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TOXICOLOGICAL AND PHYSIOLOGICAL EFFECTS OF METHYL CHLOROFORM
1,1,1-TRICHLOROETHANE

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This review has considered important published and unpublished reports relative to the toxicological and physiological effects of methyl chloroform (1,1,1-trichloroethane) in mammals with emphasis on human toxicity. In order to maintain a reasonable length, not every paper is discussed, particularly if the paper duplicates or confirms similar information. Contact Health and Environmental Sciences, Dow Chemical U.S.A., Midland, Michigan if you have questions concerning these or other papers.

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(1,1,1-Trichloroethane)

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THE TOXICOLOGICAL AND PHYSIOLOGICAL EFFECTS OF METHYL CHLOROFORM

SUMMARY

Methyl chloroform (1,1,1-trichloroethane) has been extensively studied and shown to be one of the least toxic of the chlorinated hydrocarbons; however, gross overexposure has resulted in death due to anesthesia and/or cardiac arrhythmias. Contact with the undiluted liquid causes mild to moderate corneal irritation, but no permanent eye injury is likely. Prolonged skin contact may cause irritation due to defatting, but toxicity due to skin absorption is not a problem. The oral LD50 in rats is 12.3 g/kg indicating a low order of acute toxicity. At high vapor concentrations the material acts as an anesthetic and cardiac sensitizer. Humans exposed to 800-1000 ppm experience minimal impairment of coordination. At levels above 1700 ppm, equilibrium may be impaired. In tests with beagle dogs, concentrations greater than 1% (10,000 ppm) produced cardiac sensitization to epinephrine (adrenaline). No such effects have been reported at or near the TLV (350 ppm).

Chronic toxicity due to methyl chloroform is low. Animals exposed to vapors at 1000-10,000 ppm for 3 months showed mild pathologic changes in the liver and lungs of some species. Repeated exposure to 500 ppm for 6 months did not cause any toxic effects in rats, guinea pigs, rabbits or monkeys and exposure to 1750 ppm for one year caused no adverse effects in rats.

Methyl chloroform is readily absorbed through the lung, the GI tract and to a lesser degree through the skin, but is only slightly metabolized. Essentially, all is exhaled unchanged after gavage, ingestion or inhalation.

Methyl chloroform has been shown to be negative in most mutagenic test systems, causing no more response than sucrose in a large battery of mutagenic tests. Animal studies for reproductive and teratogenic effects have been consistently negative as have carcinogenic studies in rats and mice.

Human experience confirms the experimental data from animals and indicates no chronic effects although acute deaths have occurred from anesthesia (and possibly cardiac arrhythmias) following massive accidental or deliberate exposure to concentrations of several percent. Short of death, recovery has generally been rapid and complete.

EFFECTS OF ACUTE AND SHORT-TERM EXPOSURE

ORAL INGESTION - Methyl chloroform has consistently been shown to be low in oral toxicity. It is absorbed from the GI tract and primarily exhaled unchanged through the lungs. Aspiration of the liquid into the lung can cause pneumonitis. Hence, induction of vomiting is not recommended. If it is considered necessary to induce vomiting, it must be done in a manner that will prevent aspiration of emesis.

Animals Studies - The following are typical acute oral LD50s which have been published for several species for both uninhibited and inhibited methyl chloroform:

<u>LD50 (103)</u>	<u>Uninhibited</u>	<u>Inhibited</u>
Male Rats	12,300 mg/kg	14,300 mg/kg
Female Rats	10,300 mg/kg	11,000 mg/kg
Female Mice	11,240 mg/kg	9,700 mg/kg
Female Rabbits	5,660 mg/kg	10,500 mg/kg
Male Guinea Pigs	9,470 mg/kg	8,600 mg/kg

The antidotal efficacy of liquid paraffin in oral methyl chloroform intoxication was investigated in dogs. A group of 4 dogs received 1 ml/kg of methyl chloroform by gastric intubation. After a prolonged interval the same animals were given 5 ml/kg of liquid paraffin. Administration of liquid paraffin in conjunction with methyl chloroform did not significantly effect the absorption process (54).

Instillation of liquid methyl chloroform in the lungs of rats produced pneumonitis, indicating that if vomiting occurs, aspiration of emesis could result in serious injury similar to that seen when liquid kerosine is inhaled (103).

Human Experience - A 47-year old workman gulped 1 ounce of a fluid he had been told was whiskey. He immediately realized he had not ingested whiskey because of the burning sensation in his mouth and upper gastrointestinal tract, as well as the foreign flavor. Thirty minutes later,

he became nauseated, but ate his lunch on schedule. One hour after solvent ingestion, he began vomiting and diarrhea became incapacitating. He was taken to a hospital emergency room where gastric lavage with 2 liters of tap water was carried out. Four hours after methyl chloroform ingestion, physical examination revealed a pale well-developed, well-nourished, apprehensive man who was vomiting and passing frequent stools. The patient was well-oriented and was not experience difficulty with coordination or drowsiness. His blood pressure was 120/80 mg Hg and his pulse rate was 84 beats per minute. His temperature and respiratory rate were normal. There was no tenderness in the abdomen or costovertebral angle. Active peristalsis was present. Liver, spleen, and kidneys were not palpable. A detailed neurological examination revealed no abnormalities. Six hours following solvent ingestion, the diarrhea and vomiting subsided. At this time, the patient's only complaint was fatigue, and he was allowed to sleep. He awoke the next day in an asymptomatic state, but was kept hospitalized for an extended observation period. Results of repeated physical and neurological examinations were normal during the next two weeks (99).

SKIN CONTACT - Liquid methyl chloroform causes defatting if confined on the skin, but is not likely to cause more than mild dermatitis. Absorption through the skin does occur, but is not toxicologically significant.

Animal Studies - A dose of 3980 mg/kg failed to kill any of eight rabbits whose skin was exposed for 24 hours. A dose of 15,000 mg/kg failed to kill 50% of the rabbits treated (103). Anesthesia was apparent.

The approximate lethal dose for guinea pigs was found to be greater than 7125 mg/kg (117).

Two ml of methyl chloroform was applied to 3.1 cm³ of the clipped skin of 20 guinea pigs. No mortality was observed but the weight gain was significantly reduced when compared to untreated controls (117).

The percutaneous absorption of methyl chloroform was determined on mouse skin by applying 0.5 ml of the solvent to an area of 2.92 cm^2 . After 15 minutes the amount of solvent retained in whole body and the amount in expired air were determined. These amounts were 235 and 32 μg , respectively. The percutaneous absorption rate was determined to be $24.4 \text{ nmoles/min/cm}^2$ of skin (110).

Slight reddening and scaliness were observed after a pad of absorbent cotton saturated with methyl chloroform was held in contact with the shaven belly skin of rabbits (103).

Methyl chloroform was tested on the skin of 6 rabbits. Its level of irritation was rated at 3.7 on a scale of 0 (no irritation) to 8 (severe irritation) (30).

Human Studies - In a series of human absorption experiments, the skin of the hands was exposed to liquid methyl chloroform. The amount of the compound exhaled in the alveolar air during and after the exposure was determined. The results were as follow:

<u>No. of Subjects</u>	<u>Length of Exp. (Min.)</u>	<u>Skin Exposed</u>	<u>Mean Peak Breath Conc. After Exp.</u>	<u>Mean Breath Conc. 2 Hrs After Exp.</u>
6	30	Thumb(immerse)	1.0 ppm	0.31 ppm
1	30	Hand (immerse)	21.5 ppm	1.55 ppm
1	30	Hand (topical)	0.65 ppm	0.31 ppm

A slight prickling or mild burning sensation was noted on the dorsal surface of the thumb after immersion for 10 minutes. Following removal of the thumbs from the solvent, a mild erythema and fine scaling were noted. The erythema subsided within 30 to 60 minutes. One subject immersed his hand in methyl chloroform for 30 minutes. Four minutes after immersion slight irritation was noted on the dorsum of the hand which increased to become a mild burning sensation within an additional two minutes. Ten minutes following immersion, the burning was described

as severe enough to preclude comfortable immersion. Twenty minutes after immersion the dorsum of the hand felt as if it were packed in ice, and the burning sensation subsided. Upon removal of the hand from the solvent, the cold sensation persisted for ten minutes. A fine, chalky-white scale was noted on the exposed surface and this scale was readily removed by rinsing the hands in water. A mild erythema was present which subsided within 60 minutes. The amount of methyl chloroform in the alveolar air was related to the area of skin exposed (100).

