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Health Assessment Document for 1,1,1-Trichloroethane (Methyl Chloroform)

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HEALTH ASSESSMENT DOCUMENT FOR 1,1,1-TRICHLOROETHANE (METHYL CHLOROFORM)

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U.S. Environmental Protection Agency

PREFACE

The Office of Health and Environmental Assessment, in consultation with an Agency work group, has prepared this health assessment to serve as a "source document" for Agency-wide use. Originally the health assessment was developed for use by the Office of Air Quality Planning and Standards, however, at the request of the Agency Work Group on Solvents, the assessment scope was expanded to address multimedia aspects. This assessment will help insure consistency in the Agency's consideration of the relevant scientific health data associated with methyl chloroform.

In the development of the assessment document, the scientific literature has been inventoried, key studies have been evaluated and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses are placed in perspective with observed environmental levels.

TABLE OF CONTENTS

		Page
LIST OF TABLES		vii
LIST OF FIGURES		ix
1.	SUMMARY AND CONCLUSIONS	1-1
2.	INTRODUCTION	2-1
3.	GENERAL BACKGROUND INFORMATION	3-1
	3.1 CHEMICAL AND PHYSICAL PROPERTIES, ANALYTICAL METHODOLOGY	3-1
	3.1.1 Chemical and Physical Properties	3-1
	3.1.2 Analytical Methodology	3-3
	3.1.2.1 Sampling and Sources of Error	3-5
	3.1.2.2 Calibration	3-8
	3.1.2.3 Standard Methods	3-10
	3.2 PRODUCTION, USE, AND EMISSIONS	3-10
	3.2.1 Production	3-10
	3.2.2 Usage	3-12
	3.2.3 Emissions	3-14
	3.3 ATMOSPHERIC TRANSPORT, TRANSFORMATION AND FATE	3-14
	3.3.1 Residence Time and Tropospheric Removal Mechanisms	3-14
	3.3.2 Impact Upon the Ozone Layer	3-21
	3.3.3 Laboratory Studies	3-26
	3.4 AMBIENT MIXING RATIOS	3-27
	3.4.1 Global Atmospheric Distributions	3-27
	3.5 REFERENCES	3-36
4.	METABOLIC FATE AND DISPOSITION	4-1
	4.1 ABSORPTION, DISTRIBUTION AND ELIMINATION	4-1
	4.1.1 Oral and Dermal Absorption	4-1
	4.1.2 Pulmonary Uptake and Body Burden	4-3
	4.1.3 Tissue Distribution	4-13
	4.1.4 Pulmonary Elimination	4-15
	4.1.5 Elimination by Other Routes	4-17
	4.2 BIOTRANSFORMATION	4-17
	4.2.1 Magnitude of Methyl Chloroform Metabolism	4-18
	4.2.2 Kinetics of Blood and Urine Metabolites	4-21
	4.2.3 Enzyme Pathways of Methyl Chloroform Metabolism	4-26
	4.3 SUMMARY AND CONCLUSIONS	4-32
	4.4 REFERENCES	4-34
5.	TOXIC EFFECTS	5-1
	5.1 HEALTH EFFECTS IN HUMANS	5-1
	5.1.1 Experimental Studies	5-1
	5.1.2 Occupational Studies	5-8
	5.1.3 Accidental Exposure	5-11

CONTENTS (cont.)

	Page
5.2 EFFECTS ON ANIMALS	5-15
5.2.1 Acute and Subacute Effects	5-15
5.2.2 Central Nervous System Effects	5-21
5.2.3 Cardiovascular Effects	5-21
5.3 TERATOGENICITY, MUTAGENICITY, AND CARCINOGENICITY	5-29
5.3.1 Teratogenicity, Embryotoxicity, and Reproductive Effects	5-30
5.3.1.1 Overview	5-30
5.3.1.2 Human Studies	5-33
5.3.1.3 Animal Studies	5-33
5.3.1.3.1 Rats	5-33
5.3.1.3.2 Mice	5-35
5.3.1.3.3 Chicken embryos	5-35
5.3.2 Mutagenicity	5-36
5.3.3 Carcinogenicity	5-38
5.4 SUMMARY OF ADVERSE HEALTH EFFECTS AND LOWEST OBSERVED EFFECTS LEVELS	5-43
5.4.1 Inhalation Exposure	5-43
5.4.1.1 Effects of Single Exposures	5-44
5.4.1.2 Effects of Intermittent or Prolonged Exposures	5-50
5.4.2 Oral Exposure	5-53
5.4.3 Dermal Exposure	5-55
5.5 REFERENCES	5-56
6. BIBLIOGRAPHY	6-1
7. APPENDIX: THE CARCINOGEN ASSESSMENT GROUP'S CARCINOGEN ASSESSMENT OF METHYL CHLOROFORM	7-1

