 1961, the frequency for city inhabitants was 0.22% and the frequency among the chloroform workers was 7.50%. In 1962 the frequency of viral hepatitis was 0.38% for city inhabitants and 4.4% for workers using chloroform. The authors suspected that the toxic liver changes occurring as a result of exposure to chloroform promoted a viral infection in such cases, but they did not give information on the incidence of viral hepatitis among other plant workers, which might have helped resolve questions about sanitary practices and facilities in the plant.

The majority of the workers who were in contact with chloroform during the investigation period covered in this study complained of headache, nausea, belching, and loss of appetite.

Among the 68 workers using chloroform, 10 cases of splenomegaly were found compared to none in the controls. They did not explain the splenomegaly but point out it was not present in controls.

The frequency of enlarged livers (17 out of 68) among workers exposed to chloroform exceeded the frequency of enlarged livers in the other groups (5 out of 39, and 2 out of 23). Livers were judged to be enlarged if they extended at least 1 cm beyond the rib arch in the midclavicular line. The upper margin was apparently not measured. In 3 of

the 17 chloroform workers with enlargement of the liver, toxic hepatitis was diagnosed on the basis of elevated serum enzyme activities and elevated serum gamma globulin. The measured amounts of these serum constituents in these 3 workers were not reported. In the remaining 14 cases of liver enlargement, fatty liver was diagnosed. It was claimed that the latter diagnoses were substantiated by a 79% reduction in the incidence of hepatomegaly in the people studied during a 12-month period when hygienic work conditions were improved as a consequence of the studies. [55]

In a continuing study [LD Pagnotto, written communication, December 1973] by the Department of Labor and Industries, Commonwealth of Massachusetts, worker exposure to chloroform, methylene chloride, and toluene in a plant manufacturing plastic film was investigated. The workers were exposed to levels of chloroform from 7-170 ppm, with a mean of 47 ppm.

Physical examinations and the following laboratory tests were performed regularly on all employees connected with the process: SGOT, LDH, alkaline phosphatase, blood bilirubin, BUN, creatinine, cholesterol, serum protein, urobilin, urobilinogen, urine bilirubin.

The blood tests were performed yearly and urine tests quarterly. The liver function tests have been done for more than 2 years, the kidney function tests for only 1 year. Some of the employees at times experienced what was termed "dry heaves". Laboratory findings have been normal so far, but there appeared to be a significant number of findings in the upper normal range, particularly for the blood bilirubin and BUN. There was no evidence, though, that there was a progressive increase in the values found. However, the evaluations of the laboratory findings were based on

the normal range for the general population rather than a specific control group for this particular investigation.

It is not apparent from this study what the time-weighted average exposures were.

Animal Toxicity

The majority of animal studies of chloroform toxicity have been conducted to provide supplementary information relevant to the clinical use of chloroform as an anesthetic. Consequently these animal studies include concentrations of chloroform many times greater than would be experienced in daily occupational situations except in the case of accidents. The following subsection contains a summation of some of these studies.

(a) Central Nervous System Effects

Chloroform has been reported to cause narcosis in a variety of experimental animals. [69-72] Fuhner [71] exposed 30 mice to vapor concentrations of chloroform ranging from 2,500-7,400 ppm (12-36 mg/liter). Each mouse was individually exposed in 10- to 11-liter bottles with the chloroform vaporized to the concentration desired. The method of ascertaining the concentration was not stated. The following effects were observed:

2,500-2,700 ppm (12-13 mg/liter) - some loss of reflexes, rarely narcosis, recovery in 2 hours

4,000 ppm (20 mg/liter) - narcosis in 1 hour and recovery

4,700-6,000 ppm (23-27 mg/liter) - narcosis in 3/4 hour, recovered, some died

6,800 ppm (33 mg/liter) - narcosis in 1/2 hours, death in most

7,400 ppm (36 mg/liter) - narcosis in 10 minutes

In 1936 Lehmann and Schmidt-Kehl [35] studied the acute effects of chloroform on cats. Fully grown cats weighing 2.5-3.5 kg were fasted before the experiment then exposed to concentrations ranging from 7,200-22,000 ppm (35-105 mg/liter). The concentrations of chloroform were determined by hydrolysis with alkali in alcohol. Upon exposure to chloroform, toppling, loss of righting ability, and loss of leg reflexes were observed. At 7,200 ppm (35 mg/liter) light narcosis was observed at 78 minutes and deep narcosis after 93 minutes. Exposure to 22,000 ppm (105 mg/liter) brought about light narcosis after 10 minutes and deep narcosis after 13 minutes. Depression of nervous and muscular activity was accompanied by irritation of the mucous membranes of the eyes, nose, and mouth.

Lehmann and Hasegawa [34] studied absorption of inhaled chloroform in rats exposed to concentrations of 4,100, 4,300, 11,000, and 16,400 ppm (20, 21, 54 and 80 mg/liter) for 4, 12, 10, and 10 hours, respectively. Concentrations of chloroform were determined by hydrolysis with alkali in alcohol. At a concentration of 4,000 ppm (20 mg/liter), 30.6% of the chloroform inhaled during the first 15 minutes was absorbed, 25.4% after

the first hour, and so forth, decreasing to a minimum of 4.8% after 4 hours. Concentrations of 11,000 and 16,400 ppm (54 and 80 mg/liter) similarly showed absorption decreasing with time of exposure. The initial absorption was never greater than 40%.

(b) Hepatotoxicity

Numerous studies have shown that chloroform causes fatty infiltration and necrosis of the liver. [30,73-77] None of these studies involved long-term inhalation exposures to low concentrations. However, these studies do show that the hepatotoxic effects of chloroform can occur as the result of ingestion, inhalation, or intravenous administration.

Whipple and Sperry [30] pointed out the similarity of microscopic changes in the livers of humans and experimental animals including fatty degeneration and centrilobular necrosis. They administered 1-2 oz of chloroform for 1-2 hours (implying inhalation) to dogs, often on successive days. In general, the animals recovered from the anesthesia and initially appeared to be quite well. However, vomiting began to occur (sometimes with blood) 1-4 days after exposure to chloroform and some of the animals developed diarrhea. Death then ensued. Autopsies revealed lesions of the liver, including central hyaline necrosis, acute yellow atrophy, and subcapsular hemorrhage. Less frequently the kidneys showed fatty degeneration of the convoluted tubules. Where death due to chloroform did not occur, liver repair was noted within 7-12 days.

Jones et al [74] in 1958 studied the relative hepatotoxicity of inhalation anesthetic drugs using chloroform as a standard of reference. Chloroform was given orally to 350 white mice, each weighing approximately 20 g. The mice were killed 72 hours after exposure and livers were fixed

in formalin. The authors [74] were able to estimate the following effects of acute injury from esophageal instillation of chloroform:

0.35 mg/g minimum narcotic dose (MND 50)

1.1 mg/g minimum lethal dose (MLD 50)

0.035 mg/g threshold hepatotoxic effect- minimal midzonal fatty changes

0.07 mg/g minimal central fatty change - fatty infiltration

0.14 mg/g moderate liver changes - massive fatty infiltration

0.35 mg/g severe liver changes - fatty infiltration, centrilobular necrosis

Kylin et al [78] in 1963 studied the hepatotoxic effects of inhalation exposure of 20 mice to chloroform for 4 hours. The experiments were performed on female albino mice, of a single strain, with a mean weight of 23 g. The mice were exposed to chloroform concentrations of 100, 200, 400, or 800 ppm for 4 hours in a chamber approximately 15 liters in volume. The mice were killed 1 or 3 days after exposure and tissues studied microscopically. Evaluation was limited to assessing the extent of necrosis and the degree of fat infiltration of the liver. Mice exposed to 100 ppm for 4 hours and killed 1 or 3 days later showed moderate infiltration of fat in the liver. Specifically, the liver underwent fatty degeneration involving a thin cell layer, usually in the periphery of the liver lobules, and up to 3 to 5 cell-widths in size. These alterations were seen more frequently in mice killed 1 day after exposure than in those sacrificed after 3 days. Exposure of mice to 200, 400, or 800 ppm caused increased liver alteration including some necrosis at 200 ppm, increasing in extent at 400 and 800

ppm. Associated with the microscopically demonstrable liver necrosis was the increase in activity of serum ornithine-carbamoyl transferase.

(c) Nephrotoxicity

Kidney involvement as a result of exposure to chloroform was reported as early as 1929 by Whipple and Sperry. [30] Dogs inhaling 1-2 oz chloroform during 1-2 hours often showed on successive days fatty degeneration of the convoluted tubules of the kidneys.

Plaa and Larson [79] in 1964 studied the nephrotoxic properties of chlorinated hydrocarbons in mice. In assessing kidney function, phenol-sulfonphthalein (PSP) excretion and urinary protein and urinary glucose were measured. The chlorinated hydrocarbons were dissolved in corn oil and the doses administered intraperitoneally in 10 ml corn oil/kg body weight. In mice treated with chloroform the effect on the kidney, as measured by decreases in PSP excretion 24 hours later, was dose-dependent. The presence of any glucose or 100 mg % of protein 24 hours after administration, or less than 40% PSP excretion in 2 hours, was considered significant and indicative of impaired renal function. The extent of kidney impairment, expressed in terms of the 3 function tests, increased with the dose of chloroform. The incidence of reduced PSP excretion in 2 hours decreased as the dose of chloroform decreased from 1 ml/kg-0.016 ml/kg. With a 0.5 ml/kg dose of chloroform, PSP excretion although initially reduced, returned to normal after 4 days. Tables X-9 and X-10 show the relationship of the 3 variables studied to the chloroform dosage.

Microscopic examination of kidney sections showed correlation between the percentage of mice in each group showing abnormal kidney function tests and the percentage showing necrosis of the proximal tubules.

The median effective dose of chloroform (ED50) for significant PSP excretion was 0.12 ml/kg and for increasing urinary protein and glucose, it was 0.07 ml/kg. [79]

Of all the chlorinated hydrocarbons tested, chloroform and 1,1,2-trichloroethane possessed the most marked nephrotoxic properties, causing proteinuria and glucosuria with nonlethal doses and a decrease of PSP excretion, and necrosis of the convoluted tubules in 100% of the animals at higher doses. [79]

(d) Chronic Ingestion Study

The study by Miklashevskii et al [80] exposed 18 male albino rats with an initial weight of 150-180 g, and 18 male guinea pigs with an initial weight of 220-250 g; they were divided into 3 groups of 6 animals of each species. Animals of the first group received a peroral chloroform dose of 0.4 mg/kg. In the second group, the guinea pigs received a dose of 35 mg/kg (1/50 LD50), while the albino rats received a dose of 125 mg/kg (1/50 LD50). The third group served as a control. No mention was made of the dosing schedule although the experiment ran for 5 months and daily administration was implied.