After application of methyl chloroform (2 hours/day) for 3 days to the forearm skin, the blood content reached 3-9 $\mu\text{g/ml}$ and the alveolar air contained 2-7 ppm immediately after the last application. Repeated applications increased the concentrations (33).

The skin of human volunteers was exposed to 600 ppm of methyl chloroform vapors for 3.5 hours. To avoid inhalation, the subjects wore airline respirators. The elimination of the solvent in the exhaled air and the excretion of its metabolites in the urine was followed for 24 hours. The expired air contained only 15.7 μmoles and no metabolites were detected in the urine. These small amounts suggest that methyl chloroform is an inferior penetrant in comparison to aromatic solvents and even perchloroethylene which was only slightly more absorbed.(85)

Protective Gloves - Breakthrough time was determined for several gloves exposed to liquid methyl chloroform. Breakthrough occurred within 15 minutes for all glove materials (polyvinyl alcohol, latex rubber, Neoprene®) except BUNA-N which had a breakthrough time between 30 and 45 minutes. Based on permeation rate, polyvinyl alcohol had the lowest rate while Neoprene® had the highest. BUNA-N, despite having the longer breakthrough time, had a permeation rate that was more than 2 times greater than polyvinyl alcohol (114).

Methyl chloroform penetrated all tested glove materials within 60 minutes. Dynamic gas-phase IR spectrophotometry was used to make the permeation measurements (73)

EYE CONTACT - Liquid methyl chloroform causes only a mild transient irritation in the eyes. The vapors become uncomfortable in the eyes at about 1000 ppm. No reports of significant injury in humans have been published.

Animal Studies - Rabbit eyes treated with 1,1,1-trichloroethane had moderate to mild corneal injury, iritis, and mild conjunctival irritation. It caused only mild conjunctival irritation with no significant corneal or iritic effect in eyes which were washed promptly. Corneal injury was reversible, and at 14 days all treated eyes were normal (114).

Application of 2 drops to the eyes of rabbits resulted in slight conjunctival irritation but no corneal damage. Any irritation which occurred disappeared within a few days (103).

Methyl chloroform was tested in the eyes of 6 rabbits. Its level of irritation was rated 14 on a scale of 0 (no irritation) to 110 (severe injury) (30).

Methyl chloroform caused hardly any eye irritation when tested in the Draize rabbit eye test (64).

Human Studies - See Inhalation Section

INHALATION - Inhalation of high concentrations of vapors of methyl chloroform can cause anesthesia ranging from incoordination to death. Cardiac arrhythmias may also occur at these anesthetic concentrations. The effects do not seem to be significantly potentiated by ethanol but additive effects may occur.

Animal Studies - The following LC50s are typical of those that have been reported for laboratory animals.

7-hour LC50 (rats)	=	14,000-14,250 ppm (286)
4-hour LC50 (rats)	=	17,000 ppm (86)
4-hour LC50 (rats)	=	18,400 ppm (93)
3-hour LC50 (rats)	=	18,000 ppm (2)
2-hour ALC (rat)	=	15,000 ppm (25)
2-hour LC50 (rats)	=	20,000 ppm (86)
1-hour LC50 (rats)	=	24,000 ppm (86)
15-min. LC50 (rats)	=	38,000 ppm (20)
10-hour LC50 (mice)	=	13,500 ppm (37)
6-hour LC50 (mice)	=	13,400 ppm (38)
2-hour ALC (mouse)	=	12,000 ppm (58)

Reports of the following nonlethal exposure conditions for several species have been published.

<u>Conc.</u> <u>ppm</u>	<u>Time</u>	<u>Species</u>	<u>Effect</u>
25,000	5 min.	Monkey	Moderate early respiratory depression, no bronchoconstriction, no decreased compliance (8)
18,000	18 min.	Rat	Narcosis (2)
13,500	16 min.	Mouse	ET50 (narcosis) (37)
10,000	6 hrs.	Rat	No effect on serum enzyme levels (25)
10,000	3 hrs.	Rat	Narcosis (2)
8,235	2 hrs	Mouse	Loss of reflexes (58)
8,000	7 hrs.	Rat	Narcosis (2).
7,320	2 hrs.	Mouse	Lateral postion (58)
5,000	1 hr.	Rat	Light narcosis (2)
5,000	15 min.	Rat	EC50 (CNS effects) (20)
3,000	24 hrs.	Rat	Reduced hexobarbital sleeping time; enhanced <u>in vitro</u> hepatic oxidation of hexobarbital as well as demethylation of aminophrine (56)
3,000	4 hrs.	Rat	Failure of unconditioned reflex tests, decrements in conditioned avoidance (55)
1,500	4 hrs.	Rat	No effect on unconditioned reflex tests, no decrements in conditioned avoidance (55)

Acute behavioral and lethal effects of oral ethanol and inhaled methyl chloroform, alone and in combination, were determined in mice. For lethality, ethanol shifted the methyl chloroform concentration effect curve to the left in a parallel manner, with the magnitude of the shift directly related to the dose of ethanol. Combinations of low doses of ethanol and methyl chloroform showed potentiation, while higher doses of ethanol were additive with methyl chloroform (118).

Methyl chloroform inhalation in combination with ingested ethanol did not cause serum enzyme changes in rats nor were histological changes observed following treatment (25).

Human Studies - The American Industrial Hygiene Association, in 1964, published the following table of probable effects of exposure to methyl chloroform vapors. Newer data have confirmed their recommendations, and the low systemic toxicity of the vapors. Anesthesia (slight incoordination) begins for most subjects at 800-1000 ppm of the vapors.

Probable Result of Single Exposure to the Vapors of
1,1,1-Trichloroethane (5)

Exposure Time (min)	Concentration in Air (ppm)	Expected Effect in Humans
5	20,000	Complete incoordination and helplessness (R)
	10,000	Pronounced loss of coordination (R)
	5,000	Definite incoordination (R,M)
	2,000	Disturbance of equilibrium. Odor is unpleasant but tolerable (H)
15	10,000	Pronounced loss of coordination (R)
	2,000	Loss of equilibrium (H)
	1,000	Possible beginning loss of equilibrium (H)
30	20,000	Surgical anesthesia, possible death (R)
	10,000	Pronounced loss of coordination (R)
	5,000	Obvious loss of coordination (R,M)
	2,000	Loss of coordination (H)
	1,000	Very slight loss of equilibrium (H)
	500	No detectable effect, but odor is obvious (R,H)
	100	Apparent Odor threshold (H)

H = Expected effects are based on human data; M = Expected effects are based on monkey data; R = Expected effects are based on rat data.

In conjunction with this effort the AIHA proposed the following emergency exposure limits. Exposure at the stated times and concentrations may cause definite anesthetic effects and incoordination, but no organic injury would be expected and recovery should occur within minutes after being withdrawn from exposure.

Emergency Exposure Limits

<u>Minutes</u>	<u>ppm</u>
5	2,500
15	2,000
30	2,000
60	1,000

A brief summary of several acute human exposure studies is included in the following tabulation. Several individual studies are subsequently discussed in more detail.