LIST OF TABLES

		Page
3-1	Physical properties of 1,1,1-trichloroethane	3-1
3-2	Major producers of methyl chloroform	3-11
3-3	Stabilizers used in methyl chloroform formulations	3-13
3-4	1978 emission losses to air	3-15
3-5	Relative efficiency of halocarbons in reducing stratospheric ozone	3-24
3-6	Important atmospheric reactions that affect stratospheric ozone	3-25
3-7	Ambient air mixing ratios of CH_3CCl_3 measured at sites around the world	3-33
4-1	Partition coefficients of methyl chloroform and other solvents at 37°C	4-2
4-2	Estimated uptake of MC during a single 4-hr exposure (average body weight, 77 kg; 67 kg lean body mass), estimated uptake of MC during a single 8-hr exposure (average body weight, 74 kg)	4-8
4-3	Mean values and SEM for 12 male subjects at rest and exercise for 30-minute periods	4-10
4-4	Tissue content (rat) of methyl chloroform (MC) after chronic inhalation exposure at 500 ppm	4-14
4-5	Recovery Experiment with rats (3) intraperitoneally injected with ^{14}C-MC(700 mg/kg)	4-20
4-6	Relation between inhalation exposure and urinary metabolites of MC	4-22
5-1	Subjective and physiological responses to a constantly increasing methyl chloroform vapor concentration over a period of 15 minutes	5-4
5-2	Subjective and physiological reponses to methyl chloroform vapor concentrations of 900 to 1000 ppm	5-5
5-3	Number of subjective responses to methyl chloroform exposure	5-7
5-4	Signs and symptoms of patients surviving intoxication with methyl chloroform	5-12
5-5	Acute toxicity of methyl chloroform	5-16
5-6	The relative hepatotoxic efficacy of chlorinated solvents	5-21
5-7	Probable result of single exposure to the vapors of methyl chloroform	5-22
5-8	Left ventricular and hemodynamic effects of methyl chloroform	5-25
5-9	Concentration of chemicals causing cardiac sensitization and their physical properties	5-27
5-10	Oncogenic and terotogenic testing of methyl chloroform	5-31
5-11	Summary of NCI chloroethane bioassay results as of July 1978	5-39

LIST OF TABLES (cont.)

	Page
5-12 Summary of neoplasms in rats and mice ingesting methyl chloroform	5-41
5-13 Summary of neoplasms in rats inhaling methyl chloroform for 52 weeks	5-42
5-14 Human fatalities associated with methyl chloroform inhalation	5-45
5-15 Non-lethal effects of methyl chloroform on humans	5-47

LIST OF FIGURES

		Page
3-1	Global distribution of methyl chloroform.....	3-30
4-1	Absorption and pulmonary elimination of MC, and blood concentration.....	4-6
4-2	Data from one subject exposed to 30-min periods of MC.....	4-11
4-3	Postulated pathways of hepatic biotransformation of MC.....	4-27

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1. SUMMARY AND CONCLUSIONS

1,1,1-Trichloroethane (methyl chloroform, MC) is a chlorinated hydrocarbon compound which is manufactured and used in large quantities. Since its commercial introduction in the mid-1900s, it has been used increasingly as an industrial solvent and in consumer products, such as spot removers. In recent years, the U.S. production of MC has grown significantly; current production is estimated to have increased from 266 million pounds (121 million kg) in 1970 to 716 million pounds (325 million kg) in 1979. The compound is produced by three manufacturers with a total annual production capacity of 975 million pounds. Methyl chloroform's popularity is apparently due primarily to early studies which indicated that it had a very low toxicity in comparison to other halogenated hydrocarbon solvents with similar physical properties.

It is estimated that approximately 88 percent of the MC consumed in the United States is lost directly to the environment through dispersive use, largely by evaporation to the atmosphere. Three-quarters of the air emissions are attributed to metal cleaning operations which consume 66 percent of the total production. There are no known natural sources of MC. In addition to the workplace, ambient air and water measurements indicate that it is found in a variety of urban and non-urban areas of the United States and other regions of the world. Measurable amounts of MC have been reported in the atmosphere, soil, rainwater, marine and fresh surface waters, and ground water in the low part per billion (ppb) level. Residues of MC have been measured at similar levels (low ppb) in the tissues of aquatic and terrestrial plants and animals,

and in food items. In addition, MC has been detected in human expired air, at levels of 0.03-140 µg/h/ subject. Based on available information, an average ambient air concentration of about 1 ppb (5.4 $\mu g/m^3$) would be expected for some large urban centers, while air samples from rural areas average around 100 parts per trillion (ppt).

Chlorine atoms are released from MC by photodissociation in the stratosphere and react with ozone (O_3) thus contributing to a reduction of stratospheric O_3. Therefore, MC may contribute to the effects of ozone depletion on human health, i.e., an increased incidence of certain types of skin cancers due to increased UV-B radiation reaching the earth's surface. However, the approximate extent to which stratospheric ozone is depleted by all halocarbons and the extent to which past, current and future emissions of MC contribute to this depletion can only be estimated through computer modeling of the stratosphere. It is not currently possible to verify by direct measurement an ozone depletion of less than 2 percent per decade. Unlike chlorofluorocarbons, which are not known to be removed by mechanisms in the troposphere, MC is removed to a substantial extent through reaction with hydroxyl radicals. The tropospheric lifetime of MC is generally assumed to be within a range of 5 to 12 years in spite of the lack of scientific agreement on the global average concentration of hydroxyl radicals. It has been estimated that this period of time allows from 10 to 20 percent of the MC emitted to survive tropospheric removal mechanisms and reach the stratosphere. The National Academy of Sciences has recently estimated that MC currently contributes one-quarter to one-half the number of chlorine atoms reaching the stratosphere, as do either of the chlorofluorocarbons F-11 or F-12. Assuming the same rates of production, MC has been calculated to be approximately 15 and 20 percent as

effective as chlorofluorocarbon F-11 and F-12, respectively, in destroying ozone. This estimate assumes a 9-year tropospheric lifetime for MC. If it replaces other solvents in the future, or as new uses for MC are found, it will necessarily play a more significant role in ozone photochemistry.

Methyl chloroform production has been rising in recent years, and estimates of tropospheric levels show a corresponding rate of increase of 17 percent annually. The most recent measurements indicate a global average mixing ratio of about 110 ppt.