Rats and guinea pigs given the 0.4 mg/kg dose of chloroform showed no changes in conditioned reflexes or in autonomic or cardiac activity, blood protein ratios, catalase concentrations, or phagocytic capacity. There was an increase in ascorbic acid in the adrenals of the guinea pigs. [80]

Some guinea pigs given doses of 35 mg/kg died during the course of the experiment. Five of the guinea pigs lived longer than 2 months, but only 2 of these lived longer than 3 months. The ratio of blood protein

fractions in the guinea pigs given 35 mg/kg was altered by the end of the first month. These changes consisted of an increase in the globulin content (from 32.9±1.09 to 40.9±2.22%) involving the alpha and gamma fractions and a decrease in the albumin content, so that the albumin-globulin ratio decreased from 2.1-0.4. The change in this ratio was even more pronounced at the end of the second month. The guinea pigs in the 35 mg/kg groups also showed a decrease in blood catalase activity from 2.0±0.13-1.2±0.11 (no units given) in the second month of the experiment. [80]

The guinea pigs which had died from a dose of 35 mg/kg of chloroform had structural lesions of the liver, heart muscle, and stomach wall upon microscopic examination. Microscopic changes included fatty infiltration, necrosis and cirrhosis of the liver parenchyma, lipoid degeneration, proliferation of interstitial cells in the myocardium and acute edema of the submucosal and muscular layers of the stomach. [80]

The rats of the group that received doses of 125 mg/kg showed no significant changes in the conditioned reflexes after one month, but during the fourth and fifth month, ability to develop new conditioned reflexes was impaired.

Studies of the autonomic regulation of cardiac activity indicated a decrease in cholinergic activity. [80]

(e) Carcinogenicity

Eschenbrenner [81] in 1945 studied the effect of repeated oral doses of chloroform on induction of hepatomas in mice. This study followed the format of an additional study by the same author that showed induction of hepatomas by repeated feeding of carbon tetrachloride in olive oil solution, in amounts sufficient to produce liver necrosis. [82]

Accordingly, a graded series of necrotizing and nonnecrotizing doses of chloroform were administered. Three-month-old strain A mice which had an incidence of spontaneous hepatomas of less than 1% at 16 months were given intragastric doses of oil solutions of 5 μl/kg body weight. The chloroform content of the solutions varied so that the chloroform doses were respectively 1.6, 0.8, 0.4, 0.2, or 0.1 μl/kg.

The presence or absence of liver necrosis was determined by microscopic examination of liver sections taken 24 hours after a single dose of chloroform. The livers of animals receiving doses of 0.2 and 0.1 μl/kg of chloroform showed no necrosis. However, with these doses, necrotic areas were observed in the kidneys of males, but not of females. This sex difference of renal necrotic lesions was observed at all concentrations. No sex difference was observed for liver necrosis. Twenty-four hours after a single dose of 0.4 μl/kg or more of chloroform there was extensive necrosis of liver cells around the central veins. Thirty doses were given at 4-day intervals to test for any carcinogenic effect. (This was the schedule under which a hepatoma incidence of 100% was obtained when carbon tetrachloride was used.) Hepatomas were found only in animals that received necrotizing doses of chloroform and which were killed 1 month after the last dose. [81] These were seen only in female mice, which could reflect the greater sensitivity of males, ie the males might have died earlier, before onset of malignant changes. The authors inferred that necrosis was a prerequisite to tumor induction. The significance of this study on occupational exposures is not clear; more studies to clarify questions of carcinogenicity of chloroform need to be conducted.

(f) Teratogenicity

Schwetz et al [83] in 1973 evaluated the effects of repeated exposures to chloroform on rat embryo and fetal development. Pregnant Sprague-Dawley rats were exposed to 30, 100, or 300 ppm of chloroform for 7 hours a day on days 6 through 15 of gestation. Day 0 of pregnancy was considered to be the day on which sperm were seen in vaginal smears. Concentrations of chloroform in the exposure chambers were continuously monitored by combustion analysis. An infrared spectrophotometer with a multipath gas cell was used 3 times daily to analyze the chamber air and substantiate the concentration calculations.

The effect of chloroform on rats exposed to 300 ppm was confused by changes in dietary intake. It was not possible to determine whether decreased food consumption was the result of loss of appetite or the inability to eat due to narcosis. [83]

Exposure of pregnant rats to 100 ppm on days 6 through 15 of gestation revealed a significant incidence of fetal abnormalities as compared to controls. There were significant increased incidences of acaudia, imperforate anus, subcutaneous edema, missing ribs, and delayed skull ossification.

Rats exposed to 30 ppm showed significant incidences of delayed skull ossification and wavy ribs, but no other effects. [83]

The teratogenicity of oral doses of chloroform was studied in rats and rabbits. [84] There was no evidence of teratogenicity in either species at any dosage level tested. However, in both species reduced birth weights (7.5% in rats and 1.1% in rabbits) were observed with the highest dosages, 126 and 50 mg/kg, respectively.

(g) Metabolism and Mechanism of Action

In 1961, Butler [85] demonstrated that chloroform is found in the expired air from dogs receiving carbon tetrachloride and that this conversion can be reproduced by the incubation of carbon tetrachloride with tissue homogenates or with reduced glutathione or with cysteine. When chloroform was incubated for a day with homogenates of mouse liver, chromatograms revealed the presence of methylene chloride in concentrations of 30-90 μg/ml. However, no methylene chloride was found in the expired air of dogs receiving chloroform by inhalation.

Paul and Rubinstein, [86] in 1963, studied the metabolism by rats of carbon 14 labeled carbon tetrachloride and chloroform. With intraduodenal doses of 1 ml/kg, some carbon tetrachloride was converted to chloroform. There was no evidence that other chloromethanes were formed from either administered carbon tetrachloride or administered chloroform. Eighteen hours after dosing, 74% of the radioactivity from chloroform had appeared in the exhaled air as chloroform and 3.6% as carbon dioxide. More carbon dioxide was formed from chloroform than from carbon tetrachloride, both in vivo and in vitro, but never more than 5% of the administered chlorinated hydrocarbon was metabolized to carbon dioxide. Homogenation of the liver markedly diminished carbon dioxide production from both carbon tetrachloride and chloroform.

The mechanisms of the biochemical effects of chloroform on the liver were studied by Scholler [87] and Reynolds and Yee. [88] Scholler [87] tried to determine whether structural damage affecting protein synthesis occurs when chloroform acts on the liver of a rat. Twenty Sprague-Dawley rats were fasted for 10 hours and 4 were exposed to 1 vol % chloroform

(10,000 ppm) for a period of up to 5 hours in an anesthesia chamber. Preliminary examinations of all animals anesthetized showed a slight increase in respiratory acidosis but no signs of arterial hypoxemia or metabolic acidosis. After 4 1/2 hours of chloroform anesthesia, the livers of most exposed rats showed gross enlargement of the centrilobular hepatic cells. The cells also showed a striking paleness, and upon staining of frozen sections, fatty degeneration was also observed. On electron microscopy it was found that chloroform produced an early dilation of the granular endoplasmic reticulum with detachment of the ribosomes producing a marked reduction of centrilobular protein synthesis. Additionally, after anesthesia with chloroform, extensive necrosis of portions of the renal tubular epithelium was found, while the lung revealed severe leucocytic infiltrations in the alveolar septa. In light of this latter finding, it should be noted that in 1966 Wattenberg [89] stated that kidney and lung tissue also contain hydroxylating enzyme systems. This enzymatic activity is less intense than in the liver, but can be increased by some lipid-soluble compounds. Scholler [87] concluded that the toxic effect of chloroform on the liver, kidney, and lung as observed in animal experiments and in humans can be explained by the formation of toxic metabolites by hydroxylating enzyme systems in the cells of damaged organs.

Reynolds and Yee in 1967 [88] compared the patterns of incorporation of isotopic carbon from chloroform, carbon tetrachloride, methylene chloride, and methyl chloride into chemical constituents of liver organelles 2 hours after oral introduction of the chloromethanes. This investigation was based on the hypothesis that the hepatotoxicity of the compounds was related to the binding of reduction products of the chemical

components to the endoplasmic reticulum and to the formation of chloromethylated lipids and proteins. They used 2 indicators of early damage to the endoplasmic reticulum: 1) The ability to suppress glucose-6-phosphatase activity in the centrilobular portion of the liver in 1 hour; and 2) the ability to cause increases in cellular ribonucleic acid (RNA) content 2 hours after exposure. These indicators were compared with labeling of cellular constituents and with the ability of these agents to cause centrilobular necrosis 24 hours after exposure.

In the experiment, young male rats weighing between 100 and 300 g each were fed doses of either 830 or 2,600 μmoles of chloromethanes per 100 g of rat weight in an equal volume of mineral oil, by polyethylene stomach tube. Control animals received an equal volume of mineral oil. Animals were killed 1, 2, and 24 hours after dosing. Radioactive carbon incorporation from labeled chloroform, carbon tetrachloride, methylene chloride, or methyl chloride dissolved in 0.24 ml of mineral oil and fed to animals after a fast of 16 hours was studied. Control animals received either labeled sodium bicarbonate in 0.5 ml of 0.01 N NaOH or labeled formaldehyde in 0.25 ml of water. Bicarbonate and formaldehyde are chloromethane oxidation products and these served as comparisons to the incorporation patterns of the 4 agents used. [88]

Two hours after oral introduction both carbon tetrachloride and, to a lesser extent, chloroform caused an increase in RNA content of the liver and centrilobular necrosis at 24 hours. The concentrations of chloroform found in the liver within the first few hours after dosing were slightly greater than those of carbon tetrachloride. However, the extent of necrosis from chloroform was less. The carbon labeled chloroform was re-

covered in an amino acid locus corresponding to methionine. The amount of labeled radioactive carbon found in lipids and microsomes was related to the chlorine content of the chloromethanes.

(h) Potentiation

Alcohols, barbiturates, and some other chemicals such as DDT when administered before chloroform increase the toxic effects of chloroform, apparently by lowering the threshold for its necrotic action. [90-93]

Kutob and Plaa [90] found that ethanol pretreatment of mice increased the toxic effect of chloroform on the liver. Male Swiss albino mice weighing 20-30 g were initially treated with an oral dose of ethanol (5 g/kg) in a 25% aqueous solution. The ethanol pretreatment was followed by single, subcutaneous, minimally hepatotoxic doses of chloroform (0.08 ml/kg) given in a 1.6% olive oil solution. Time interval between ethanol pretreatment and dosing with chloroform was systematically shortened from 15 days to 12 hours to determine the shortest period before administration of chloroform in which administration of ethanol would increase the susceptibility to chloroform. The time lag between ethanol and chloroform was purposely chosen so that the ethanol would be metabolized by the time the chloroform was administered. Each experiment consisted of 4 groups of animals: 1) untreated; 2) treated with ethanol; 3) treated with chloroform; and 4) treated with ethanol followed by chloroform. Liver function was studied 24 hours after the administration of chloroform by determining 1) pentobarbital (45 mg/kg) sleeping time, 2) BSP retention, and 3) liver succinic dehydrogenase activity. Tissue slides were also studied to corroborate the liver function tests.