<u>Conc. (ppm)</u>	<u>Duration</u>	<u>Results</u>
450	2 x 4 hrs	No impairment in performance or phycho-physiological functions, some eye irritation (57)
450	4 X 8 hrs	Productivity decreased (88)
500	78-186 min	Slight eye irritation in 3/6. Balance and coordination were not affected (101)
506	450 min	Moderate smell which tended to disappear. Examination made before and after exposure found no significant changes in pulse, respiration, blood pressure, reflexes, and equilibrium. Tests for urinary urobilinogen, thymol turbidity, and excretion of bromo-sulphalein did not indicate any significant changes in liver function (103).
546	90 min	No effect other than smell of the chemical (103).
600	3 hrs	No adverse effects (36)
900-1000	20-75 min	Mild eye irritation, lightheadedness, decreased in ability to do simple mental tasks, unpleasant odor, no apparent equilibrium disturbances (101,103)

<u>Conc. (ppm)</u>	<u>Duration</u>	<u>Results</u>
1900	5 min	Very noticeable odor, obvious equilibrium disturbances (103)
2650	15 min	At the end of the exposure 5/7 showing anesthetic effects (101)
10,000-26,000		Complete surgical anesthesia, decrease in blood pressure, irregular heart beat (29)

The effect of methyl chloroform on psychophysiological functions, such as reaction time, perceptual speed and manual dexterity, was studied in 12 healthy, male subjects. Each subject was repeatedly tested during exposure to 250, 350, 450, or 550 ppm of methyl chloroform. Every other minute during the trials, samples were taken of the alveolar air. Very high correlations were obtained for 2 subjects and a linear relation was noted between the concentrations in alveolar air and arterial blood. Subject reaction time, perceptual speed, and manual dexterity were all reportedly impaired during exposure (35).

Twenty adults (humans) of both sexes were exposed repetitively to 1,1,1-trichloroethane vapor concentrations of 0, 100, 350, or 500 ppm for periods of 1, 3, and 7 1/2 hours in a controlled-environment chamber for two purposes: 1) to develop a practical "biologic" test which would indicate the magnitude of an industrial exposure; 2) to monitor the physiological response of healthy adults to different vapor concentrations and durations of exposure. These studies were designed to simulate the type of exposures encountered in the industrial setting and consisted of both steady, non-fluctuating vapor concentrations as well as widely fluctuating vapor concentrations.

Repetitive vapor exposure to the current TLV of 350 ppm produced no untoward subjective or objective health responses in the healthy subjects other than the objection to the solvent's odor by the majority of the female subjects. (184)

Four cases of occupational exposure to methyl chloroform have been reported. The primary effect of their exposure was a functional depression of the central nervous system proportional to the magnitude of exposure. The earliest symptoms were dizziness and lassitude. Recovery was quite rapid (96).

Twelve healthy subjects were exposed for 30 minutes to 250 and 350 ppm of methyl chloroform in air during rest and physical exercise. The concentration of methyl chloroform in the alveolar air and arterial blood was of the same magnitude at an exposure of 350 ppm at rest as at 250 ppm during light exercise (7).

See epidemiology section for more information on human response, 2nd Appendix A for additional related references.

INJECTION - Injection studies have confirmed the low systemic toxicity of methyl chloroform and helped to establish its low metabolism and rapid excretion.

Intraperitoneal - The following LD50s have been reported:

LD50 (mice)	3700 mg/kg (38)
LD50 (mice)	2560 mg/kg (2)
LD50 (rats)	5080 mg/kg (49)
LD50 (dogs)	4140 mg/kg (50)
LD50 (guinea pigs)	7125 mg/kg (117)

Ornithine carbamyl transferase (OCT), an enzyme found predominantly in the liver, is released into the blood stream when liver cells are ruptured. The measure of serum OCT activity is a convenient, specific, and sensitive assay of liver damage. This test was used to evaluate the effect of methyl chloroform on the livers of guinea pigs. Methyl chloroform was administered i.p. to groups of 4 guinea pigs at dose levels of 75, 150, 300, or 600 mg/kg. Serum OCT levels were measured 24 hours later. Methyl chloroform failed to increase serum OCT activity (28).

Mice were administered methyl chloroform by i.p. injection of a corn oil suspension. Twenty-four hours later a blood sample was taken and the serum glutamic pyruvic transaminase (SGPT) activity determined. The 24-hour LD50 was found to be 4936 mg/kg. The dose required to produce a significant SGPT elevation in 50% of the animals within 24 hours was 3336 mg/kg (37).

Hepatic function was determined in mice by sulfobromophthalein (BSP) retention and SGPT activity following the i.p. injection of methyl chloroform. Median effective doses for inducing dysfunction were calculated and compared to the lethal dose. The dose required to cause significant BSP retention and SGPT elevation in 50% of the animals was 2.8 and 2.5 ml/kg, respectively. The LD50 was determined to be 3.8 ml/kg. Histopathological examination revealed an enlargement of hepatocytes with cellular infiltration and vacuolation. Necrosis was slight and was found only in the lethal range. While methyl chloroform was capable of causing liver injury, it is nowhere comparable to that produced by carbon tetrachloride or chloroform. Pretreatment of the mice with alcohol significantly increased the BSP retention (48).

Chlorinated hydrocarbons differ in their capacity to produce liver damage. The comparative effects of carbon tetrachloride, chloroform, methyl chloroform and 1,1,2-trichloroethane were studied in rats. CCl_4 produced the highest increase in hepatic triglycerides. No enhanced hepatic triglyceride level was demonstrated with methyl chloroform. The LD50 for methyl chloroform was determined to be 3.8 ml/kg (49).

Dogs were injected with dichloromethane, chloroform, carbon tetrachloride, methyl chloroform, 1,1,2-trichloroethane, trichloroethylene, and perchloroethylene. Median effective doses for inducing liver and kidney dysfunction were calculated and compared to the lethal dose. Methyl chloroform had an LD50 of 3.1 ml/kg and produced slight liver dysfunction in 50% of the animals at 0.87 ml/kg. No evidence of kidney dysfunction was found. No potentiation of the induced liver function by alcohol could be demonstrated (50).

The acute nephrotoxic property of methyl chloroform was studied in mice, using phenosulfonaphthalein (PSP) excretion, the presence of proteinuria and glucosuria, and histopathology. At a dose of 2.5 ml/kg, one of three mice showed significant urinary protein. However, at a dose of 5 ml/kg, none of three mice showed significant urinary protein. None of the animals showed a significant increase in urinary glucose. Methyl chloroform treatment did not result in necrosis of abnormal renal function. However, it did cause tubular swelling at these high doses (77).

The oral pretreatment of mice with acetone or isopropanol 18 hours before the i.p. administration of a threshold dose of methyl chloroform, failed to increase the hepatotoxicity (104).

Subcutaneous - Methyl chloroform was injected subcutaneously in mice at doses of 5203, 10,406, 13,342, and 16,010 mg/kg. The ability of methyl chloroform to cause liver injury was evaluated by the prolongation of pentobarbital sleeping time. The dose causing liver damage in 50% of the animals was estimated to be 11,207 mg/kg. The LD50 was calculated to be 16,010 mg/kg (78).

Intravenous - A previously described experimental model for studying the effects on the CNS of rabbits, specifically the vestibular apparatus has been applied to methyl chloroform. To achieve a steady concentration the solvent was infused as a lipid emulsion. Vestibular function was studied by recording the involuntary eye movements, nystagmus. At blood levels of methyl chloroform above 75 ppm a so called "positional nystagmus", indicated vestibular disturbances, is demonstrated (57). See Related References, Appendix A for additional information.

EFFECT OF CHRONIC AND EXTENDED EXPOSURES

Studies in which animals have been treated repeatedly with or exposed to methyl chloroform have consistently shown a low chronic toxicity. Liver changes (mild and reversible) have been only observed at frankly anesthetic levels. Methyl chloroform has been consistently shown to be negative in carcinogenic, reproductive, and teratogenic studies.