At levels of methyl chloroform necessary for anesthesia (10,000 to 50,000 ppm), significant cardiovascular effects have been observed in animals and humans. Even at 1000 ppm, MC inhalation produces cardiovascular effects in humans that include sensitization of the heart to spontaneous or catecholamine-provoked arrhythmias and hypotension. This cardiovascular response is, in part, the result of MC's ability to depress the conduction system of the heart.

More recent studies have also shown that MC is not entirely innocuous to human health at the lower concentrations likely to be encountered in the workplace (TLV-TWA* = 350 ppm), although single exposures to concentrations less than 5000 ppm are probably not potentially life threatening to humans. The lowest observed adverse effect level† (LOAEL, 500 - 350 ppm) produces subjective symptoms of lightheadedness, syncope, stuffiness, mild headache,

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*TLV-TWA (Threshold Limit Value - Time Weighted Average): is defined as the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek to which nearly all workers may be exposed repeatedly, day after day, without adverse effect.

†LOAEL: is defined as the lowest exposure level in a study or group of studies which produces statistically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

nausea, and mild irritation of eye, nose, and throat. No significant abnormal blood chemistry or organ function tests have been noted. The most adverse effects are neurological symptoms, which have been diagnosed by subjects' impaired performance of cognitive and manual tasks.

The incidence of adverse health effects at low ambient air mixing ratios (~ 100 ppt) is unknown. However, because there is evidence that MC accumulates in the body, long-term or lifetime exposure to even low ambient air concentrations might represent a health hazard. A no observed effect level (NOEL*) for long term occupational exposure of humans to MC is presently assumed to be around 53 ppm.

Methyl chloroform has been demonstrated to have mutagenic activity in the Ames test, with and without metabolic activation, and in cultured mammalian cell transformation systems. If the metabolism and pharmacokinetics of this compound in humans result in metabolic products which can interact with DNA, as is the case for bacteria, it may cause mutagenic effects in humans as well. It may also possibly have teratogenic potential, thereby showing similarity to other halogenated hydrocarbon compounds. In tests conducted to date, MC has not appeared to be carcinogenic; however, the fact that it is mutagenic in Salmonella warrents further examination of its carcinogenic potential.

The pharmacokinetics and metabolism of MC have been studied in man. Like other halogenated hydrocarbon solvents, inhalation and lung absorption of MC vapor in the air is the most important and rapid route of absorption into the body. It is estimated that for an 8 hour exposure at the TLV-TWA (350 ppm), about 2 grams will be absorbed into the body of a normal 70 kg man. The total

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*NOEL: is defined as the exposure level at which there are no statistically significant increases in frequency or severity of effects between the exposed population and its appropriate control.

amount absorbed increases in direct proportion to inspired air concentration and to length of exposure and physical activity. However, at equilibrium, only approximately 30 percent of the inspired air concentration is retained. Because of its lipophilic nature, MC is expected to cross membrane barriers in the body and diffuse into the brain and the milk of nursing mothers, as well as into the fetus during pregnancy. There is strong evidence that tissue concentration of MC, particularly into adipose tissue, will occur with chronic or long term exposure to even low ambient air concentrations. Methyl chloroform is metabolized in man to a very limited extent (about 6 percent of the total retained dose).

The primary route of elimination of MC is via the lungs. The only identified uninary metabolites are trichloroethanol and trichloroacetic acid. Metabolism of MC is enhanced by other chemicals and drugs such as phenobarbital, and there is some evidence that MC may enhance its own metabolism.

As stated above, some of the health hazards of exposure to MC concern the possible mutagenic, teratogenic, and carcinogenic potential of the compound. The extent to which its possible carcinogenic potential can be realized is linked to the biochemical mechanisms of its metabolism in the liver. Methyl chloroform may be biotransformed to "reactive intermediate" metabolites which may contribute to tissue and organ toxicities, as well as carcinogenesis. However, the evidence for reactive intermediate metabolites of MC is fragmentary at present. Methyl chloroform has been demonstrated to be mutagenic in the Ames test, with and without metabolic activation, and in a cultured mammalian cell transformation system. However, animal bioassays performed by the National Cancer Institute (NCI) and others have not provided definitive evidence of carcinogenicity. At the present time, there is inadequate evidence to properly evaluate MC as a chemical carcinogen (see attached CAG report).

There are only a few studies on the teratogenicity and fetotoxicity of MC and the limitations of the available data do not allow for a full assessment of the effects. Further testing is required to determine whether this toxicity is a health hazard to humans, particularly at low ambient concentrations.

Until there is considerably more information available on the biological effects of MC and its role in contributing to an increased incidence of skin cancer as a result of ozone depletion, a definitive evaluation of all the health hazards associated with its use in the workplace and its presence in the ambient environment is not possible. For example, there is very little data on synergistic or antagonistic effects of MC with other compounds; e.g., anesthetic or vasoactive agents. In addition, a lifetime animal bioassay under the National Toxicology Program using both rats and mice is currently nearing completion. It should be noted that the MC being used in this study has only a very low percent (0.002%) of dioxane, a stabilizer thought possibly to contribute to the positive results obtained in the mutagenicity and cell transformation tests.

2. INTRODUCTION

1,1,1-Trichloroethane (methyl chloroform, MC) belongs to a family of saturated chlorinated compounds widely used in industrial cold cleaning and vapor degreasing operations, in the synthesis of vinylidene chloride, and in consumer products. This document provides an evaluation of the health hazards of MC and a review of the relevant scientific literature. In order to provide a perspective in evaluating the health hazards of MC, this document contains background chapters relating to analytical methodologies, production, sources and emissions, ambient air concentrations, and levels of exposure.