All experiments showed reduced liver function as indicated by prolonged pentobarbital sleeping times and elevated BSP retention. The liver succinic dehydrogenase activity was depressed when chloroform was administered 12 or 24 hours after ethanol, but not when it was administered 48 hours after ethanol. Ethanol alone or chloroform alone did not significantly depress succinic dehydrogenase activity.

In mice pretreated with ethanol 15 hours, or 1, 2, or 4 days before the administration of chloroform, microscopic examination revealed livers with cytoplasmic vacuolization in pericentral cells. The pericentral cells were also enlarged and almost completely devoid of eosinophilic material. [90]

In a similar study, Sipes et al [91] pretreated rats with isopropanol and reported enhanced ability to covalently bind radioactive carbon labeled chloroform to microsomal protein.

Dingell and Heimberg [92] studied the hepatic metabolism of aminopyrine and hexobarbital in rat liver microsomes after the administration of chloroform or carbon tetrachloride or methylene chloride. The chlorinated hydrocarbons were administered in equimolar doses by gastric intubations and killed 24 hours later. Liver microsomes were prepared from rat livers weighing from 250-375 mg. Either 5 μmoles of aminopyrine or 1.9 μmoles of hexobarbital was added to a mixture of enzyme substrates.

The rate of metabolism of hexobarbital was measured by estimation of the disappearance of substrate. The rate of demethylation of aminopyrine was measured by estimation of the amount of formaldehyde formed. For both the aminopyrine and hexobarbital pretreatment before carbon tetrachloride decreased the rate of metabolism significantly to 14 and 29%, respectively,

of control values. Chloroform, however, only decreased metabolism of aminopyrine to 61% and hexobarbital to 95% of control values.

McLean [93] fed male mice either stock diet or protein free diets for 1 week before intragastric administration of chloroform. Some of the mice of each group were also given sodium phenobarbital in the drinking water (1 mg/ml) for 1 week before chloroform administration; others were given a single subcutaneous injection of DDT (100 mg/kg) 1 week before chloroform. The purpose of DDT and the phenobarbital administration was to stimulate liver hydroxylating enzyme activity. The purpose of the protein deficient diet was to reduce the liver hydroxylating enzyme activity, but in this experiment this was not realized. Phenobarbital and DDT increased the liver hydroxylating enzyme activity and the toxicity of chloroform was more than doubled by the phenobarbital and DDT pretreatment as measured by the LD50.

Correlation of Exposure and Effect

The use of chloroform as an anesthetic agent has provided information about the effects to be expected from acute exposure. Exposures during anesthesia have usually been to concentrations of around 20,000 ppm, [58] and exposure times have been from 30-240 minutes. [30,45,94] One or 2 days after chloroform anesthesia, nausea, jaundice, and vomiting may develop, often followed by elevated temperature and pulse, epigastric pain, muscle twitching, delirium, and coma. In some cases, death has occurred 3-10 days after anesthesia. [30,45,46,51] Autopsies have demonstrated fatty infiltration of the liver with diffuse central necrosis, and enlarged, soft, congested kidneys with cloudy swelling of the

epithelial lining of the convoluted tubules, and yellow striations marking the pyramids. [24,45,51,54,94]

Habitual inhalation of 1 oz daily of chloroform for 7 years followed by 2 oz/day for 5 more years was associated with delusions, restlessness, depression, convulsions, ataxia, dysarthria, tremor of the tongue and fingers, and insomnia; at autopsy, the brain showed slightly thickened meninges in the frontal lobe, many fibroblasts and dilated blood vessels. [36] In other cases of habitual chloroform inhalation for periods of time ranging up to 30 years, hallucinations, delirium, and tremors were common manifestations. [36] The exposures (Table X-4) are difficult to evaluate, but they were chronic and the effects on the central nervous system were definite.

Lehmann and Hasegawa [34] and Lehmann and Schmidt-Kehl [35] performed the only controlled exposure experiments with humans. The exposures were for a maximum of 30 minutes, and response measurements were limited to subjective responses of the subjects. These experiments provide information about responses of people exposed to 160 ppm (0.8 mg/liter or 800 mg/cu m) through a range of concentrations up to 7,200 ppm (35.3 mg/liter), as follows:

160 ppm (0.8 mg/liter) for unspecified time - no odor
205 ppm (1.0 mg/liter) for unspecified time - light transient odor
390 ppm (1.9 mg/liter) for 30 minutes - light transient odor
920 ppm (4.5 mg/liter) for 7 minutes - stronger, lasting odor; dizziness, vertigo after 3 minutes

680 ppm (3.3 mg/liter) to 1,000 ppm (5.0 mg/liter) for 30 minutes - moderately strong odor; taste

1,100 ppm (5.4 mg/liter) for 5 minutes - still stronger, permanent odor; dizziness, vertigo after 2 minutes

1,400 ppm (6.6 mg/liter) to 1,800 ppm (8.57 mg/liter) for 30 minutes - stronger odor, tiredness, salivation, giddiness, vertigo, headache, taste

3,000 ppm (14.46 mg/liter) for 30 minutes - all above plus pounding heart, gagging

4,300 ppm (20.8 mg/liter) to 5,000 ppm (25 mg/liter) for 20 minutes - dizziness and light intoxication

5,100 ppm (25 mg/liter) for 20 minutes - dizziness and light intoxication

7,200 ppm (35.3 mg/liter) for 15 minutes - dizziness and light intoxication as above but more pronounced

The data presented by Challen et al [67] provide some quantitative information about exposure and effect, even though some of the information about exposure was obtained after the fact. Employees in a confectionery manufacturing medicinal lozenges had complained of nausea, flatulence, loss of appetite, frequent and burning micturition, lack of mental concentration, depression, and irritability. Measurements were made of an atmosphere created under conditions which were considered to simulate those in existence at the time the employees were affected. The average chloroform concentrations based on 30-minute samples ranged from 77-237 ppm. It was noted that reducing work to part time in this environment relieved the employees' complaints. No studies were made on the exposed

workers during the time of the exposure which covered the years 1950-1954. Measurements of liver and kidney function made in 1958, 3-4 years after the exposure, were normal.

Another group of 10 workers were later engaged in the same jobs after ventilation was improved. These workers had been working 4 hours a day for 10-24 months under conditions where 30-minute average chloroform concentrations ranged from 23-71 ppm, except for 1 operation which ran 4 times a day for a total of about 2 hours in which the exposure during operation averaged 128 ppm, with 4 exposures each lasting 1 1/2-2 minutes at 1163 ppm.

In 9 of the latter workmen studied by Challen et al, [67] only 2 did not report unpleasant experiences. Among the other 7, 5 reported dryness of the mouth and throat at work; 2 were subject to lassitude in the evening; 1 complained of lassitude and flatulence at work; and the complaints of 2 others were similar to those experienced by the original workmen. Liver function tests were normal in these workers.

In the study of Bomski et al, [55] workroom concentrations of chloroform in a pharmaceutical industry fluctuated between 2 and 205 ppm, but no further information about environmental exposure concentrations was given. The incidence of viral hepatitis (4.4-16.7%) was much higher among the people working in the chloroform environment than among the general population (0.22-0.35%); and 10 cases of splenomegaly and 17 cases of enlarged liver were found among the 68 chloroform workers.

Sixty-eight workers who had been exposed to this chloroform environment for 1-4 years were studied in detail, along with 3 control groups: 1) 30 previously chloroform-exposed workers; 2) 23 nonchloroform exposed-

workers who had previously had viral hepatitis; and 3) 165 nonchloroform exposed workers with no history of viral hepatitis. Seventeen of the 68 chloroform-exposed workers had enlarged livers. Three of these 17 workers had toxic hepatitis on the basis of elevated serum enzyme activities and elevated serum gamma globulin. The other 14 workers with enlarged livers were judged to have fatty liver, though admittedly without confirmation by biopsy.

The incidence of enlarged livers among these 68 workers was significantly higher than in the controls. It was noted that there was a reduction in hepatomegaly in 79% of the people studied during the 6-12 month period when hygienic conditions at work were improved. [55]

Schwetz et al [83] studied the effects of 30, 100, and 300 ppm of chloroform on pregnant rats for 7 hours/day on days 6 through 15 of gestation. There were significant incidence of delayed skull ossification and "wavy ribs" in litters from dams exposed to 30 ppm of chloroform.

The authors [83] found that in litters from dams exposed to 100 ppm there were significant incidences of acaudia, imperforate anus, subcutaneous edema, missing ribs, and delayed sternebrae ossification. Rats exposed to chloroform at 300 ppm ate so little food (1 g/day) that it would be impossible to consider any of the other effects as characteristic of chloroform. [83]

Kylin et al [78] found that mice exposed to 100 ppm chloroform for 4 hours showed moderate fatty infiltration and degeneration at the periphery of the liver lobules, one day after exposure. These effects were found less frequently 3 days after exposure, indicating a certain amount of regeneration. A direct dose-response relationship, evidenced by increasing

liver alterations and necrosis, was observed at concentrations ranging from 100 to 800 ppm. Further indication of a dose-response relationship was the increase of the serum ornithine carbamoyl transferase with increasing concentrations of chloroform.

Animal studies [95] have shown that chloroform is capable of causing liver and kidney injury after 130 repeated 7-hour exposures to concentrations as low as 25 ppm. Injury at that exposure level was minor and reversible; at higher concentrations (50 and 85 ppm) repeated exposure produce more severe injury but no changes in clinical chemical tests for such injury. Repeated 4-hour exposures to 25 ppm caused no effect. From this study, it was suggested that a ceiling of 25 ppm would be more appropriate, with the TWA concentration not to exceed 10 ppm.

A summary of concentration-responses data is presented in Table X-11.

IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION

Environmental Concentrations

Environmental data derived from the manufacture and use of chloroform are very scarce. The only industrial environmental data available are from surveys of the pharmaceutical industry where the chloroform consumed is less than 10% of the total produced. Although fluorocarbon refrigerants and resins account for almost 90% of the chloroform used in the United States, [96] there are no studies on workroom concentrations of chloroform used in their production.