ORAL INGESTION - Methyl chloroform was fed to rats at a level of 1650 mg/kg daily for 7 days. No effect was seen on growth and the response of the liver was generally unremarkable. The most significant changes were increases in both microsomal and cell-SAP protein concentrations (79).

Groups of 10 rats and 10 mice were administered 1000, 1780, 3160, 5620, or 10,000 mg/kg/day, 5 days/week for 6 weeks. No mortality, signs of toxicity or pathological changes were seen in the animals given 1000, 1780 or 3160 mg/kg/day. At 5620 mg/kg/day, 2 rats died and weight gain in the survivors was reduced. At 10,000 mg/kg, 2 rats died and weight gain was reduced. In the mice, no death, signs of toxicity or pathological changes were seen at any of the doses up to 5620 mg/kg/day. At 10,000 mg/kg/day only 2/10 animals survived. No compound-related pathology was observed in any of the surviving animals sacrificed after 2 weeks of observation and deaths were possibly due to anesthesia from those high dosages (71).

As part of a multigeneration reproduction study, mice were fed water containing methyl chloroform so that daily dosage levels were 0, 99, 2640 or 8520 mg/kg. There were no dose-dependent effects on reproduction, survival or weight gain. Gross necropsy of the F/0 generation failed to reveal compound or dose related effects. (182)

The carcinogenesis bioassay of technical grade* 1,1,1-trichloroethane was conducted using Osborne-Mendel rats and B6C3F1 mice. 1,1,1-Trichloroethane was administered orally by gavage in corn oil to 50 animals of each sex and species at two dose levels 5 days/week for 78 weeks. The experiment was originally started with rats using doses of 3,000 and 1,500 mg/kg of body weight. After a few weeks the study was terminated, and the animals discarded because of marked signs of intoxication. The experiment was re-started with rats 7 weeks of age that were put on doses of 1500 and 750 mg/kg. There was a moderate depression of body weight in the first year of the study. During the second year, a yellow discoloration of the fur of the lower abdomen and increased eye and nasal discharge and dyspnea were noted. Both males and females given the test chemical exhibited early mortality when compared with the untreated controls, and the statistical test for dose-related trend was significant ($P < 0.04$). All surviving animals were killed at 117 weeks of age (71).

Male and female weanling mice were started on test at 5 weeks of age and killed at 96 weeks of age. Initially, the doses for male and female mice were 4000 and 2000 mg/kg body weight. During the 10th week of study, doses were increased to 5000 and 2500 mg/kg, since the animals apparently could tolerate a higher dose. Doses were again increased at week 20 to 6000 and 3000 mg/kg and maintained at these levels to the end of the study. Time-weighted-average doses for the high-and low-dose mice were 5615 and 2807 mg/kg, respectively. There was a moderate depression of body weight throughout the study in both sexes of mice and the survival was significantly decreased. In the female mice, there was a positive dose-related trend ($p = 0.002$) in the proportions surviving.

A variety of neoplasms were represented in both 1,1,1-trichloroethane-treated and matched-control rats and mice. However, each type of neoplasm has been encountered previously as a lesion in untreated rats or mice. The neoplasms observed are not believed attributable to 1,1,1-trichloroethane exposure, since no relationship was established between the dosage

* Contained 3% p-dioxane as a stabilizer

groups, the species, sex, type of neoplasm, or the site of occurrence. Even if such a relationship were inferred, it would be inappropriate to make an assessment of carcinogenicity of 1,1,1-trichloroethane on the basis of this test, because of the abbreviated life spans of both the rat and the mice (71).

SKIN CONTACT - Daily dosages of 500 mg or less per kg of body weight, 5 days/week for 90 days caused no adverse effect in rabbits. Skin at the site of repeated application showed slight, reversible irritation (103).

INHALATION - Inhalation studies are listed according to increasing duration of exposure.

Animal Studies - Rabbits were repeatedly exposed for 4 hours to 5000 ppm of methyl chloroform. Determination by the glutamic oxolacetic and glutamic pyruvic transaminases and ornithine carbamyl transferase concentrations in their blood showed no significant changes indicative of liver injury (108).

A group of 10 rats was exposed to 500 ppm, 6 hours/day for 4 days. This exposure caused an accumulation of the solvent in perirenal fat. This accumulation could be demonstrated 17 hours after the exposure. The behavior of the rats did not differ significantly from that of the controls after the 4-day exposure (90, 115).

A group of 9 guineapigs was exposed 7 hours/day to 3000 ppm 20 times in a 29-day period. The animals showed a definite retardation of growth throughout the experimental period. Both the average final body weights and the average gains in weight of the exposed groups were significantly less than those of the control groups. Along with this body weight response, the exposed guinea pigs showed definite, although slight, central fatty degeneration of the liver. In frozen sections stained with oil red O, many small, distinct, brilliantly stained globules were observed in the

central zone of each lobule. No other ill effects occurred in these animals as judged by organ weights, blood urea nitrogen concentrations or the results of histopathologic examinations (2).

Two rabbits were exposed 7 hours/day during 31 days in a 44-day period to 5000 ppm of methyl chloroform. The exposed animals showed slight retardation of growth; however, no discernible ill effects were observed on gross and microscopic examination of tissues (2).

A group of 10 rats was exposed 7 hours/day to 5000 ppm. During the course of the experiment 2 males of the exposed groups and 2 of the control group were lost because of acute pulmonary infection; all of the survivors in the exposed groups received 31 exposures in 44 days. The rats showed slight unsteadiness and lethargy when removed from the chamber. The female but not the male rats showed slight retardation of growth during the first two weeks of the experiment; however, the gain in weight of both sexes over the entire experimental period was almost as good as that of the controls. These exposed rats, as judged by organ weights, blood urea nitrogen values, and the results of histopathological examinations, suffered no ill effects (2).

A group of 10 guinea pigs was exposed 7 hours/day for a total of 32 exposures in a 45-day period to 5000 ppm. The exposed animals lost weight during the first 3 weeks of the experiment, then gained slowly, with a final weight increase of 6 and 19 percent for the females and males, respectively, compared with 39 and 38 percent for the controls. All the exposed guinea pigs showed slight to moderate central fatty degeneration of the liver; however, no necrosis was observed. The males also showed varying degrees of testicular degeneration probably due to failure to eat and loss of weight. No histopathologic changes were observed in the kidney or other organs examined. The blood concentration of urea nitrogen was 25.9 mg/dl in the exposed guinea pigs, compared with 28.6 mg in the controls (2).

A group of 15 rats, 15 guinea pigs, 3 monkeys, 3 rabbits, and 2 dogs was exposed to 2220 ppm of methyl chloroform for 8 hours/day, 5 days/week for 6 weeks. None of the animals died and no signs of toxicity were noted. Rabbits and dogs showed a body weight loss. Gross and histopathologic examination did not reveal any abnormalities (80).

A group of 20 guinea pigs (12 males, 8 females) was subjected to 44 exposures for 7 hours each in a 60-day period at 1500 ppm. Both the males and females showed some retardation of growth, especially at the start of the experiment. Except for this body weight response, no demonstrable toxic effects as determined by studies of organ weights and histopathological examination were observed (2).

A group of 13 rats was subjected to 47 or 48 repeated 7-hour exposures in a 66- or 67-day period at a concentration of 3000 ppm. The exposed rats and the controls grew equally well throughout the experimental period, and no discernible ill effects occurred in these animals as judged by final body weights, organ weights, blood concentrations of urea nitrogen and the results of histopathologic examinations (2).