Methyl chloroform is released into the ambient air as a result of evaporation during production, storage, and manufacturing or during general consumer use. It is not known to be derived from natural sources. In recent years, a great deal of attention has been focused upon the role of MC in the destruction of stratospheric ozone, indirectly resulting in increased ultraviolet radiation at the earth's surface and contributing to an increased incidence of skin cancer. MC is one of the many atmospheric pollutants whose reactivity is sufficiently low to allow it to be transported to the stratosphere; its trophospheric lifetime is estimated to be 5 to 12 years. Concentrations in ambient air sampled around the nation reflect methods used to control emissions and the transport and transformation processes in the atmosphere.

The scientific literature on MC is limited in reference to its effects on humans. There are relatively few epidemiological studies. What is known

about the effects of MC has been primarily learned from studies involving individuals exposed occupationally or accidentally to it. In such exposures, the concentrations of MC associated with adverse effects to human health were either unknown or far in excess of the concentrations measured in ambient air. Controlled exposure studies have been carried out at TLV-TWA* concentrations (350 ppm) and have been directed toward elucidation of the pharmacokinetic parameters of MC exposure. These studies have established that vapor inhalation is the principal route by which MC enters into the body; it is widely distributed into all organ systems and is metabolized to a limited but significant extent. MC is eliminated from the body primarily as the parent compound via the lungs, but metabolites are excreted mostly in the urine. Given evidence that MC accumulates in the body, particularly in fatty tissues, long-term or lifetime exposure to even low ambient air concentrations may represent significant health hazards. Epidemiological studies provide some information about the impact of MC on human health, but it is necessary to rely on animal studies to derive indications of potential harmful effects for chronic low exposure. These studies are reviewed in chapters 4 and 5.

Apart from the important questions of carcinogenicity and teratogenicity, other human biological effects relate to the narcosis potential of MC and to evidence that low ambient concentrations may have accumulative neurological and cardiovascular effects. The full detrimental consequences to human health of MC have not been determined at present and require further study. These questions are discussed in chapter 5.

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*TLV-TWA (Threshold Unit Value - Time Weighted Average): is defined as the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek to which nearly all workers may be exposed repeatedly, day after day, without adverse effect.

The potential of MC or its metabolites to act as chemical carcinogens and/or mutagens represents a most serious hazard to human health. This document summarizes the available mutagenicity studies and the animal bioassay studies that relate to the carcinogenic potential of MC. Methyl chloroform's potential to cause human cancer is discussed in chapter 5. According to the EPA Carcinogen Assessment Group and Reproductive Effects Assessment Group Reports (January, 1981), it remains suspect at the present time; however, a final judgment on the carcinogenicity of MC has been deferred until further information becomes available, particularly the results of the current National Toxicology Program bioassay in rats and mice.

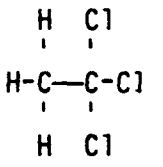
Permissible levels of MC in the working environment have been established in various countries. The U.S. Occupational Safety and Health Administration (OSHA) health standard requires that a worker's exposure to MC at no time exceed an 8 hr time-weighted average of 1,900 mg/m^3 (350 ppm) in the workplace air in any work shift of a 40 hr week.

3. GENERAL BACKGROUND INFORMATION

3.1 CHEMICAL AND PHYSICAL PROPERTIES, ANALYTICAL METHODOLOGY

3.1.1 Chemical and Physical Properties

1,1,1-Trichloroethane (CH_3CCl_3), also called methyl chloroform (MC), is a colorless nonflammable liquid which has a characteristic odor. Its line formula is:



Chemical Formula $C_2H_3Cl_3$

Chemical Abstracts Service Registry Number 71-55-6

Synonyms and Identifiers

Aerothene TT	Inhibisol
Chloroethane NU	Methyl Chloroform
Chlorotene	Methyltrichloromethane
Chlorothane NU	NCI-C04626
Chlorothene	Alpha-T
Chlorothene NU	Trichloroethane
Chlorothene VG	1,1,1-Trichloroethane
Chlorten	α-Trichloroethane
Ethane, 1,1,1-Trichloro	

Table 3-1 shows some of its important chemical and physical properties.

TABLE 3-1. PHYSICAL PROPERTIES OF 1,1,1,-TRICHLOROETHANE

Solubility in water @ 25°C	0.44 gm/100gm
Boiling point @ 760 torr	74°C
Vapor pressure @ 20°C	100 torr
Vapor density (air = 1)	4.6
Molecular weight	133.41
1 ppm	5.4 mg/m^3

In the atmosphere, MC is subject to free radical attack and reaction with hydroxyl radicals is the principal way in which it is scavenged from the atmosphere. Photooxidation products of MC include hydrogen chloride, carbon oxides, phosgene, and acetyl chloride (Christiansen et al., 1972). Ihe principal tropospheric photooxidation product has been reported to be trichloroacetaldehyde (U.S. Environmental Protection Agency, 1975). Data discussed in Section 3.3 indicate that MC is relatively stable in the troposphere and that significant amounts are conveyed to the stratosphere.

In water, methyl chloroform is slowly hydrolyzed to predominantly acetic and hydrochloric acids (Dilling et al., 1975). Dilling et al. (1975) reported a half-life of hydrolysis of 6 months at 25°C (dark reaction).

Anhydrous MC is generally noncorrosive, but in the presence of water it can react to form hydrochloric acid, which is a corrosive of metals (Keil, 1979). Ihe addition of epoxides can neutralize the generated acid (Keil, 1979). Anhydrous MC, when heated to 360° to 440°C, decomposes to 1,1-dichloroethylene and hydrogen chloride. When MC is heated in the presence of water at temperatures between 75° and 160°C, it decomposes, upon contact with metallic chlorides or sulfuric acid, to acetyl chloride, acetic acid, and acetic anhydride. Noweir et al. (1972) have observed that when MC comes in contact with iron, copper, zinc, or aluminum at elevated temperatures, phosgene is produced.