Challen et al [67] in 1958 studied chloroform concentrations in a confectionery manufacturing plant in England, in which chloroform vapor were given off during the production of medicinal lozenges. Employees had complained about exposure to chloroform and subsequently a system of exhaust ventilation was installed. An air sample was taken continuously in the breathing zone of the operator during a period of 20 minutes coinciding with the duration of the ingredient mixing process. The sample was drawn through 2 U tubes containing dried silica gel at the rate of 1 liter/min. Additionally, at a point in the operation where a peak concentration was expected, a 6-liter grab sample was taken. Air samples of 30-minute durations were also taken in the breathing zones of cutting room operators performing 3 different operations during 2 periods of production on the same day under the current ventilation conditions. For purposes of allowing a comparison, the original conditions in the cutting room were simulated by closing the doors and windows and shutting off the ventilation system. On the day of the simulated conditions, air samples of 30-minute

durations each were taken during 3 periods of production in the breathing zone of operators performing the 3 different operations and in the general room air. All samples were analyzed by the alcohol KOH combustion method (alkali hydrolysis).

Under the current conditions of ventilation, the continuous sample taken during the mixing operation contained 128 ppm, and a peak value of 1,163 ppm of chloroform lasting 1 1/2 minutes was found in the grab sample of air adjacent to the emptying of the mixer. The mixing operation occurred no more than 4 times daily for a total of about 2 hours. In the cutting room, the environmental concentrations were: feeding operation, 71 and 57 ppm; dusting operation, 35 and 31 ppm; and tray removal, 23 and 29 ppm.

Chloroform concentrations in the air found by Challen et al [67] during the simulation of the original conditions were as follows: feeding operation, 219, 237, and 161 ppm; dusting operation, 110, 158, and 155 ppm; removing trays, 77 and 92 ppm; general atmosphere at the center of the room, 82 and 92 ppm.

Concentrations of chloroform during the years 1968-72 in a plant manufacturing film were supplied by the Department of Labor and Industries, Commonwealth of Massachusetts. [LD Pagnotto, written communication, December 1973] A solvent mixture containing 75% methylene chloride, 22% chloroform, and toluene was used in the operation. Samples were collected by drawing air at a rate of 0.5 liters/min for 90-120 minutes through a U-tube filled with 7 g of silica gel and desorbed by soaking in isopropyl alcohol for 2 hours. Aliquots of this solution were hydrolyzed by

potassium hydroxide (KOH) for 17 hours, and for 65 hours in order to estimate both chloroform and methylene chloride.

To differentiate between the amounts of chloride recovered from chloroform and methylene chloride, it was necessary to use empirical chloride recovery factors determined from control samples analyzed in parallel. During the first 17 hours of hydrolysis, averages of about 4% of the methylene chloride and about 80% of the chloroform were hydrolyzed. During hydrolysis an average of about 20% of the methylene chloride, but virtually no additional chloroform was hydrolyzed. It was necessary to run methylene and chloroform controls for each determination.

Over the 5 years of surveillance, a total of 79 samples were determined by this method. The measured concentrations of chloroform ranged from 7-170 ppm, with a mean of 47 ppm. On 2 consecutive days in 1973, samples were collected on charcoal and analyzed by GC. On these 2 days concentrations ranged from 30-585 ppm, and in general, appeared to be higher than concentrations previously observed by the silica gel-alkaline hydrolysis method.

Bomski et al, [55] while investigating the health of workers in a pharmaceutical plant in Poland, repeatedly measured chloroform concentrations in the air of the production rooms. No information was given about the time span covered by the investigation, the number of air samples collected, or the duration of individual sampling times. The range of concentration reported was between 2 and 205 ppm (0.01-1.0 mg/liter) determined by the method of Grabowicz. [68] This method is a modification of the Fujiwara colorimetric method which is explained in detail in the following section.

Environmental Sampling and Analytical Method

(a) Collection Methods

Most of the analytical methods are dependent on the effectiveness and reproducibility of the sorption of chloroform on or in different collecting media.

Air samples should be collected and transported to a laboratory, then desorbed or chemically treated, and finally analyzed quantitatively. Silica gel has been used extensively in the past as a collection medium. [67,97] Silica gel is a polar adsorbent and shows pronounced selectivity in adsorbing polar molecules, particularly water. Hence, when sampling large volumes, the atmospheric moisture may compete for the adsorptions sites and displace the chloroform being sought. When sampling large volumes (more than 3 liters), the silica gel adsorption tube may become saturated with water thus impairing the retentive properties of the collection medium. [98]

Activated charcoal as a collection method has been used in conjunction with gas chromatography. [99] Activated carbon is nonpolar and will consequently adsorb organic vapors in preference to water vapor so that sampling of volumes higher than 3 liters can be accomplished without noticeable moisture interferences. [98]

Williams and Umstead [100] have developed a collection method in which atmospheric samples are concentrated on porous polymer beads. The same column utilized for sample collection is subsequently used for GC analysis. The advantage of this method is that it integrates collection and

analysis into one operation. However, it has not yet been developed for field use.

Liquids have been used as collection absorbers of chloroform contaminated atmospheres. Impingers containing m-xylene [101] were used as collectors for gas chromatographic analysis and bubbler bottles containing a pyridine solution were also used as the collection method in conjunction with colorimetric analysis. [97] The use of liquid impingers and bubblers poses problems in field measurements due to difficulties in collecting breathing zone samples without spilling of liquid and the added problem of transporting liquid samples for laboratory analysis.

Other investigators have collected the contaminated atmospheres directly by grab samples using a variety of containers ranging from plastic bags to hypodermic syringes. [99] However, the small amounts collected do not accurately represent the atmosphere in a plant location during a work shift.

(b) Desorption Methods

When solid collection media are used it is necessary to desorb the contaminant collected on the medium. Isopropyl alcohol and heat were used by the Massachusetts Department of Labor and Industries to desorb chloroform from silica gel. Desorption from charcoal was studied by Otterson and Guy. [99] They recommended the use of different desorbing agents depending upon the comparative gas chromatograph retention times for the desorber and the contaminant. Carbon disulfide was determined to be the best desorbent for chloroform.

(c) Analysis

Several methods have been used to determine the concentration of chloroform in the air. The analytical methods can be divided in 2 broad categories: 1) methods based on chloroform chemical reactions; and 2) methods based on chloroform physicochemical characteristics.

The 3 chemical methods that have been used extensively are: 1) dechlorination of collected vapor samples with strong alkalis followed by titration of the chloride ion (alkali hydrolysis) [34,67]; 2) colorimetric measurement of the reaction products of chloroform and pyridine heated in alkali solution (Fujiwara reaction) [102]; and 3) direct reading colorimetric indicators. [103]

The dechlorination method (alkali hydrolysis) requires collection of the chloroform contaminated atmosphere over a suitable collection medium followed by hydrolysis in isopropyl alcohol. Solid KOH is added and the mixture is allowed to sit overnight (about 20 hours). After neutralization the liberated chloride ion is titrated with silver nitrate. [97] The percentage of chlorine hydrolyzed is determined by comparison between samples and known controls. This method has the disadvantage of a long and elaborate procedure in which the amount of chloride ion liberated depends on the duration of the process of alkali dechlorination. When a mixture of chlorinated hydrocarbon vapors is analyzed, there is the additional problem of specificity; it is necessary then to differentiate the contribution of each chlorinated compound to the total amount of chloride ion liberated. [LD Pagnotto, personal communication, 1973]

In the colorimetric analytical method based on the Fujiwara reaction, [102] a stream of air containing chloroform is passed through a

washer bottle containing pyridine at a rate of 0.5 liter/min. After collection in pyridine, methylethyl ketone and NaOH are added to an aliquot of the sample. A control and an aliquot of the former solution are heated in a boiling water bath, and cooled during a fixed time period. The absorption is then determined with a suitable spectrophotometer. This method requires less time than the dechlorination method, but the problem of specificity in the presence of mixtures of other chlorinated hydrocarbons remains.

The third chemical method consists of direct reading indicators, [103] which are glass tubes packed with solid chemicals that change colors when measured and controlled flow of air containing chloroform passes through the packed material. There are 2 types of sampling procedures: 1) direct passing of the test vapor through the tube followed by comparison with a calibration chart; 2) drawing the test vapor into a pyrolyzer accessory prior to detection. [104] Both methods are nonspecific for chloroform since the liberated halogen ion produces the stain to be read and any halogen or halogenated compounds will interfere. Regulations on detector tubes are found in 42 CFR Chapter I, subchapter G, Part 84, Subpart B, paragraph 84.20 (e). These regulations provide that measurement with colorimetric indicator tubes should be correct within ± 25% of the values read. There are commercially available detector tubes which fulfill this criterion.

The category of analytical methods, based on the physicochemical properties of chloroform, includes: gas chromatography (GC), [105] infrared spectrometry (IR), [106] and photodetector analyzers (Davis Halide Meter). [107] The gas chromatographic method of analysis provides a specific

quantitative analytical method. [105] Gas chromatographic analysis is specific for different chlorinated hydrocarbons since every compound has a specific retention time in a given chromatograph column. However, there is the possibility that several compounds in a mixture may have similar retention times. This problem is easily overcome by altering the stationary phase of the chromatograph column by changing the column temperature or other analytical parameters. Altering conditions will usually change the retention times and separate the components.

A mass spectrometer in conjunction with the gas chromatograph could be used to identify unknown chemicals passing through the chromatograph column. A charcoal capillary tube is employed to trap and transfer the observed unknown GC peak to a mass spectrometer for qualitative identification as described by Cooper et al. [108]

The use of an infrared spectrophotometer [106] provides the advantages of an instantaneous reading of exposure levels of vapors and, in conjunction with a recorder, can document concentration levels during a complete operation cycle. The IR spectrophotometer eliminates the necessity of collecting and transporting samples to a laboratory for analysis. This analytical method has been used for continuous monitoring of industrial operations with chlorinated hydrocarbon exposures. [106] However, complicated instrumentation is necessary to draw the samples and record the data continuously. There is also the need to assure that the atmosphere of relevant working stations is sampled and that such samples correspond to the breathing zone of the workers at the working stations. [106] There are also possibilities of interferences with other air contaminants which are

not easy to detect or resolve without expertise in infrared spectrophotometry.

Halide meters (Davis Halide Meters and modifications) are based on the detection of the increased brightness of an a-c arc (metal electrode) when enveloped by an atmosphere contaminated with halogenated hydrocarbons. [107] The instrument is sensitive to all halogens and halogenated compounds and consequently is nonspecific for chloroform. The Halide meter seems suitable for continuous monitoring if there is only chloroform present as the air contaminant.

(d) Conclusions and Recommendations

(1) Compliance Method

On the basis of the review of the analytical methods it is recommended that gas chromatography be chosen as the compliance method. The method is recommended in conjunction with activated charcoal tubes as a collection method and the use of carbon disulfide as a desorbent.

The combined collection-desorption analytical method was first evaluated in laboratory trials by Otterson and Guy. [99] Fraust and Hermann [109] evaluated the optimal charcoal granule size, sampling rates and total volume for charcoal sampling tubes. White et al [110] applied the findings of Fraust and Hermann [109] and in addition determined the optimal cross section of the charcoal tubes and the optimal number of collecting sections. The tubes were further modified for use as personal samplers for chlorinated hydrocarbon vapor exposures. [111]

The reasons for the choice of gas chromatography - activated carbon collection as the compliance method are:

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

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

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

(D) Gas chromatography identifies chloroform in combination with many other compounds.