A single female monkey was exposed 53 times, 7 hours/day to 3000 ppm in a 74-day period. Throughout this experimental period the monkey appeared to be in excellent condition and gained weight normally. At the end of the experiment no pathological changes were observed on gross and microscopic examination of the following organs: lung, heart, liver, kidney, spleen, adrenal gland, pancreas, lymph nodes, stomach, small and large intestine, bladder, thyroid gland, and voluntary muscle (2).

Mice were exposed to either 250 ppm or 1000 ppm in air continuously, 24 hours/day for 14 weeks. Significant changes in the liver were seen in the 1000 ppm group. Mild to minimal changes were seen in the 250 ppm group (66).

Rats were exposed for 5-6 hours/day, 5 days/week during 15 weeks to 1100 ml/m^3 (approximately 270 ppm). Incorporation of thymidine- ^3H into liver DNA increased by 67% after 4 exposures and subsequently leveled off to control values. Histological examination revealed no changes (107).

Groups of 5 guinea pigs were exposed to 2000 ppm for 30, 12, 6 or 3 minutes/day, 5 days/week for 3 months. Animals exposed for 30 minutes/day showed signs of lung irritation and fatty changes in the liver. Animals exposed 12 minutes/day showed microscopic evidence of interstitial inflammation of the lungs (103).

Separate groups of 5 female guinea pigs were exposed to 1000 ppm for 3.0, 1.2, 0.6 or 0.3 hours/day, 5 days/week for 3 months. Animals exposed 3.0 hours/day showed evidence of inflammation in the lungs and changes in the liver. Animals exposed 1.2 hours/day showed microscopic evidence of inflammation of the lungs (103).

Two groups of 15 rats, 15 guinea pigs, 3 monkeys, 3 rabbits, and 2 dogs were exposed continuously to either 379 or 139 ppm of methyl chloroform for 90 days. At 379 ppm, none of the animals died and no toxic signs were noted. There was less body weight gain in the dogs and rabbits than in control animals. Gross and histopathologic examination did not reveal any abnormalities. Microscopic examination of tissue showed nonspecific inflammatory changes in the lungs of all species. At 139 ppm 2/15 rats died on days 27 and 77, and 1/3 rabbits died on day 38; the survivors exhibited no toxic signs. Body weight patterns were normal. Varying degrees of lung congestion and pneumonitis were noted in all species and in a number of the controls. Because of this pneumonitis, no positive conclusion could be drawn as to whether the effects were associated with the exposure (80).

A group of 19 guinea pigs (9 males, 10 females) was subjected to 65-66 7-hour exposures in a 92-93 day period at a concentration of 650 ppm. The control groups of 10 animals of each sex were repeatedly exposed to air in a manner similar to that followed with the trichloroethane-exposed guinea pigs. In a second experiment, groups of 8 male and 6 female guinea

pigs were subjected to 40-41 exposures of 7 hours each in 57 to 58 days; in this case both air-exposed and unexposed controls were used. In all cases the guinea pigs exposed to trichloroethane showed only a depression of growth similar to that observed in the guinea pigs exposed to 1500 ppm (2).

Groups of mice were exposed continuously 24 hours/day for 100 days to either 245 or 992 ppm of methyl chloroform. The low level of exposure had no effect on the liver whereas the high level exposure caused an increase in liver weight and elevation of liver triglycerides (62).

Exposure of rats or cats to 73 ppm of methyl chloroform, 4 hours/day during 4 months did not effect the aminotransferase activity, erythrocyte and leukocyte numbers of the hemoglobin level in the blood. Some reversible dystrophic changes in the liver, kidneys, myocardium and lungs were observed (109).

Groups of 5 rats exposed to 10,000 ppm for 1.0, 0.5, 0.2, 0.1 or 0.05 hours/day, 5 days/week for 6 months showed various degrees of anesthesia ranging from ataxia to semiconsciousness. The only evidence of organic injury was a barely significant increase in the liver weights or rats exposed for one hour/day (103).

Groups of 20 female rats, 8 guinea pigs of each sex, 2 rabbits of each sex, and 2 female monkeys were exposed to 500 ppm, 7 hours/day, 5 days/week for 6 months. Growth, general appearance, and mortality records showed no evidence of adverse effects when compared to the controls. Hematological values were within normal limits. Gross and microscopic pathological examination showed no significant differences between the exposed and control animals (103).

Gerbils were exposed to 320 ppm of trichloroethylene ($\text{CHCl}=\text{CCl}_2$) for 9 months. Eleven days after the end of the trichloroethylene exposure the animals were exposed to 2300 ppm of methyl chloroform for 6 hours. This treatment was repeated every other day with behavioral changes identified

by placing the gerbils in a symmetrical maze. This test was repeated again 75 days after the trichloroethylene exposure. Trichloroethylene pre-exposed animals made more correct choices in the maze on days of exposure to methyl chloroform than on days when not exposed. These data were discussed in conjunction with clinical solvent testing. Thus the feeling that a discrepancy exists between results from the clinical testing (under well controlled and stress-free conditions) of subjects thought to be adversely affected by solvents and their actual life situation, where feedback reactions between alcohol, stress, and psychosocial factors could easily develop, might have an explanation in the presented findings (47).

In a lifetime study, groups of 200 rats were exposed to 875 or 1750 ppm, 6 hours/day, 5 days/week for 12 months, and then observed until their natural death or until they reached the age of 31 months. Total tumor incidence, listed below, in the treated animals was similar to that of untreated concurrent controls.

	<u>No. Animals</u>		<u>Total Neoplasms/Animal</u>	
	<u>Male</u>	<u>Female</u>	<u>Male</u>	<u>Female</u>
Control	189	189	1.06	2.97
875 ppm	91	92	0.85	2.67
1750 ppm	93	93	1.11	3.23

No increase in tumor type was observed which was related to exposure (113).

Human Studies - Anesthesia (incoordination) but no significant organic injury has been demonstrated on excessive exposure to methyl chloroform vapors greater than 800-1000 ppm).

Eleven human subjects were experimentally exposed to 500 ppm of methyl chloroform for periods of 6.5 to 7 hours/day for 5 days. The subjective untoward responses reported were mild, inconsistently present, and of doubtful clinical significance. The only adverse objective response was an abnormal modified "Romberg's test" observed in two of the subjects during exposure. No clinical laboratory test performed during or following the vapor exposures revealed any abnormality or organ function (97).

Twenty adults of both sexes were exposed repetitively to 1,1,1-trichloroethane vapor concentrations of 0, 100, 350 or 500 ppm for periods of 1, 3, and 7 1/2 hours in a controlled-environment chamber for two purposes: 1) to develop a practical "biologic" test which would indicate the magnitude of an industrial exposure; 2) to monitor the physiological response of healthy adults to different vapor concentrations and durations of exposure. These studies were designed to simulate the type of exposures encountered in the industrial setting and consisted of both steady, nonfluctuating vapor concentrations, as well as widely fluctuating vapor concentrations.

Repetitive vapor exposure to the current TLV of 350 ppm produced no untoward subjective or objective health responses in healthy subjects other than the objection to the solvent's odor by the majority of the female subjects. See Metabolism/Pharmacokinetic and Biochemical Studies for more details (184).

CARCINOGENIC POTENTIAL - Two carcinogenic studies in animals have been negative. The neoplasms observed in a long-term feeding study were not attributable to 1,1,1-trichloroethane, since no relationship was established between the dosage groups, the species, sex, type of neoplasm, or the site of occurrence (71). The details of the study are presented in the section on Chronic and Extended Studies.

No significant increase in the incidence of tumors was seen in a long-term lifetime inhalation study in rats (113). The details of this study are presented in the section on Chronic and Extended Studies.

NCI has a second 2-year oral bioassay in rats and mice underway. The animals will be sacrificed in May 1981. Lifetime inhalation studies are also underway.