Bonse and Henschler (1976) have considered the general chemical reactivity of MC. By virtue of the electron-inductive effects of the chlorine substituents, destabilization occurs at the C-C bond. Radical reaction mechanisms would be favored as a result of the delocalization of the unpaired electron drawn from the C-C bond.

3.1.2 Analytical Methodology

Io detect very low levels of methyl chloroform in ambient air, sophisticated analytical techniques have been employed. Ihe two most generally useful methods for detection and analysis of MC have been gas chromatography with electron capture detection (GC-ECD) and gas chromatography-mass spectrometry (GC-MS). Both systems have a lower limit of detection on the order of a few parts per trillion (ppt). Ihe utility of GC-ECD over GC-MS is that it can be used in the field to provide nearly continuous measurements through intermittent sampling (every 15 to 20 minutes).

In a comparison between GC-ECD and GC-MS, Cronn et al. (1976) judged GC-ECD to be superior in precision. Standards for four halocarbon compounds, measured by GC-ECD, had coefficients of variation ranging from 0.5 to 3.5 percent. Of 11 halocarbon compounds measured by GC-MS, coefficients of variation ranged from 4 to 19 percent. Iemperature programming or isothermal operation of the gas chromatograph yielded comparable results (Cronn et al., 1977). Ihe precision with temperature-programming was 4.3 percent versus 3.5 percent with isothermal operation for MC.

A close agreement between the levels of MC and other halocarbons detected by both GC-ECD and GC-MS (on the same ambient air samples) was obtained by Russell and Shadoff (1977). A difference of 10 ppt was reported between the systems. Air samples were sorbed onto Porapak N porous polymer and desorbed onto the column by heating the collection tube rapidly to 200°C. Ambient air mixing ratios measured by this method were in the range of 90 to 110 ppt.

Ihe electron capture detector, as well as the mass spectrometer in the selective ion monitoring mode (Cronn and Harsch, 1979a; Pellizzari, 1974), is specific in the detection and quantitation of many halogenated hydrocarbons, whereas nonhalogenated hydrocarbons are not detected. Ihus, a high background

level of hydrocarbons in ambient air samples does not preclude analysis of trace quantities of MC. In the electron capture detector, MC is ionized by primary electrons released from an internal radioactive source. The net result is removal of electrons from the gaseous mixture with substitution by negative ions of greater mass. The measured effect is a net decrease in ion current because the mobility of the ions is less than that of the electrons.

Samples of tropospheric air were analyzed by Cronn and coworkers (1977) both by preconcentrating the samples according to the method of Rasmussen et al. (1977) and by direct injection. The detection limit was 3 ppt. The precision of the method using preconcentration was ±4 percent. The internal consistency between direct GC-ECD analysis of MC and using the preconcentration method was reported to be good (Cronn et al., 1977).

A detection limit of 2 ppt for MC was achieved by Harsch and Cronn (1978) with a low pressure sample-transfer technique. Precision was ±7 percent with the Rasmussen et al. (1977) preconcentration technique. Calibration was accomplished by use of secondary standards that were compared to static dilutions of pure and commercially prepared mixtures of MC (10 ppm) in helium. Robinson (1978) reported a detection limit of 6 ppt with a precision of ±4.2 percent with secondary standards in a system using dual GC-ECD.

Pellizzari and Bunch (1979) reported an estimated detection limit of 12.45 ppt (66×10^{-6} mg/m^3) using high resolution gas chromatography/mass spectrometry. The detection limit was calculated on the basis of the breakthrough volume for 2.2 grams of Tenax GC, at 21°C. The accuracy of analysis was reported at ± 30 percent. Sources of error are discussed in section 3.1.2.1. Water

The relatively high volatility of MC was used to advantage by Piet et al. (1978) in measuring the content of MC in water samples. A direct headspace

method was used with MC volatilizing into the air above the surface of the water sample in a sealed container. A GC-ECD system was used for separation and quantitation. The systematic error of the method was reported to be less than 5 percent. The detection limit for MC was 0.05 µg per liter. The OV 225 capillary GC column provided good separation of MC from CCl_4.

3.1.2.1 Sampling and Sources of Error--The National Academy of Sciences (1978) has reviewed common approaches used to sample ambient air for trace gas analysis. These approaches include:

1. Ambient pressure samples. An evacuated chamber is opened and allowed to fill until it has reached ambient pressure at the sampling location. If filling is conducted at high altitude, contamination of the low pressure sample is likely when samples are returned to ground level.
2. Pump pressure samples. A mechanical pump is used to fill a stainless steel or glass container to a positive pressure relative to the surrounding atmosphere.
3. Adsorption on molecular sieves, activated charcoal, or other materials. Sorbents that have been used to collect MC include Porapak Q, Tenax GC, and Chromosorbs 101, 102, and 103.
4. Cryogenic sampling. Air samples are transferred to a loop held at the temperature of liquid oxygen. Components, including MC, are concentrated by freezeout while other gases (oxygen, nitrogen) pass through.

In the analysis of whole air samples of compounds such as MC which are present in ambient air in the ppt range, small uncontrolled errors in the system could result in inaccurate results. Errors in the analysis can occur during sampling, in the gas chromatograph, in the EC detector, and in calibration of the instruments.

Rasmussen and Khalil (1981) reported that, in an interlaboratory comparison of two samples of MC in ambient air, a majority of the 19 participating laboratories reported values lower than those determined by the authors. It was concluded that common standards are needed if atmospheric measurements from different laboratories are to be pooled.