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

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

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

(2) Monitoring Methods

It is also recommended that direct reading colorimetric tubes (gas detection tubes) be used as an inexpensive way to determine whether exposure, as defined in Chapter I, exists. The tubes must be used with manufacturer's instructions and for monitoring purposes only.

For situations in which there is a continuous and constant chloroform use (fluorocarbon refrigerants and resins production, manufacture of chloroform, and some pharmaceutical uses), the establishment of a continuous monitoring system of the working location is suggested. The work place should be monitored by a multiprobe continuous air sampler in different working locations, at the breathing zone of the workers

involved. An appropriate motion-time study at the different probe locations will determine the worker TWA exposure.

The analytical apparatus for continuous monitoring should be a calibrated infrared spectrophotometer or, if the only halogenated hydrocarbon present is chloroform, a halide meter. If various other halohydrocarbons are present a gas chromatograph should be used. The continuous monitoring findings should be corroborated with the compliance method described in Appendix I.

Biologic Evaluation of the Environment

Lehmann and Hasegawa [34] are the only investigators who have studied concentrations of chloroform in exhaled air of persons with known exposures. The data are presented in Table X-3. One subject was exposed to 4,400 ppm (21.5 mg/liter) for 30 minutes, and the concentrations in the exhaled air were followed during the first 30 minutes after the end of exposure. The average concentrations in the exhaled air collected during the 3 immediately consecutive 10-minute postexposure periods were 1.70, 0.97, and 0.85 mg/liter, respectively.

The other subject was exposed by Lehmann and Hasegawa [34] for 15 minutes to chloroform at 7,200 ppm (35.3 mg/liter) and the concentration in the exhaled air was followed for 20 minutes after the end of exposure. The average concentrations in the exhaled air collected during the 3 immediately consecutive 5-minute postexposure periods were 2.31, 1.48, and 1.04 mg/liter, respectively. These data show that exhaled breath concentrations of chloroform are dependent upon exposure concentration, exposure time, and the time after exposure that the air is sampled. In order to

evaluate exposure to chloroform, data are needed which take these 3 factors into consideration.

Chloroform concentrations in the blood have been measured during and following anesthesia. [44,50] These data show that chloroform in the blood is eliminated rapidly at first but that some remains for at least 8 hours after exposure to anesthetic concentrations. These data are inadequate for evaluating industrial exposure.

V. DEVELOPMENT OF A STANDARD

Basis for Previous Standards

In 1946, the Sub-Committee on Threshold Limits of the ACGIH published a list entitled "Maximum Allowable Concentrations of Air Contaminants for 1946", with the understanding that the list would be revised each year. [112] The list of values was compiled from 3 sources:

(a) The list reported by the Sub-Committee on Threshold Limits at the 5th Annual Meeting of the ACGIH in 1942.

(b) The then comprehensive list published by Cook in Industrial Medicine. [113]

(c) Published values of the Z-37 Committee of the American Standards Institute.

The value proposed for chloroform by the ACGIH [112] was 100 ppm.

In 1959, the Threshold Limit Value (TLV) for chloroform was reduced to a time-weighted average of 50 ppm for a normal working day by the ACGIH [114] in their annual review of the TLV values.

In 1962, the ACGIH [115] published its Documentation of Threshold Limit Values (TLV's) in which it cited the recommendations of Cook [113] that exposures to chloroform be kept below 50 ppm, and the study of Challen et al. [67] The 1968 TLV, which was unchanged from the 1962 recommendation, was promulgated as a regulation by OSHA. This was published, apparently in error, as a ceiling value of 50 ppm, in the Federal Register, volume 39, page 23541, dated June 27, 1974.

In 1969, the ACGIH changed the time-weighted average limit to a ceiling and documented this in 1971. [116] This ceiling limit of 50 ppm

was considered adequate to prevent any serious short-term effects on the liver, but it was recommended that chloroform be used with close medical surveillance, particularly with those workers who consume alcohol. The recommendation was based in part on the studies of Challen et al, [67] Bomski et al, [55] and unpublished data from the Massachusetts Division of Occupational Hygiene. A notice of intended change for chloroform from 50 (ceiling) to 25 ppm (time-weighted average) was made by the ACGIH in 1972 [117] and 1973. [118]

The AIHA Hygienic Guide Series of 1965 for Chloroform [95] suggested that a time-weighted average (TWA) of 10 ppm be used with a ceiling of 25 ppm. This recommendation was based on unpublished experimental animal data.

In 1970, the International Labour Office in Geneva published tables of Permissible Levels of Toxic Substances in the Working Environment for many countries. [43] The chloroform standards for 8 different countries are listed below; it is not clear from the reference whether these are time-weighted averages or ceiling concentrations.

Country	Standard, ppm
Bulgaria	10
Czechoslovakia	10
Czechoslovakia	50*
Finland	50
Hungary	4
Hungary	20*
Japan	50
Poland	10
Rumania	10
Yugoslavia	50

*for brief exposures

Basis for Recommended Environmental Standard

The major exposure to chloroform has been as an anesthetic [33,44,50,58] and most experiments have been related to this use. Cardiac arrhythmias have occurred, especially when chloroform anesthesia has been prolonged beyond 30 minutes. [56,57] Liver and kidney injuries have also been found, sometimes resulting in death several days after anesthetic exposure. [30,36,44,46,47,53,94]

It is difficult to evaluate the total exposure to chloroform during anesthesia since concentrations frequently were not reported. However, it should be noted that the concentrations in anesthesia are extremely high and are not constant throughout the exposure period. Whipple and Sperry

[30] demonstrated in experiments with dogs that chloroform anesthesia for a period of 1-2 hours caused central liver necrosis. At autopsy of a woman who had died from delayed chloroform poisoning, they found liver changes that resembled changes found in dogs. The only other experimental study of liver changes after inhalation of chloroform was that by Kylin et al [78] in 1963 who exposed 20 mice to 100, 200, 400, and 800 ppm for 4 hours. In this study, the mice exposed to 100 ppm did not develop demonstrable liver necrosis, however, moderate fatty infiltration of the liver was noted. In mice exposed to 200 ppm, some necrotic areas appeared in the liver and there was an increase in serum ornithine-carbamoyl transferase. Exposures to 400 and 800 ppm resulted in increasing necrosis and serum enzyme activity.

Although Schwetz et al [83] did not report detailed studies of liver changes in female rats exposed to chloroform 7 hours/day for 10 days, they did report that liver weights, both absolute and relative, increased as a result of exposure to 100 and 300 ppm but not to 30 ppm. However, embryo and fetal anomalies, including delayed skull ossification and the formation of wavy ribs, were found in the offspring of the rats exposed to 30 ppm.

The only account of liver abnormalities among industrial workers exposed to chloroform is a report by Bomski et al. [55] These investigators found 17 cases of hepatomegaly in a group of 68 workers exposed to chloroform in concentrations ranging from 2-205 ppm for 1-4 years in a pharmaceutical firm. Three of the 17 workers with hepatomegaly were judged by the authors to have toxic hepatitis on the basis of elevated serum enzymes, and elevated serum gamma globulin. This group of workers was also considered to be much more susceptible to viral hepatitis than the

inhabitants of the city in which the plant was located, but the basis for this inference is tenuous, since no information was given on possible contributions to the problem by poor sanitation, for example the incidence of viral hepatitis in other plant workers was not mentioned.

In the study by Challen et al [67] no liver abnormalities were found among 17 workers exposed to chloroform. Nine workers were exposed to chloroform at TWA concentrations ranging from 23-71 ppm, but for only 4 hours/day. These workers had been working under these conditions for 10-24 months. Another group of workers who had previously been exposed to chloroform in concentrations estimated to have ranged from 77-237 ppm for up to 8 hours/day, also had no abnormal liver findings. However, it had been many months since this latter group had been exposed to chloroform.

These studies indicate that liver damage may occur in workers from exposure to chloroform in varying concentrations up to 205 ppm. [55] The studies with mice showed some liver cell necrosis from 4 hours' exposure to 200 ppm and fatty infiltration of the liver from 100 ppm for 4 hours. [78] The studies with rats showed increased liver weights from 10 consecutive 7-hour daily exposures to 100 ppm, but not to 30 ppm exposures. [83] The studies by Challen et al [67] indicated no liver injury from 4 hours per day exposure of workers to 23-71 ppm chloroform.

While the exposure conditions studied by Challen et al [67] (23-71 ppm chloroform for 4 hours/day) seem below the threshold for liver injury, they are not adequate to protect workers from other undesirable responses such as dryness of the mouth and throat at work, and lassitude in the evening, which occurred among the workers exposed to 23-35 ppm chloroform for 4 hours a day. It seems reasonable to infer from these observations

that the lassitude reflects central nervous system depression and that dry mouth and throat and the digestive tract symptoms reflect a local irritant action in those areas.

It can be interpreted from the study of Challen and co-workers [67] that a safe level to exposure for workers lies somewhere between 23 and 35 ppm for 4-hour workdays, or about 10 to about 18 ppm for 8-hour workdays. The appropriate limit within this range is not clear, but because of mild effects in this group (mouth and throat dryness and evening fatigue) and because of the fetal abnormalities found in rats exposed to 30 ppm, [83] it is concluded that the environmental limit to be recommended should be the lowest in this range, namely 10 ppm, as a time-weighted average.

The absorption of chloroform resulting from exposure to a given time-weighted average concentration for 8 hours a day, 5 days a week, would be about the same as that absorbed for 10 hours a day, 4 days a week. Thus, the same time-weighted average limit is applicable whether the 40-hour workweek is applied over 5 8-hour days or 4 10-hour days.

It is likely that a central nervous system depressant, such as chloroform, might at briefly high concentrations affect attention, judgment or perception sufficiently so that if an emergency were to occur the worker might not take appropriate action. This suggests the need for a ceiling concentration to be observed, as a limitation on excursions above the time-weighted average and as a limit applicable to occasional and brief use of chloroform. However, after detailed consideration of the data applicable to derivation of such a ceiling, no basis from the scientific data appears. The ceiling proposed by American Industrial Hygiene Association [95] in its Hygienic Guide Series is based on animal data that seem more applicable to

development of a time-weighted average limit. Thus, a ceiling limit of 50 ppm based on a 10-minute sampling period is proposed on the basis of good practice.