MUTAGENIC POTENTIAL - Because many samples of methyl chloroform used for mutagenic testing have subsequently been shown to contain an epoxide stabilizer, caution is necessary in interpreting the results of these studies. When the sample has been known to contain no epoxy inhibitor, the results have been negative.

Methyl chloroform was included in a series of 42 chemicals by 65 investigators in a National Toxicology Testing Program. Twenty-nine tests were included: 9 bacterial, 5 fungal, 8 mammalian, 5 in vivo, and 2 miscellaneous. Methyl chloroform was classified as noncarcinogenic (179).

Uninhibited methyl chloroform was found nonmutagenic in S. typhimurium TA100 with and without induced rat liver microsomes. (42)

Methyl chloroform and methylene chloride were reported to be weakly positive when studied in vitro to determine their transforming potential in a Fischer rat embryo cell system (81). However, when the principle investigator, Dr. Paul Price, attempted to repeat the work he could not do so with a fresh cell line and a higher purity methylene chloride. Furthermore, using the sample previously thought to cause a positive test, he was unable to do so (180). A second attempt to duplicate Price's results was also negative and it has been concluded that the cell lines used by Price were too old to be useful (187).

Methyl chloroform was found negative in mutagenicity tests with yeast Saccharomyces cerevisiae (181).

Methyl chloroform was mutagenic to Salmonella typhimurium strains TA 1535 and TA 100 when incubated within a desiccator in the presence of a beaker containing the solvent. When incubated in the standard plate-incorporation method of Ames, methyl chloroform was not mutagenic (Epoxy stabilizer was present in these studies). (74)

Methyl chloroform was weakly mutagenic in the Ames test both in the presence and absence of an activation system (Epoxy stabilizer was present). (94)

Methyl chloroform was mutagenic in Salmonella strains TA 1535 and TA 1537 (equivocal) but not in TA 1538 (Epoxy stabilizer was present). (113)

Methyl chloroform was not mutagenic when tested in a host--mediate bioassay in mice (60, 112) or in the multigeneration study described in the next section (182).

EMBRYOTOXIC AND REPRODUCTIVE STUDIES - Teratogenic and reproductive studies in animals have been consistently negative.

Groups of pregnant rats and mice were exposed to 875 ppm of methyl chloroform, 7 hours/day on days 6-15 gestation. No significant maternal, embryonal, fetal toxic or teratogenic effects were seen (91).

Female Long-Evans rats were exposed repeatedly to 2100+200 ppm of methyl chloroform vapors 2 weeks before breeding and until day 20 of gestation without effect on teratogenicity or subsequent neurobehavioral studies of the offspring allowed to deliver normally (185).

A multigeneration reproduction study was modified to include screening for dominant lethal and teratogenic effects. Mice were fed water containing methyl chloroform so that daily dosage levels were 0, 99.4, 2640 or 8520 mg/kg. According to the authors "There appeared to be no dose-dependent effects on fertility, gestation, viability, or lactation indices. Pup survival and weight gain were not adversely affected. Gross necropsy of male and female F/O generation mice treated with 1,1,1-TCE failed to reveal compound or dose-related effects" (182).

INDUSTRIAL EXPERIENCE

Single Exposure - More than 30 fatalities have been associated with methyl chloroform, mostly due to deliberate inhalation or to accidental occupational exposures in confined spaces. Deaths have been due to anesthesia and/or cardiac arrhythmias (13,17,95).

Deaths have resulted from abuse or gross misuse of an aerosol decongestant containing methyl chloroform (6).

Three cases are reported of acute intoxication due to a solvent containing mostly methyl chloroform (76).

Four workmen entered an underground vault and proceeded to remove grease from conduits with rags dipped into methyl chloroform. Three of the men experienced symptoms of giddiness and lightheadedness emerged into fresh air. The fourth also left the vault but returned shortly thereafter. Upon leaving the vault a second time he collapsed and stopped breathing. Toxicological analysis showed excessive concentrations of methyl chloroform in the blood, kidney, brain, and liver (51).

Methyl chloroform possesses anesthetic and pulmonary irritating properties. Two cases are presented in which death occurred secondary to its abuse. The mechanisms involved were chemical pneumonia and respiratory arrest, respectively. This report is unique in that it reports that methyl chloroform causes lung irritation. A method is described for detection of trichloroethanol in the blood (41).

In a twenty-year-old apprentice mechanic who had deliberately inhaled methyl chloroform, an episode of vomiting was followed by ventricular fibrillation with a fatal outcome despite intensive care in a hospital. Autopsy revealed no anatomical cause of death (39).

Methyl chloroform was indicated in the accidental death of a woman cleaning up a paint spill in an enclosed, poorly ventilated room. Blood and tissue concentrations of methyl chloroform were compared with levels found in previous fatal cases. It was concluded that the demonstrable presence of methyl chloroform in blood at a concentration above 1.0 to 1.5 mg/100 ml would be consistent with death (17).

A death associated with inhalation abuse of methyl chloroform cleaning fluid by an 18-year-old sailor is reported (105).

Twenty-two female subjects working in a factory in which 1,1,1-trichloroethane was the only solvent used were investigated by means of clinical, neurophysiological and psychometric methods so that the neurotoxicity of the solvent could be evaluated. On the basis of the ambient air concentrations of 1,1,1-trichloroethane ranging from 110 to 990 ppm, the workers

were divided into three risk groups and compared with a reference group. No significant difference was observed between the exposed and unexposed females with respect to clinical features, maximal motor conduction velocity, conduction velocity of slow fibers, and psychometric data. The most frequent complaints of the workers were of the "neurotic" type with a slightly higher, but not significant, difference in the exposed group. The results obtained favor the absence of a manifest neurotoxic effect of 1,1,1-trichloroethane under the specific work conditions of the investigation; generally unfavorable work conditions seem to have played a prominent role in the genesis of the neurotic complaints. The importance of a global methodological approach in the study of work-related risks, particularly in neurological and psychological surveys is stressed (63).

Epidemiological Studies - A study of 151 matched pairs of employees was conducted in two adjacent textile plants, one of which was inhibited 1,1,1-trichloroethane as a general cleaning solvent. Employees in the study population had exposures to the solvent for 6 years or less at varying concentrations which were measured by breathing zone sampling, and personal monitoring.

While cardiovascular and hepatic observations were of primary interest, other health parameters were also studied. Application of sensitive statistical techniques and careful examination of all data did not reveal any clinically pertinent findings that were associated with exposure to 1,1,1-trichloroethane (52).

METABOLISM, PHARMACOKINETIC, AND BIOCHEMICAL STUDIES - Methyl chloroform is absorbed from the lungs, GI tract, and, to a limited degree, through the skin. Most is excreted rapidly unchanged in expired air with only a few percent metabolized in man to trichloroethanol and trichloroacetic acid which have been found in the urine. A limited amount appears to be metabolized to carbon dioxide, but the quantity is small. Being lipophilic, it is preferentially absorbed in the fat, but even this is excreted rapidly when exposure ceases.

Animal Studies - In acute and subacute studies rats were exposed to methyl chloroform. In the acute exposures, groups of 20 rats were exposed to 220 and 440 ppm. In the subacute exposure one group of 20 rats was exposed 8 hours/day, 5 days/week for 14 weeks to 204 ppm. The rats were placed in metabolic cages after exposure. No toxic symptoms were seen. The concentrations of methyl chloroform and trichloroethanol in the blood and the concentration of trichloroacetic acid in the urine remained constant. The urinary trichloroethanol excretion increased until the 10th week, then it fell and remained constant at a level somewhat below the maximum concentration. Methyl chloroform was not detectable in organ tissue (31).