Singh and coworkers (1978a) used electrochemically-polished stainless steel sampling vessels. The sampling vessels were flushed with ultra-pure helium until background contamination was reduced to less than 2 to 3 percent of the expected background concentration of a given trace constituent. Cronn and coworkers similarly employed electropolished stainless steel containers whose interior surfaces had been passivated by electropolishing (Cronn and Robinson, 1978; Cronn et al., 1976; 1977).

Harsch and Cronn (1978) have evaluated sample transfer techniques. Most analytical procedures involve the collection of pressurized air samples. Sample transfer under positive pressure minimizes serious contamination possibilities posed by laboratory air containing many times the ambient mixing ratios of most halocarbons. However, collection of low pressure samples, such as stratospheric air samples, is a specialized situation in which careful precautions against sample contamination are necessary. A technique applicable to collection of whole air samples at altitudes up to 21 kilometers showed a 7 percent standard deviation when the MC mixing ratio was 105 ppt (Harsch and Cronn, 1978). Electropolished sampling bottles were evacuated to 30 microns prior to sample collection. Transfer of contents to a freezeout loop (Rasmussen et al., 1977) (immersed in liquid O_2) was made by vacuum assist. Preconcentration was followed by injection onto a temperature-programmed column. The detection limit for MC with the GC-ECD procedure was 2 ppt. To minimize the number of potential sources of leaks, system components

were silver soldered. Ihe technique was applicable when gross halocarbon levels were not present in laboratory air. However, it was noted that if laboratory air contained ppb levels of halocarbons, high-boiling halocarbons were adsorbed onto the surfaces of the fittings of the sampling containers and associated plumbing during times when the system was exposed to laboratory air.

The EC detector can be a source of error because water vapor and oxygen may cause reduced sensitivity for certain halocarbons. Lillian and Singh (1974) used an ascarite trap between the GC column and the detector to absorb sample moisture. Carrier gas for the GC is purified by passage through traps containing activated charcoal, anhydrous calcium sulfate, and an ascarite or molecular sieve (Cronn, 1980). Oxygen contamination in the detector can be minimized by preconcentration of air samples on porous polymers (Russell and Shadoff, 1977). Significant oxygen contamination is often caused by fitting leaks in the GC rather than by carrier gas contamination.

A freezeout concentration method was employed by Rasmussen et al. (1977) to determine atmospheric levels of MC in the presence of other trace vapors. The detection limit of MC was reported to be 0.8 ppt for 500 ml aliquots of ambient air when measured by GC-ECD. Precision was 4.3 percent. Standards were prepared by static dilutions in helium. During the procedure, the oven of the GC was cooled to - 10°C. When freezeout was complete, the loop containing the concentrated air sample was immersed in heated water and the carrier gas swept the contents of the sample loop onto the column.

Pellizzari and Bunch (1979) reported the use of Tenax GC, a porous polymer based on 2,6-diphenyl-p-phenylene oxide, to absorb MC from ambient air. Recovery was made by thermal desorption and helium purging into a freezeout trap. Included among the inherent analytical errors were (1) the ability to

accurately determine the breakthrough volume, (2) the percent recovery from the sampling cartridge after a period of storage, and (3) the reproducibility of thermal desorption from the cartridge and its introduction into the analytical system. To minimize loss of sample, cartridge samplers should be enclosed in cartridge holders and placed in a second container that can be sealed, protected from light, and stored at 0°C.

3.1.2.2 Calibration--In general, calibration of the instrumentation for GC-ECD analysis of methyl chloroform has involved static, multiple dilutions of pure material in the ppm range to ppt levels (Cronn et al., 1976; 1977; Harsch and Cronn, 1978; Lillian and Singh, 1974; Singh et al., 1977a). Singh et al. (1977b) have cautioned that, in some cases, multiple dilutions of materials to ppt levels are tedious and prone to inaccuracies. In order to overcome the difficulties in generating low-ppb primary standards of MC, Singh et al., (1981) has reported that permeation tubes offer the most accurate means. Permeation tubes were conditioned for at least two weeks and, during standard generation, were kept in holders maintained at 70 ± 0.1°C. Error in the permeation rate (980 mg/min) were ± 15 percent. A reproducible means of generating low-ppb primary standards was judged essential since there are considerable difficulties in storing long-term secondary standards. Various investigators have used GC-ECD systems to quantitate MC in ambient air samples (Cronn et al., 1976; 1977; Lillian and Singh, 1974; Rasmussen et al., 1977; Singh et al., 1977c). An interlaboratory calibration (Cronn et al., 1976) of six real ambient air samples gave a precision (percent standard deviation) of 11.4 ppt. A similar comparison calibration was reported by Singh et al., (1981).

Rasmussen and Khalil (1981) reported that primary standards of MC (~ 139 and 52 ppt) remained stable for up to about one year, even though the pressure in the master tanks had decreased significantly.

Because the ionization efficiency of MC in the EC detector is only 20 percent, use of dual EC detectors in series have been used to achieve higher accuracy (Lillian and Singh, 1974). The dual detection system, as employed by Singh et al. (1977c), enables MC to be quantitated coulometrically according to the following equation:

$$\text{Coulombs} = 96{,}500\ pW;$$

where

p = ionization efficiency

and

W = moles of compound

Determination of the ionization efficiency can be made by use of the following expression which relates p to the signals (X_1 and X_2) of two identical EC detectors in series:

$$p = 1 - \frac{X_2}{X_1}$$

$$X_1 = 96{,}500\ pW$$

$$X_2 = p\ (96{,}500W - 96{,}500\ pW)$$

The ionization efficiency should be determined for the operating conditions and once established, can be used in the coulometric calibration.