It is recognized that many workers handle small amounts of chloroform or are working in situations where, regardless of amounts used, there is only negligible contact with the substance. Under these conditions, it should not be necessary to comply with all provisions of this recommended standard, which has been prepared primarily to protect worker health under hazardous circumstances. On the other hand, concern for worker health requires that protective measures be instituted below the enforceable limit to ensure that exposures stay below that limit. For these reasons, "exposure to chloroform" has been defined as exposure above half the environmental limit, thereby delineating those work situations which do not require the expenditure of health resources for environmental and medical monitoring and associated recordkeeping. Half the environmental limit has been chosen on the basis of professional judgment rather than on quantitative data that delineate nonhazardous areas from areas in which a hazard may exist. However, it is recommended that appropriate work practices and protective measures to prevent skin and eye contact and to prevent exposure to pyrolysis products be required, regardless of air concentrations of chloroform.

VI. WORK PRACTICES

The principal method for the manufacture of chloroform is chlorination of methane, [1] and suitable controls for safe use of methane and chlorine should be used. Engineering controls required for the safe handling of chlorine are available. [119]

Further information concerning specific work practices for chloroform such as engineering controls, preventive measures, medical management, first aid, training, safety, etc, can be found in the Manufacturing Chemists' Association Safety Data Sheet SD-89. [120]

(a) Bulk Handling

Of primary concern in bulk loading or unloading operations is the possibility that an emergency situation may arise as a result of equipment breakdown or failure to follow proper work procedures. All piping and valves at the loading or unloading station should be carefully inspected prior to connection to the transport vehicle and periodically during the operation. Personal protection must be provided during both inspection and connection. Eye wash and safety shower installations should be readily available in the immediate area. Unloading areas must be posted "Danger: loading or unloading chloroform".

(b) Storage and Use

Although chloroform is noncombustible, decomposition to toxic compounds including phosgene, tetrachloroethylene, hydrogen chloride, chlorine and carbon dioxide may occur in case of a fire. [1]

Protective measures include use of closed systems whenever feasible, personal protective equipment, protective clothing, purging of equipment

prior to and during servicing and maintenance, and well designed and properly functioning laboratory hoods and exhaust systems. In general, good engineering practices should be used to control continuous low-level exposures and to minimize excursions. For example, good ventilation practices are recommended in Industrial Ventilation-A Manual of Recommended Practice [121] published by the American Conference of Governmental Industrial Hygienists. Special handling and disposal procedures are also required because of the ability of chloroform to undergo chemical reactions with other materials. For example, chloroform reacts violently with acetone in the presence of alkali and also with alkali metals. It reacts less violently with caustic. For these reasons, chloroform should not be disposed of along with other waste solvents. The ability of some chlorinated solvents to react with aluminum producing anhydrous aluminum chloride suggests that chloroform should not be stored in aluminum containers.

Safety showers and eye wash fountains are necessary in areas where accidental exposure is likely to occur.

(c) Maintenance of Equipment

All equipment used for handling chloroform must be emptied and purged prior to entry or disassembly. Under conditions where it is necessary to enter or otherwise work with chloroform contaminated equipment maintenance personnel must use either a self-contained breathing apparatus, pressure demand type, with an impervious protective suit; or a combination supplied air suit with auxiliary self-contained air supply. Safety precautions for emergency rescue require that all maintenance personnel be informed of wearing personal protective equipment. [2]

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

(e) Respiratory Protection

For adequate respiratory protection against the multiplicity of conditions which may be encountered in individual operations, many types of respirators have been developed and approved. Each has a particular field of application and limitations from the viewpoint of protection, as well as advantages and disadvantages from the viewpoint of operational procedures and maintenance. Detailed information on the selection and use of respirators can be obtained from the respiratory protection devices manual [122] published by the AIHA and the ACGIH in 1963. The American National Standards Practices for Respiratory Protection, ANSI Z88.2-1969, [123] also classifies, describes, and gives the limitations of respirators.

Respirators generally fall into the following classification according to their mode of operation:

(1) Atmosphere-Supplying Respirators

(A) Self-contained.

(B) Hose mask.

(C) Airline.

(D) Combination self-contained and airline.

(2) Air-Purifying Respirators

(A) Gas and vapor (gas mask and chemical cartridge).

(B) Particulate (dust, fog, fume, mist, smoke, and sprays).

(C) Combination gas, vapor, and particulate.

(3) Combination Atmosphere-Supplying and Air-Purifying Respirators

The factors that affect the overall performance of an air-purifying respirator are the reliability of the face seal, the efficiency of the filters and/or absorbent canisters and other variables, such as leakage from exhalation valves. The performance of filters, canisters, and exhalation valves is predictable and controllable when test data are available. However, the current state of knowledge of the wearer's face size and shape and the respirator size and shape is such that the face seal is unpredictable and variable.

During the past several years, NIOSH has funded research and development projects to make quantitative respirators-man tests on all types of respirators to measure their performance and/or efficiency. The results of these tests made on half mask and quarter mask facepieces, operated with a negative pressure in the facepiece, show that the facepiece

leakage is the major limitation of these devices. From the test results, it has been demonstrated that the half mask or quarter mask facepiece may be used for protection up to 10X the TWA. The full facepiece, operated with a negative pressure, may be used up to 100X the TWA. The majority of the wearers can obtain a higher degree of protection. However, for purposes of uniform regulations, covering the many face sizes and shapes of the US working population, it is necessary to use these guides. These maximum use concentration guides do not take into account additional leakage from filters or canisters.

When providing respiratory protection against chloroform, the concentration immediately dangerous to life must be considered. In this document, it is assumed that any concentration of chloroform greater than 2,500 ppm is immediately dangerous to life.

In selecting and using gas masks and chemical cartridge respirators, the service life must be considered. The approval tests (under 30 CFR 11) for these 2 devices specify only carbon tetrachloride for the service life test. Based on recent tests by Nelson and Harder [124] 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 chloroform. With a test concentration of 1,000 ppm of chloroform, they reported that the standard organic vapor cartridge has a service life of 33 min before a breakthrough of 10 ppm of chloroform. Under the same test conditions, a service life of 77 min for carbon tetrachloride was obtained. Since the approval test for organic vapor cartridges and canisters specifies carbon tetrachloride as a test atmosphere, it is possible to extrapolate or calculate service life at

various concentrations of chloroform. For example, 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 min before a breakthrough of 5 ppm. Extrapolation indicates that the same canister would provide a service life of 4 hours against 1,000 ppm of carbon tetrachloride. However, the same organic vapor canister is much less efficient for chloroform. If it is assumed that carbon tetrachloride absorption is 100% efficient on activated charcoal, then chloroform absorption is only 43% efficient. From this, the service life against 1,000 ppm of chloroform for an industrial size canister is estimated at 2 hours. The chin-type canister with a much smaller volume of sorbent has a service life of 4 hours against 100 ppm of chloroform. The shortest service life is the chemical cartridge approved for use on chemical cartridge respirators. It has a service life of 3 hours against 100 ppm for chloroform.

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

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VIII. APPENDIX I

SAMPLING AND ANALYTICAL PROCEDURES FOR DETERMINATION OF CHLOROFORM

Atmospheric Sampling

(a) General Requirements

(1) The measurement of air concentrations shall be within the breathing zone of workers and shall meet the following criteria in order to evaluate conformance with the standard:

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

(3) Sampling data sheets shall include a log of:

(A) The date and time of sample collection

(B) Sampling duration

(C) Total sample volume

(D) A description of the sampling location

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

(F) Other pertinent information

(b) Breathing Zone Sampling

(1) Breathing zone samples shall be collected as near as practicable to the face of workers without interfering with freedom of movement and shall characterize the exposure from each job or specific operation in each production area.

(2) An approved, calibrated, battery-operated personal sampling pump plus an activated charcoal tube shall be used to collect the sample.

(3) The activated charcoal tube shall be attached to the clothing of the worker; the shirt collar is convenient for this purpose.

(4) Breathing zone samples shall be collected to permit determination of TWA workday exposures for every job involving exposure to chloroform in sufficient numbers to express the variability of the work situation. The minimum number of TWA's to be determined is listed in Section 7 of this standard, according to the number of employees involved.

(c) Apparatus

(1) Pump, battery-operated, complete with clip for attachment to the worker or a reliable, calibrated hand pump. All pumps and flowmeters must be calibrated with a representative charcoal tube in the line.

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

(d) Calibration of Sampling Instruments

(1) Air sampling instruments shall be calibrated with a representative charcoal tube in line, over a normal range of flowrates (50-

1000 ml/min) and pressure drops. Calibration curves shall be established for each sampling pump and shall be used in adjusting the pump prior to field use. Also calibration curves shall be established for each sampling pump after making any repairs or modifications to the sampling system.

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

(e) Collection and Handling of Samples

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

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

(3) The charcoal tube should be placed in a vertical position during sampling with the inlet facing down.

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

(5) The flowrates, sampling time involved and/or the total volume of air sampled must be measured accurately. The sample can be taken at flow rates of 50-1000 ml/min. Total sample volumes of 1-30 liters are recommended. It is also recommended that the sampling be less than 4 hours.

(6) Measure and record the temperature and pressure of the atmosphere being sampled.

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

(8) One charcoal tube should be handled in the same manner as the sample tube (break, seal, and transport) except that no air is sampled through this tube. This tube should be labeled as a blank.

(9) Capped tubes should be packed tightly after sampling to minimize tube breakage during transport.

(10) Charcoal tubes should be shipped separately from bulk samples.

Sample Analysis

(a) Principle of the Method

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

(2) The charcoal in the tube is transferred to a small test tube and desorbed with carbon disulfide.

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

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

(b) Range and Sensitivity

(1) The lower limit for detection of chloroform at a 16 x 1 attenuation on a gas chromatograph with a 10:1 splitter is 0.10 mg/sample. This value can be lowered by reducing the attenuation or by eliminating the 10:1 splitter.

(2) The upper limit value for chloroform is 2.0 mg/sample. This is the estimated amount of chloroform which the front section will hold before this compound is found on the backup section. If a particular atmosphere is suspected of containing a large amount of chloroform, it is recommended that a smaller sample volume be taken.

(c) Interferences

(1) When the amount of water in the air is so great that condensation actually occurs in the tube, chloroform will not be trapped.

(2) Any compound which has the same retention time as chloroform at the operating conditions described in this method could be an interference.

(d) Advantages of the Method

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

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

(3) Interferences are minimal, and most of those which do occur can be eliminated by altering chromatographic conditions.

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

(e) Disadvantages of the Method

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

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

(3) Other chlorinated hydrocarbons may displace chloroform from the charcoal.

(f) Apparatus

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

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

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

(4) Glass stoppered microtubes. The 2.5-ml graduated microcentrifuge tubes are recommended.