After intraperitoneal injection into the rat, methyl chloroform labeled with ^{14}C was rapidly and almost totally excreted via the respiratory system. When doses of near 700 mg/kg were given to 3 rats, 98.7% of the dose could be accounted for as unchanged methyl chloroform in the expired air. One-half of one percent was converted to CO_2 , while much of the remainder appeared as the glucuronide of 2,2,2-trichloroethanol in the urine (40).

Groups of 6 rats were exposed to 200 ppm of methyl chloroform for 8 hours. Analyses of their urine revealed small amounts of trichloroacetic acid and trichloroethanol. When the compound was administered by i.p. injection (371 mg/kg) the results were essentially the same as those obtained from inhalation experiments. The low metabolite levels are in accordance with the observation that methyl chloroform is almost completely excreted in the expired air (46).

The maximum concentration of methyl chloroform in expired air following the i.p. injection into rats of 200 mg/kg was observed at 10-20 minutes and decreased thereafter with a half-life of 60 minutes. The total amount excreted by respiration was about 90% of the given dose in hours. Fat contained >10 times the methyl chloroform of any other tissue (4).

Groups of mice were exposed to 10 and 100 ppm from 30 minutes to 24 hours and to 1000, 5000, or 10,000 ppm for up to 6 hours. Concentrations of methyl chloroform in the blood, liver, kidney, and brain were determined. There was fairly good correlation between the inspired air concentration and the tissue concentrations at different exposure times. A pharmacokinetic model with both uptake and elimination of the first-order fitted the empirical data better than a model with zero-order uptake and first-order elimination (44).

Methyl chloroform is dechlorinated only to a very small extent and is excreted mainly unchanged via the lungs. However, trichloroethanol and, to a smaller extent, trichloroacetic acid may be recovered in the urine of both rodents and man (18). The occurrence of a toxic metabolite is indicated by the fact that the induction of cytochrome P-450 in the rat with phenobarbital increases and hepatotoxic effect of methyl chloroform (18).

The pharmacokinetics of inhaled methyl chloroform in the rats and mice has been studied following single exposure and after 16 months repeated daily exposures. Following single 6-hour inhalation exposure to 150 or 1500 ppm mice and rats excreted 87 and 97% (mice) and 94 and 98% (rats). The material exhaled was essentially all unchanged methyl chloroform with the remaining radioactivity found in exhaled $^{14}\text{CO}_2$ or as metabolites in the urine. The mouse metabolized 2.7 and 1.7 times as much per kg body weight as the rat at 150 and 1500 ppm, respectively indicating saturation of metabolism by the tenfold increase in exposure concentration. Similar results were obtained when rats and mice which had been repeatedly exposed for 16 months were given single inhalation exposures to 1500 ppm ^{14}C -methyl chloroform. When compared to sham exposed controls no significant differences were observed in the various routes of excretion or in tissue distribution of radioactivity. Old rats and mice metabolized more than younger animals. Repeated exposure to methyl chloroform did not significantly induce its own metabolism (113,183).

Methyl chloroform was not dechlorinated by a microsomal enzyme system (116).

The in vitro activity of liver microsomal enzymes to metabolize some aromatic and chlorinated hydrocarbons was enhanced remarkably in fasted rats of both sexes, although fasting produced no significant increase in the microsomal protein and cytochrome P-450 contents (70).

Twenty-three chemicals, differing widely in cytotoxic and hepatotoxic potency in vivo, were tested to determine their ability to release glutamic oxaloacetic transaminase (GOT) from hepatocytes isolated by a nonperfusion method from rat liver. In all but 2 cases, thioacetamide and allyl alcohol, there was a good correspondence between chemicals active in the assay and those that elevate serum transaminase and cause liver injury on short-term exposure in vivo (111). Also, see related references 177 and 178.

See related references 145 to 160 for additional data.

Human Studies - Five male volunteers were exposed to 500 ppm of methyl chloroform, 7 hours/day for 5 consecutive days. Twenty-four hour urine collections obtained before, during and following these vapor exposures were analyzed for trichloroethanol (TCE) and trichloroacetic acid (TCA). These data are presented as follow:

<u>Exposure</u>	<u>TCA</u> <u>(mg/24-hr)</u>	<u>TCE</u> <u>(mg/24-hr)</u>
1st day	7.5 (2.6-10.5)	20.1 (7.9-49)
2nd day	10.9 (8.3-19.3)	30.1 (14.8-66.5)
3rd day	12.3 (5.6-27)	29.3 (19.1-51)
4th day	14.1 (7.8-19.2)	46.6 (23.4-93.6)
5th day following last exp.	18 (13-26)	7 (1-14.9)
12th day following last exp.	17.5 (8-22)	<1 (<1.0)

Human males were exposed for 8 hours to 72 or 213 ppm. The absorption rate changed continuously with a retention rate between 26-32%. Pulmonary elimination over a period of 8 days was approximately 90%. Urinary excretion of the metabolites, trichloroacetic acid and trichloroethanol, was slow and lasted about 12 days (68).

A group of 6 human volunteers was exposed for 4 hours to 70 and 145 ppm while at rest. Additionally, they were exposed to 142 ppm combined with a 100 watt workload. Minute volume and concentration in exhaled air were measured to estimate the uptake of methyl chloroform under these conditions. Methyl chloroform and its metabolites trichloroethanol and trichloroacetic acid were determined in the blood, exhaled air, and urine. The uptake/minute decreased in the course of exposure to 30% of the initial uptake. The total uptake was more influenced by minute volume than by body weight or amount of adipose tissue. During the workload, the uptake increased to 2.3-fold and the minute volume to threefold the value at rest. In the post-exposure period, the quotients of the concentrations in blood and in exhaled air for methyl chloroform and trichloroethanol remained nearly constant at 8.2 and 14,000, respectively. Following exposure about 60-80% of the amount taken up was excreted unchanged by the lungs, while 70 hours after exposure the amount of TCE and TCA excreted in the urine represented about 2% and 0.5% of the uptake (67). Because of the small partition coefficient between blood and air and insignificant metabolism, the capacity of the body to absorb methyl chloroform is relatively small and in consequence the uptake/minute decrease fast in the course of exposure (45).

A survey was carried out in 4 itaglio printing factories where methyl chloroform, the sole organic solvent in the entire process, was employed to remove excess ink. The medical interview and clinicolaboratory examinations revealed no-dose-consistent adverse effects among the 4 groups of workers who had been exposed at the average concentrations of 4, 25, 28, or 53 ppm, respectively. A linear relationship was observed between

environmental vapor concentrations and total trichlor-compound levels in the urine of workers exposed. Increased levels of urinary metabolites towards the weekend, together with the biological half-life of 8.7 hours as measured from the decrease in the urinary metabolites, suggested the storage of methyl chloroform in the body after repeated exposures (92).

Methyl chloroform was applied to the skin 11 times a day, 10 minutes/exposure, for 5 consecutive days. It caused the urinary excretion of trichloroethanol at 2-6 mg/kg on the first day and 10-20 mg/day on the fifth day. The urinary excretion of trichloroacetic acid was slightly increased. In the expired air, methyl chloroform was found 30-60 minutes after application and the concentration reached 3-7 ppm after 2 hours. Dipping hands into methyl chloroform solutions, 7 times/day for 4 days also caused the urinary excretion of trichloroethanol at 5-15 mg/day and methyl chloroform concentrations in the expired air ranged from 5 ppm to 11 ppm (34).

Experiments are described in which a range of halogenated hydrocarbons, labeled with radioactive chlorine-38, were administered to volunteer subjects in a single breath. The excretion of absorbed material in breath was followed for an hour after administration. The compounds excreted most rapidly in breath were FC-113 and methyl chloroform (69).

CARDIAC EFFECTS - Cardiac arrhythmias have been produced in experimental animals exposed and human subjects (surgical patients) exposed to several percent methyl chloroform vapors. The nature of deaths reported in humans at this high concentration is consistent with either anesthesia and cardiac fibrillation. Injected adrenaline markedly enhances the effect in animals.