The accuracy of the GC-ECD approach has been reported by Singh (1977a) to be better than 10 percent for compounds such as MC that have ambient air mixing ratios of 20 ppt or greater. An overall system accuracy of ± 10 percent was reported by Singh et al. (1977a) in analyses of MC in ambient air samples. Two gas chromatographs, each equipped with two EC detectors, were employed. An ascarite trap was placed between the GC column and the EC detector to prevent moisture interference. Precision was reported to be better than 5 percent and instruments were calibrated using multiple dilutions of pure material. Singh et al., (1981) recently reported linearity of dual frequency-modulated ECD's over a wide concentration range for MC, down to low-ppt levels.

3.1.2.3 Standard Methods--The analytical method S335, suggested by NIOSH for organic solvents in air, utilizes adsorption on charcoal followed by desorption with carbon disulfide. The resulting effluent is analyzed by gas chromatography. This method was recommended for the range 96 to 405 ppm. Interferences are minimal and those that do occur can be eliminated by altering chromatographic conditions. However, one disadvantage is that the charcoal may suffer breakthrough, thus limiting the amount of air that can be sampled.

3.2 PRODUCTION, USE, AND EMISSIONS

Methyl chloroform is principally used for the cold cleaning and vapor degreasing of fabricated metal parts. Because of its volatility and dispersive use pattern, much of the MC produced worldwide is emitted into the atmosphere. There are no identified natural sources of emissions. Once in the atmosphere, MC is subject to atmospheric transport and transformation. To better gauge the effects of present and future emissions of MC on human health, this section profiles MC production, usage, and emissions.

3.2.1 Production

Methyl chloroform is produced by several manufacturing processes (Jordan, 1979; Lowenheim and Moran, 1975; U.S. Environmental Protection Agency, 1979b):

1. Hydrochlorination of 1,1-dichloroethylene (vinylidene chloride)

$$CH_2 = CCl_2 + HCl \xrightarrow{FeCl_3} CH_3CCl_3$$

2. Hydrochlorination of vinyl chloride

$$CH_2 = CHCl + HCl \xrightarrow{FeCl_3} CH_3CHCl_2$$

$$CH_3CHCl_2 \xrightarrow[Cl_2]{400°C} CH_3CCl_3 + HCl$$

3. Chlorination of ethane

$$CH_3CH_3 + 3Cl_2 \xrightarrow{370° \text{ to } 480°C} CH_3CCl_3 + 3HCl + \text{byproducts}$$

In order to prevent catalyst deactivation, hydrochlorination reactions should be anhydrous (Jorden, 1979). Temperature control of thermal reactors for chlorination must be maintained to ensure MC stability (Jordan, 1979). In reaction (3) above, ethyl chloride and vinylidene chloride are byproducts. Increased yields of MC can be obtained through recycling of these byproducts.

In 1975, over 60 percent of the U.S. production of MC was derived from the hydrochlorination of vinyl chloride; derivation from vinylidene chloride accounted for 30 percent (Lowenheim and Moran, 1975).

In 1977, the U.S. production figure for MC was 288,565 metric tons (U.S. Environmental Protection Agency, 1979b; U.S. International Trade Commission, 1977). The major producers and their production capacities for 1977 are shown in Table 3-2. Quoting production estimates supplied by Dow Chemical U.S.A., Singh and coworkers (1979a) reported that production of the chlorocarbon has been increasing and, in recent years, this increase has been at the annual rate of 12 percent. Estimates did not take into account production in the

TABLE 3-2. MAJOR PRODUCERS OF METHYL CHLOROFORM[†]. (Cogswell, 1978)

Organization	1978 capacity metric tons
Dow Chemical, Freeport, TX	204,000
PPG Industries, Inc., Lake Charles, LA	79,000
Vulcan Materials Co., Geismar, LA	29,000

[†]Production capacity estimated to increase significantly at PPG Industries and at Vulcan Materials facilities for 1982 (Chemical and Engineering News, 1979; Chemical Marketing Reporter, 1979; Chemical Week, 1978).

Soviet Union and other eastern European countries. The Dow Chemical estimate for global production in 1977 was 470,000 metric tons. The annual production growth rate through 1977 was reported to be 7 to 10 percent by trade sources (Chemical and Engineering News, 1979). SRI International estimated an average production growth between 5.5 and 7.5 percent annually up to 1982. Future growth in production depends on the status of other chlorinated solvents under regulation for which MC may be substituted.

3.2.2 Usage

In 1975, cold cleaning and vapor degreasing operations accounted for 75 percent of the total end use of MC. Approximately 12 percent was used in the synthesis of vinylidene chloride (Lowenheim and Moran, 1975). Use in metal cleaning operations was reported to total 67 percent of 1977 production (Cogswell, 1978).

MC is also used as a solvent in adhesive formulations, as a spot remover, as a film cleaner, and as an additive in metal cutting oils (Jordan, 1979; Keil, 1979; Lowenheim and Moran, 1975). Stabilizers used in MC are shown in Table 3-3 and protect it in the following ways (Jordan, 1979): (1) prevent or retard oxidation, (2) chelate metal ions, (3) scavenge HCl, and (4) passivate metal surfaces. Vapor degreasing grades of MC contain 3 to 7 percent (w/w) stabilizers and additives (Jordan, 1979); principal stabilizers include nitromethane, 1,3-dioxolane, 1,4-dioxane, butylene oxide, sec-butyl alcohol, isobutyl alcohol, N-methylpyrrole, and toluene (Jordan, 1979). In film cleaning applications, a low concentration of alcohol is used as a stabilizer (Jordan, 1979).

SRI International reported that between 11,000 and 13,000 metric tons of MC are used annually in personal care products (Cogswell, 1978). Expected growth in this area is 15 to 20 percent annually (Cogswell, 1978).