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

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

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

(g) Reagents

(1) Spectroquality carbon disulfide

(2) CHC13, preferably chromatoquality grade

(3) Bureau of Mines Grade A helium

(4) Prepurified hydrogen

(5) Filtered compressed air

(h) Procedure

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

(2) Preparation of samples

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

(3) Desorption of Samples

Prior to analysis, 0.5 ml of carbon disulfide is pipetted into each test tube. ALL WORK WITH CARBON DISULFIDE SHOULD BE PERFORMED UNDER A HOOD BECAUSE OF ITS HIGH TOXICITY AND ITS FLAMMABILITY. Tests indicate that desorption is complete in 30 minutes if the sample is stirred occasionally during this period. The use of graduated glass-stoppered, microcentrifuge tubes is recommended so that one can observe any apparent change in volume during the desorption process depending on the surrounding temperature. The initial volume occupied by the charcoal plus the 0.5 ml carbon disulfide should be noted and corresponding volume adjustments should be made whenever necessary just before analysis.

(4) Gas chromatographic conditions

Operating conditions for a typical gas chromatograph are:

(A) 85 cc/min (70 psig) helium carrier gas flow

(B) 65 cc/min (24 psig) hydrogen gas flow to detector

(C) 500 cc/min (50 psig) airflow to detector

(D) 200 C injector temperature

(E) 200 C manifold temperature (detector)

(F) Oven temperature 80 C isothermal

(5) Injection

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

(6) Measurement of Area

The area of the sample peak is measured by an electronic integrator or some other suitable form of area measurement, and preliminary sample results are read from a standard curve prepared as discussed below.

(7) Calibration and Standards

(A) Preparation of Standards

It is convenient to prepare standards in terms of mg chloroform per 0.5 ml of carbon disulfide because samples are desorbed in this amount of carbon disulfide. To minimize error due to the volatility of carbon disulfide, 20 times the weight can be injected into 10 ml of carbon disulfide. For example, to prepare a 0.3 mg/0.5 ml standard, 6.0 mg is injected into exactly 10 ml of carbon disulfide in a glass stoppered flask. The density for chloroform is used to convert 6.0 mg into microliters for easy measurement with a microliter syringe. A series of standards are 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.

(B) Determination of Desorption Efficiency

It is necessary to determine the percentage of chloroform on the charcoal that is removed in the desorption process. This desorption efficiency is determined once for a given compound provided the same batch of charcoal is always used.

Activated charcoal, equivalent to the amount in the first section of the sampling tube (100 mg), is measured into a 2-inch long tube, with an inside diameter of 4 mm, flame-sealed at one end. This charcoal must be from the same batch as that used in obtaining the samples and can be obtained from unused charcoal tubes. The open end is capped with parafilm.

A known amount of the compound is injected directly into the activated charcoal with a microliter syringe, and the tube is capped with more parafilm.

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

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

$$\text{desorption efficiency} = \frac{\text{Desorption sample area - Blank area}}{\text{Desorption standard area}}$$

Sample Calculations

(a) Read the weight of chloroform corresponding to the peak area for chloroform from the standard curve. No volume corrections are needed because the standard curve is based on mg $CHCl_3$/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 chloroform on the front and backup sections of the charcoal tube.

(c) Corrections must be made to the chloroform weights determined on both the front and backup sections for the weights of the respective sections of the blank charcoal tube.

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

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

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

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

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

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

Where:

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

V = measured volume of air in liters sampled

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

T = temperature of air in degree centigrade at time of sampling measured

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

(1) μg/liter = 1000 M/V'

(2) mg/cu m = 1000 M/V'

(3) ppm = 205 M/V'

IX. APPENDIX II

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to chloroform shall be provided in the appropriate section of the Material Safety Data Sheet or approved form. If a specific item of information is inapplicable, the initials "na" (not applicable) should be inserted.

(a) Section I. Source and Nomenclature.

(1) The name, address, and telephone number of the manufacturer or supplier of the product.

(2) The trade name and synonyms for a mixture of chemicals, a basic structural material, or for a process material; and the trade name and synonyms, chemical name and synonyms, chemical family, and formula for a single chemical.

(b) Section II. Hazardous Ingredients.

(1) Chemical or widely recognized common name of all hazardous ingredients.

(2) The approximate percentage by weight or volume (indicate basis) which each hazardous ingredient or the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, 10-20% by volume; 10% maximum by weight.

(3) Basis for toxicity for each hazardous material such as an established standard in appropriate units.

(c) Section III. Physical Data.

Physical properties of the total product including boiling point and melting point in degrees Fahrenheit; vapor pressure in millimeters of

mercury; vapor density of gas or vapor (air=1); solubility in water, in parts per hundred parts of water by weight; specific gravity (water=1); percentage volatile, indicate if by weight or volume, at 70 degrees Fahrenheit; evaporation rate for liquids (indicate whether butyl acetate or ether=1); and appearance and odor.

(d) Section IV. Fire and Explosion Hazard Data.

Fire and explosion hazard data about a single chemical or a mixture of chemicals, including flash point, in degrees Fahrenheit; flammable limits in percentage by volume in air; suitable extinguishing media or agents; special fire fighting procedures; and unusual fire and explosion hazard information.

(e) Section V. Health Hazard Data.

Toxic level for total compound or mixture, effects of exposure, and emergency and first-aid procedures.

(f) Section VI. Reactivity Data.

Chemical stability, incompatibility, hazardous decomposition products, and hazardous polymerization.

(g) Section VII. Spill or Leak Procedures.

Detailed procedures to be followed with emphasis on precautions to be taken in cleaning up and safe disposal of materials leaked or spilled. This includes proper labeling and disposal of containers holding residues, contaminated absorbents, etc.

(h) Section VIII. Special Protection Information.

Requirements for personal protective equipment, such as respirators, eye protection, clothing, and ventilation, such as local exhaust (at site of product use or application), general, or other special types.

(i) Section IX. Special Precautions.

Any other general precautionary information.

U.S. DEPARTMENT OF LABOR
Occupational Safety and Health Administration

Form Approved
OMB No. 44-R1387

MATERIAL SAFETY DATA SHEET

Required under USDL Safety and Health Regulations for Ship Repairing, Shipbuilding, and Shipbreaking (29 CFR 1915, 1916, 1917)

SECTION I

MANUFACTURER'S NAME	EMERGENCY TELEPHONE NO.
ADDRESS *(Number, Street, City, State, and ZIP Code)*	
CHEMICAL NAME AND SYNONYMS	TRADE NAME AND SYNONYMS
CHEMICAL FAMILY	FORMULA

SECTION II - HAZARDOUS INGREDIENTS

PAINTS, PRESERVATIVES, & SOLVENTS	%	TLV (Units)	ALLOYS AND METALLIC COATINGS	%	TLV (Units)
PIGMENTS			BASE METAL		
CATALYST			ALLOYS		
VEHICLE			METALLIC COATINGS		
SOLVENTS			FILLER METAL PLUS COATING OR CORE FLUX		
ADDITIVES			OTHERS		
OTHERS					

HAZARDOUS MIXTURES OF OTHER LIQUIDS, SOLIDS, OR GASES	%	TLV (Units)

SECTION III - PHYSICAL DATA

BOILING POINT (°F.)		SPECIFIC GRAVITY (H_2O=1)	
VAPOR PRESSURE (mm Hg.)		PERCENT, VOLATILE BY VOLUME (%)	
VAPOR DENSITY (AIR=1)		EVAPORATION RATE (_____ =1)	
SOLUBILITY IN WATER			
APPEARANCE AND ODOR			

SECTION IV - FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (Method used)	FLAMMABLE LIMITS	Lel	Uel
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARDS			

(Continued on reverse side)

SECTION V - HEALTH HAZARD DATA

THRESHOLD LIMIT VALUE
EFFECTS OF OVEREXPOSURE
EMERGENCY AND FIRST AID PROCEDURES

SECTION VI - REACTIVITY DATA

STABILITY	UNSTABLE		CONDITIONS TO AVOID
	STABLE		
INCOMPATIBILITY (*Materials to avoid*)			
HAZARDOUS DECOMPOSITION PRODUCTS			
HAZARDOUS POLYMERIZATION	MAY OCCUR		CONDITIONS TO AVOID
	WILL NOT OCCUR		

SECTION VII - SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED
WASTE DISPOSAL METHOD

SECTION VIII - SPECIAL PROTECTION INFORMATION

RESPIRATORY PROTECTION *(Specify type)*		
VENTILATION	LOCAL EXHAUST	SPECIAL
	MECHANICAL *(General)*	OTHER
PROTECTIVE GLOVES	EYE PROTECTION	
OTHER PROTECTIVE EQUIPMENT		

SECTION IX - SPECIAL PRECAUTIONS

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORING
OTHER PRECAUTIONS

GPO 934-110

TABLE X-1

PHYSICAL PROPERTIES OF CHLOROFORM

Chemical Abstracts serial number	000067663
Synonyms	Trichloromethane Trichloroform Methenyl trichloride Formyl trichloride Methyl trichloride Methane, trichloro-
Molecular formula	CHC13
Molecular weight	119.38
Boiling point	61.3 C, 142.3 F (760 mm Hg)
Melting point	-63.2 C, -81.7 F
Vapor pressure	200 mm Hg (25 C)
Specific gravity	1.48069 (25 C), (water = 1.000 at 4 C)
Solubility	1.0 g/100 ml water at 15 C; soluble in ethanol, ethyl ether, benzene, acetone, and carbon disulfide
Explosive limit	None
Flash point	None
Vapor density	4.00 g/liter (25 C; 760 mm Hg)
Conversion factors 25 C; 760 mm Hg	1 mg/liter = 205 ppm 1 mg/cu m = 0.205 ppm 1 ppm = 4.89 mg/cu m

Adapted from references 1,2,3,4

TABLE X-2

PERCENTAGE ABSORPTION OF CHLOROFORM
AFTER INHALATION BY TWO SUBJECTS

Subject	A	A	A	B	B	B
	Inhalation Concentration					
ppm	4,448	4,920	5,125	4,264	4,715	4,920
mg/liter	21.7	24	25	20.8	23	24
	Percent Absorbed					
Exposure Period (min)						
0- 5	74.5	73.2	75	68.4	49.4	66.4
5-10	72.4	73.2	75	61.6	63.0	64.2
10-15	68.6	69.0	77	51.2	61.6	64.6
15-20	67.6	60.9	76	50.2	53.0	54.4

Adapted from Lehmann and Hasegawa [34]

TABLE X-3

ABSORPTION OF CHLOROFORM BY SUBJECT C IN CONSECUTIVE 5-MINUTE PERIODS OF INHALATION OF DIFFERENT CONCENTRATIONS OF CHLOROFORM AND EXCRETION OF CHLOROFORM AFTER EXPOSURE

Exposure	Inhalation Concentration ppm	Inhalation Concentration mg/liter	Exposure Period min	Percent Absorbed	Postexposure Period min	CHC13 Excretion mg/liter
1	4407	21.5	0-5	80.0		
			5-10	74.3		
			10-15	76.9		
			15-20	74.6		
			20-25	74.2		
			25-30	73.8		
					0-10	1.70
					10-20	0.97
					20-30	0.85
2	7236	35.3	0-5	80.7		
			5-10	79.8		
			10-15	76.8		
					0-5	2.31
					5-10	1.48
					10-20	1.04

