III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

1,1,1-Trichloroethane (CH3 CC1 3) is also known as methyl chloroform and alpha-trichloroethane. [1,2]

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

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

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

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

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

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

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

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

Historical Reports

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

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

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

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

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

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

TABLE III-1

EFFECTS OF TRICHLOROETHANE ISOMERS ON MICE

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

Adapted from Lazarew [31]

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

Effects on Humans

(a) Experimental Central Nervous System Effects

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

reaction time, manual dexterity, and equilibrium.

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

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

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

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

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

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

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

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

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

TABLE III-2

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

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

Adapted from Stewart et al [35]

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

hours. Neither balance nor coordination was affected.

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

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

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

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

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

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

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

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

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

(b) Effects on the Cardiovascular System

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

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

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

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

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

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

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

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

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

(c) Effects on other Organ Systems

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

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

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

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

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

(d) Intentional, Accidental, or Suicidal Exposures

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

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

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

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

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

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

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

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

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

cardiac sensitization to endogenous catecholamines.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(f) Absorption and Excretion

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

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

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

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

TABLE III-3

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

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

Adapted from Stewart et al [9]

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

TABLE III-4

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

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

Adapted from Stewart and Dodd [53]

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

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

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

TABLE III-5

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

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

Adapted from Stewart et al [35]

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

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

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

TABLE III-6

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

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

* This death was attributed to suffocation

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

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

TABLE III-7

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

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

Adapted from Gazzaniga et al [56]

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

TABLE III-8

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

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

Adapted from Stewart et al [35]

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

TABLE III-9

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

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

Adapted from Fukabori [55]

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

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

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

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

(g) Metabolism

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

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

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

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

TABLE III-10

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

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

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

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

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

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

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

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

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

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

(h) Effects on Mucous Membranes and Skin

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

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

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

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

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

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

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

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

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

Epidemiologic Studies

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

TABLE III-11

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

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

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

TABLE III-12

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

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

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

TABLE III-13

EXCLUSIONS FROM HEALTHY CATEGORY
BY CLASS OF DISORDER

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

Adapted from Seki et al [65]

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

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

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

Animal Toxicity

(a) Acute Lethal Doses and Concentrations

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

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

TABLE III-14

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

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

* 95% Confidence limits in parenthesis

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

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

TABLE III-15

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

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

Adapted from Torkelson et al [36]

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

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

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

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

(b) Central Nervous System Effects

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

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

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

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

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

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

TABLE III-16

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

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

Adapted from Adams et al [73]

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

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

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

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

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

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

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

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

(c) Cardiovascular and Respiratory Effects

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

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

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

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

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

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

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

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

TABLE III-17

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

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

Adapted from Belej et al [79]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(e) Hepatic and Renal Effects

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

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

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

TABLE III-18

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

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

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

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

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

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

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

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

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

TABLE III-19

EFFECTS OF 1,1,1-TRICHLOROETHANE IN RATS

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

Adapted from Adams et al [73]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(f) Absorption, Excretion, Metabolism

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

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

TABLE III-20

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

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

Adapted from MacEwen and Vernot [88]

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

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

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

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

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

TABLE III-21

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

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

Adapted from Ikeda and Ohtsuji [93]

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

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

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

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

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

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

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

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

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

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

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

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

exposure concentrations were less effective.

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

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

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

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

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

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

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

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

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

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

(h) Teratogenicity, Carcinogenicity, Mutagenicity

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

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

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

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

Correlation of Exposure and Effect

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

(a) Central Nervous System Effects

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

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

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

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

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

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

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

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

(b) Cardiovascular Effects

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

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

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

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

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

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

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

reports of other cases have found hypertension.

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

(c) Liver and Kidney Effects

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

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

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

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

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

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

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

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

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

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

(d) Effects on Skin and Mucous Membranes

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

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

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

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

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

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