Animal Studies - The ability of methyl chloroform to produce cardiac arrhythmias was studied in beagle dogs. The dogs were exposed to the chemical by means of a face mask. During the last 10 seconds of the 5-minute exposure period a bolus injection of adrenaline was given via a

cephalic vein and the ECG changes were recorded. Methyl chloroform was shown to product cardiac arrhythmias in 50% of the dogs at 7500 ppm following the adrenaline injection.

The EC50 was reported to be 7000 ppm when dogs were exposed for five minutes and injected with epinephrine (20).

The potential of methyl chloroform to elicit cardiac arrhythmia and depression of myocardial contractility was studied in the monkey, dog, and mouse. In the monkey and mouse, methyl chloroform concentrations of 50,000 ppm and 400,000 ppm, respectively, were necessary to induce cardiac arrhythmia. In mice administered exogeneous epinephrine a concentration of 400,000 was also necessary to produce an arrhythmia. Tachycardia was seen in anesthetized monkeys exposed to 50,000 ppm. Myocardial depression was observed in monkeys exposed to 25,000 ppm and in dogs at 50,000 ppm. Monkeys experienced hypotension after exposure to 25,000 ppm. Based on these data methyl chloroform was compared to FC-11 and methylene chloride in its effect on the cardiac system (3,9,10,12,14).

The intratracheal administration of 0.1 ml/kg followed in 15 seconds by the intravenous administration of epinephrine-HCl produced ventricular fibrillation in dogs. Pretreatment with 10 mg of d-pronethalol per kg caused a positive chronotropic response and an elevation of systemic blood pressure without fibrillation (61).

Dogs with experimentally-induced myocardial infarctions were used to determine whether this type of heart condition might significantly lower the threshold for cardiac sensitization. The dogs were subjected to the standard cardiac sensitization test, in which the test animal receives a control injection of epinephrine intravenously 5 minutes prior to exposure and an epinephrine challenge after breathing the test material for 5 minutes. Methyl chloroform showed no greater potential for cardiac sensitization among dogs having recovered from myocardial infarction as compared to normal, healthy dogs (106).

Anesthetized rabbits were given 1.5-minute inhalation exposures to 50,000 ppm of methyl chloroform. Peak left ventricular systolic pressure, and cardiac output were depressed by exposure and were not accompanied by significant changes in heart rate or left ventricular end-diastolic pressure. As a cardiac depressant, methyl chloroform appears to be as potent as Freon® 11 or halothane (102).

Acute exposure of anesthetized dogs to methyl chloroform produced a dose-dependent biphasic decrease in arterial pressure similar to that observed after exposure to a commercial solvent containing methyl chloroform. The initial phase of pressure decrease was associated with peripheral vasodilation whose magnitude exceeded concomitant, reflex, positive chronotropic and inotropic effects on myocardial function. The second phase of pressure decline was primarily associated with a depression of myocardial function; heart rate, stroke output and myocardial contractility decline (43).

Studies conducted on dogs and monkeys anesthetized with methyl chloroform revealed no significant change in electrocardiogram during 60 minutes of deep surgical anesthesia. However, a depressor response upon the blood pressure was observed. At the point of respiratory arrest, the blood pressure was reduced to approximately one-half of its normal value (53).

Attempts to induce anesthesia in 2 dogs without premedication led to sudden death, presumably cardiac in origin. In 5 dogs under barbital anesthesia, epinephrine was injected after administration of repeated small doses of methyl chloroform. Ventricular extrasystoles and ventricular tachycardia were produced in all animals. Maximum sensitization of the heart to epinephrine occurred after the administration of 0.25 to 0.4 cc/kg of methyl chloroform (84).

Experiments were designed to assess the cardiac sensitizing potential of Scotchgard Brand Fabric Protector FC-4101 which contains methyl chloroform. Beagle dogs were observed for possible effects of inhalation

exposure to FC-4101, alone or in combination with intravenous epinephrine and/or stress induced by a 2-second blast from an airhorn. A mild tachycardia followed exposure to FC-4101 producing a concentration of 50000 ppm methyl chloroform. Inhalation of FC-4101 did not act synergistically with exogenous epinephrine or endogenous epinephrine released in response to stress to induce cardiac arrhythmias (32).

See related references 173-176 for additional data.

TOXICITY OF THERMAL DECOMPOSITION PRODUCTS - Hydrochloric acid (HCl) is by far the major breakdown product during welding. Only limited amounts of phosgene are formed.

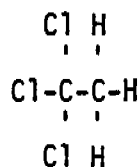
The formation of phosgene caused by short wave radiation from metal-inert gas welding in air contaminated with methyl chloroform was studied. Methyl chloroform concentrations ranged from 10 to 178 ppm. The welding time ranged from 10 to 60 seconds and 3 types of electrodes were used; carbon steel, stainless steel; and aluminum. Phosgene levels ranged from 8.4 ppb to 1.15 ppm (27).

The decomposition of methyl chloroform was studied at temperatures in the range 295-670F. The major decomposition product was always HCl with much smaller amounts of phosgene (26).

Methyl chloroform vapors were included in a series of materials studied in various types of welding. Methyl chloroform appears to be quite stable in the welding environment. Hydrogen chloride and chlorine were produced in low concentrations and these may act as a warning against overexposure to solvent decomposition products. Phosgene formation during gas tungsten arc welding will not present a hazard because the phosgene concentration is not likely to exceed its TLV in "open" welding. Gas metal arc and coated rod arc welding did not lead to detectable amounts of phosgene from methyl chloroform (186).

PHYSICAL CHEMICAL PROPERTIES

<u>Common Name</u>	Methyl Chloroform ¹
<u>Chemical Name</u>	1,1,1-Trichloroethane
<u>Synonyms</u>	CHLOROTHENE* Nu, CHLOROTHENE SM, CHLOROTHENE VG, and AEROTHENE* TT
<u>CAS Registry No.</u>	71-55-6
<u>Chemical Structure</u>	



Occupational Exposure Standards

TLV = 350 ppm (8-hour TWA) (1)
 STEL = 450 ppm (15-min. TWA) (1)
 OSHA = 350 ppm (8-hour TWA) (21)
 NIOSH = 350 ppm (15-min. TWA) (75)

Physical Properties (11)

Description:	Nonflammable colorless liquid
Molecular Weight	133.4
Boiling Point	74.1C at 760 mm Hg
Freezing Point	-32.5C
Density	1.336 g/cc at 25C
Vapor Pressure	103 mm Hg at 20C 125 mm Hg at 25C 144 mm Hg at 30C
Flash Point/Flammability	Nonflammable ²
Explosive Limits	8-10.5% (72) 10-15.5%
Solubility	Insoluble in water (0.03 g/100 g) Soluble in alcohol, ether and most organic solvents
Water/Air partition	
Coefficient: (Approx)	0.93 (89)
Blood/Air Partition	
Coefficient: (Approx)	3.3 (89 4-4.5 (113)
Odor Threshold	100 ppm - Detectable (5) 500 ppm - Definitely Noticeable (5) 1500 ppm - Objectionable (5) 2000 ppm - Strong but Tolerable (5)

Conversion Factors 1 mg/l = 183 ppm volume/volume
 1 ppm = 5.46 mg/m³

* Trademark of The Dow Chemical Company, Midland, MI 48640 U.S.A.

¹ Methyl chloroform is stablized to prevent corrosion of metal parts.

² The flammable characteristics of methyl chloroform are similar to those of trichloroethylene. It has no flash point or fire point by ASTM procedures for Tag closed cup and Cleveland open cup tests. Limits of flammability of vapors of inhibited 1,1,1-trichloroethane have been found to be 10 to 15.5% in air with hot wire ignition. A considerable amount of energy is required for ignition. It will not sustain combustion.

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