Adapted from Lehmann and Hasegawa [34]

TABLE X-4

CASES OF HABITUAL CHLOROFORM USE

Case and Reference	Daily $CHCl_3$ Use	Duration of Habit	Psychiatric and Neurologic Symptoms
1 [36]	1 oz daily for 7 years, 1 oz daily for next 5 years	12 years	Restless, distressed, easily excitable, depressed, hallucinations, convulsions, dysarthria, ataxia, tremor of tongue and fingers. Diagnosed as having chloroform poisoning with cerebellar involvement. Autopsy showed moderate degenerative changes in cerebellum, slightly thickened meninges, many fibroblasts, and dilated blood vessels
2 [37]	Small amount from 6-oz bottle	Over 1 year	Mental and physical wreck; fidgety, nervous, wakeful
3 [37]	Unspecified, every night with occasional spree	5 years	After spree - nausea, vomiting, and death wish; 2 suicide attempts
4 [37]	Unspecified, every night	3 years	Mental and physical wreck
5 [37]	Unspecified, sprees lasting for days or weeks	8-10 years	Physically and mentally sluggishness
6 [37]	Unspecified sprees lasting for days	Years	Moody, gloomy, despondent
7 [38]	20 drops on handkerchief with ether	14 years	Insomnia, depression, delirium, left hemiplegia after 9 years, right hemiplegia 5 years later
8 [39]	20-30 g pure $CHCl_3$ or 50 g $CHCl_3$ with alcohol 3-7 times/week	15 years	Nervous, unstable, temperamental, overreactive, rheumatic pain, slight tremor of hands
9 [40]	100 g	15 years	Psychologically upset (shell shock, war wounds, divorce, other failures)

TABLE X-5

LIVER FUNCTION TESTS FOLLOWING INGESTION OF CHLOROFORM

Item Measured	Day After Ingestion 1	2	3	4	5	90
SGOT, iu	30	681	8,080	5,300	297	34
SGPT, iu	15	...	9,220	10,250	3,330	
LDH, iu	204	636	9,280	5,680	630	176
Alkaline phosphatase, iu	6.1	5.2	...	6.4	...	5.0
Bilirubin (total), mg%	0.2	2.3	2.4	2.7	1.3	1.0
Prothrombin time, sec						
a) patient	14.3	19.2	...	18.4	14.3	12.3
b) control	12.6	11.9	...	12.7	11.8	12.2

iu = international units
... = not reported

Adapted from Storms [41]

TABLE X-6

SIX CASES OF DELAYED CHLOROFORM POISONING

Patient	Dose	Effects	Laboratory Test and Autopsy Findings
1 (37 yrs old) [45]	3 administrations 1. 3 capsules, each 20 minims 2. "very little" from drop bottle 3. 3 capsules, each 20 minims and anesthesia on open mask	Restless, coma and convulsions on 2nd day post partum, vomiting, jaundice, increased pulse and temperature. Died on 8th day post partum.	Blood urea: 198 mg/100 cc on 3rd day, 303 mg/100 cc on 5th day Blood NPN: 187 mg Amino acid nitrogen: 8.2 mg % Urine: acid, albumin, red blood cells, pus, high urobilin Liver: soft, yellow advanced necrosis, and fatty degeneration Kidneys: swollen, fatty deposits, necrosis Heart: fatty degeneration
2 (30 yrs old) [45]	2 inhalations of unspecified amount separated by 2 hours, and anesthesia on open mask	Drowsy, swelling of hands, jaundice, coma, increased temperature and pulse, extreme hyperpnea, no vomiting. Died 5th day post partum	Blood urea: 105 mg/100 cc on 2nd day, 360 mg/100 cc on 5th day Plasma bicarbonate: 0.003 molar Urine: uric acid, albumin, pus, 2.35% urea on 3rd day Liver: yellow, mottled, soft, diffuse centri-lobular necrosis, fat mostly in periphery
3 (25 yrs old) [45]	Full anesthesia on open mask "long time" then repeated 4 hours later	Drowsy, jaundice, coma on 4th day, muscular twitchings, increased temperature, vomiting. Died on 6th day post partum	Blood: .093 % sugar 60 mg/100 cc urea Urine: deep orange, ph 6.0, .4 % albumin, diacetic acid Liver: soft, flabby, recent shrinkage, yellow, widespread necrosis Kidneys: congestion of cortical vessels Heart: fatty changes

TABLE X-6 (continued)

SIX CASES OF DELAYED CHLOROFORM POISONING

Patient	Dose	Effects	Laboratory Test and Autopsy Findings
4 (24 yrs old) [49]	Unspecified	Restless, delirium, coma, jaundice, drowsy, increased temperature, muscle twitching, no vomiting. Recovered	Urine: showed albumin, bilirubin, urobilin other lab tests in Table X-8
5 (35 yrs old) [49]	Twice, unspecified amount	Drowsiness, mental confusion, coma, jaundice, tenderness over liver, hiccup, restless, no vomiting. Recovered	Urine: showed albumin, bilirubin, urobilin; other lab tests in Table X-8
6 (23 yrs old) [49]	Twice, unspecified amount	Jaundice, nausea general weakening, slight icterus. Recovered	No observations

TABLE X-7

CLINICAL DATA OF DELAYED CHLOROFORM POISONING IN TWO OBSTETRICAL CASES

Clinical Measurement	Patient		
	A	B	B
	3rd Day	4th day	5th day
Alkaline phosphatase (1)	21.4-22.3	21.1	...
Carbon dioxide, blood vol %	34	54	45
Blood urea, mg %	108	50	24
Blood chloride, mg %	...	570	...
Serum thymol turbidity	0-3.2	2.2	+

(1) King-Armstrong units

Adapted from Lunt [49]

TABLE X-8

CHLOROFORM IN EXHALED AIR (VOL %) COLLECTED
DURING THIRD STAGE ANESTHESIA AT INDICATED TIMES
AFTER INDUCTION OF ANESTHESIA, BY PLANE OF THIRD STAGE

Patient		Operation	Plane	Time	CHC13
age-sex				min	vol %
1	41F	Exploration and lysis of adhesions	1	10	1.78
2	73M	Biopsy tumor of face	1	10	0.83
3	57M	Excision abdominal skin tumor	1	11	0.46
4	56M	Resection mandible	1	20	0.64
5	68M	Gastric resection	1	84	0.26
5	68M	Gastric resection	1	124	0.49
6	42M	Laminectomy	1-2	40	0.31
7	58F	Radical mastectomy	2	35	0.14
8	38F	Partial gastric resection	2	26	0.62
9	44M	Gastric resection	2	40	0.24
10	53F	Gastric resection; drain gall bladder	2	50	0.34
11	59F	Resection cervical nodes	2-3	40	1.47
2	73F	Biopsy tumor of face	2-3	40	1.47
1	41F	Exploration and lysis of adhesions	3	43	1.57
9	44M	Gastric resection	3	123	0.43

Adapted from Morris [50]

TABLE X-9

THE EFFECT OF CHLOROFORM ON THE URINARY PROTEIN AND URINARY GLUCOSE OF MICE FOLLOWING 24-HOUR PRETREATMENT WITH PENTOBARBITAL

Dose ml/kg	% Showing significant protein (1)	glucose (2)
0.5	100	100
0.125	60	50
0.063	30	50
0.032	40	0
0.016	10	10

(1) Significant urinary protein = 100 mg % or more

(2) Significant urinary glucose = 250 mg % or more

Adapted from Plaa and Larson [79]

TABLE X-10

PENTOBARBITAL SLEEPING TIMES OF MICE 24-HOURS
AFTER EXPOSURES TO CHLOROFORM

Dose ml/kg	Number of animals	% Showing significant sleeping time (1)
0.016	55	11
0.032	46	22
0.25	10	40
0.5	10	50
1.0	10	80

(1) Sleeping time longer than 6 minutes

Adapted from Plaa and Larson [79]

TABLE X-11

CHLOROFORM INHALATION EXPOSURES AND EFFECTS

Author	Exposure Variables	Exposure Time	Effects
Challen [67]	Humans; 23-35 ppm (30-min averages)	Intermittent 4 hrs/day	Lassitude, dryness of the mouth, irritability
Schwetz [83]	Pregnant rats; 30 ppm	7 hr/day, 10 days	Delayed fetal skull ossification and wavy rib formation
Challen [67]	Humans; 57-71 ppm	Intermittent 4 hrs/day	Flatulence, lassitude, loss of appetite, nausea
Schwetz [83]	Rats; 100 ppm	7 hr/day, 10 days	In fetuses - increased occurrences of acaudia, missing ribs, delayed sternebrae ossification, subcutaneous edema, imperforate anus; in adults - increased liver weights
Kylin [78]	Mice; 100 ppm	4 hrs	Moderate fatty infiltration of liver
	200 ppm	4 hrs	some liver necrosis
Bomski [55]	Humans; 2-205 ppm		Headache, nausea, burping, loss of appetite, increased incidence of viral hepatitis, toxic hepatitis with elevated serum gamma globulins, splenomegaly, hepatomagoly
Lehmann and Schmidt-Kehl [35]	Humans; 205 ppm	Brief (approx. 1 minute)	Perception of light, transient odor
Schwetz [83]	Rats; 300 ppm	7 hr/day 10 days	Decreased food consumption

TABLE X-11 (Continued)

CHLOROFORM INHALATION EXPOSURES AND EFFECTS

Author	Exposure Variables	Exposure Time	Effects
Kylin [78]	400 ppm and 800 ppm	4 hrs	Liver necrosis, increased serum ornithine carbamoyl transferase activity
Lehmann and Schmidt-Kehl [35]	Humans; 922 ppm 1,107 ppm	3 min 2 min	Dizziness, vertigo Dizziness, vertigo
Lehmann and Schmidt-Kehl [35]	Cats; 7,175 ppm	7.8	Light narcosis
Lehmann and Hasegawa [34]	Humans; 7,236 ppm	15 min	Dizziness, light intoxication
Fuhner [71]	Mice; 6,765 ppm or 7,380 ppm	1/2 hr 10 min	Narcosis, eventual death, narcosis
von Oettingen [72]	Dogs; 13,950-15,596 ppm	60-285 min	Narcosis, respiratory fluctuation, decrease in blood pressure and body temperature, death
Whitaker and Jones [58]	Humans; 20,000 ppm	30-240 min	Anesthesia, nausea, vomiting, jaundice, delayed chloroform poisoning
Whipple and Sperry [30]	Dogs; 1-2 oz (total amount inhaled)	1-2 hrs	Anesthesia, central hyaline necrosis, acute yellow atrophy, fatty degeneration of the kidneys

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