TABLE 3-3. STABILIZERS USED IN METHYL CHLOROFORM FORMULATIONS

(Jorden, 1979)

3% dioxane Stabilizer

1,4 dioxane	
1,3-dioxolane	acrylonitrile
butylene oxide	β-ethoxypropionitrile
epichlorohydrin	diallylamine
methyl ethyl ketone	diisopropylamine
sec-butyl alcohol	acetaldoxime
isobutyl alcohol	nitromethane
ethyl acetate	nitroethane
N-methylpyrrole	N-methylmorpholine
ter-amylphenol	Thymol
hydroquinone monomethyl-ether	
methylal	
ethylene glycol mono and dialkyl ethers	

3.2.3 Emissions

Emissions of MC arise during primary and end product production, during dispersive use applications, from storage containers, and during disposal of waste materials.

Singh et al. (1979c) have estimated global emissions in 1977 at 95 percent of the 300,000 metric tons produced. Lovelock (1977a) estimated that 500,000 metric tons were released globally in 1975. The estimate of the global emissions rate in 1976 by the National Research Council (1979) was about 439,000 metric tons. According to McCarthy (1975), almost all the MC produced is eventually released to the atmosphere.

Recent estimates in a report prepared for the U.S. Environmental Protection Agency, Office of Toxic Substances, placed 1978 emission losses to air at 214,000 metric tons (Katz et al. 1980). Emission estimates by sources category are shown in Table 3-4. The WMO (World Meteorological Organization, 1982), using data reported by Neely and Agin (U.S. E.P.A., 1980), estimated current global annual releases at 476,000 metric tons.

3.3. ATMOSPHERIC TRANSPORT, TRANSFORMATION AND FATE

The potential for ambient air mixing ratios of MC to pose a hazard to human health is influenced by the many processes that occur in the troposphere and stratosphere. Such processes include: transformation of MC into other potentially harmful atmospheric components; urban transport; tropospheric chemical reactivity; and diffusion into the stratosphere where MC participates in ozone (O_3) destruction reactions.

3.3.1 Residence Time and Tropospheric Removal Mechanisms

Scientists generally agree that the longer the tropospheric residence time for a chemical species, the greater the likelihood of diffusion into the stratosphere. Concern that MC is destroying stratospheric O_3 and thus increasing the incidence of certain forms of skin cancer (Chapter 5) has intensified recently.

TABLE 3-4. 1978 EMISSION LOSSES TO AIR

Source	1978 emission losses to air in million pounds (kkg) and percentage of total released to air		
Production			
1. From Vinyl Chloride	0.21	(95)	0.04%
2. From Vinylidene Chloride	0.15	(67)	0.03%
3. From Ethane	0.03	(14)	0.01%
Metal Cleaning	351.70	(159,500)	75%
Aerosols	39.90	(18,100)	8%
Adhesives	38.37	(17,400)	8%
Textiles	6.44	(2,920)	1%
Paints	10.91	(4,950)	2%
Inks	6.13	(2,780)	1%
Drain Cleaners	0.61	(278)	0.1%
Pharmaceuticals	0.27	(124)	0.06%
Film Cleaning	0.48	(218)	0.1%
Leather Tanning	0.23	(104)	0.05%
Catalyst Preparation	0.06	(28)	0.01%
Miscellaneous	14.82	(16,730)	3%
Total released to the air*	470	(213,300)	(100%)

*An additional 63 million pounds (28,602 kkg) are released to the environment via solid waste and water.

Adapted from Katz et al. (1980).

A recent conference convened by the U.S. Environmental Protection Agency (1980) met to establish the facts about the distribution and persistence of MC. The results of research in atmospheric chemistry related to the question of stratospheric O_3 depletion by MC were discussed. Presentations from the various perspectives of those involved in, or concerned with, regulatory decision-making were also made.

Mass budget and other modeling estimates suggest a longer residence time than was previously predicted. Before 1977, it was commonly believed that the residence time was in the range of 1 to 2 years (National Research Council, 1976). Such a time span suggested a tropospheric reactivity great enough to preclude any serious impact on O_3 levels. The "short" lifetime for MC was predicated a global average tropospheric hydroxyl radical (OH) concentration in the range 10×10^5 to 30×10^5 molecules cm^{-3}. Reaction with OH is the principal tropospheric removal mechanism by which many compounds are scavenged from the atmosphere. The following reactions, occurring in the troposphere, would serve as a sink for MC, thus reducing the levels prior to its diffusion to the stratosphere:

$$CH_3CCl_3 + \cdot OH \longrightarrow \cdot CH_2CCl_3 + H_2O \qquad (1)$$

$$CH_3CCl_3 + O(^1D) \longrightarrow \cdot CH_2CCl_3 + \cdot OH \qquad (2)$$

[$O(^1D)$ = atomic oxygen in its singlet state]

Indications of the extent to which MC is calculated to deplete stratospheric O_3 are predominantly derived from one- and two-dimensional modeling studies. The following scenarios consider projections of atmospheric loading, residence time and photochemical processes in the atmosphere.

Campbell (U.S. Environmental Protection Agency, 1980) has calculated the rate of consumption of MC via oxidation by OH as a function of altitude and latitude. One-half of the oxidation occurs below 2.4 km. Most of the oxidation also takes place in the tropics, i.e., half the removal of MC occurs between 16°N and 16°S. These modeling efforts agreed with measured hemispheric ratios and suggested a mean lifetime for MC of 6.4 years.

Logan et al., (1981) modeled MC concentrations over time and latitude, using altitude profiles of OH averaged over an annual cycle. The model results lend support to the findings of Campbell (U.S. Environmental Protection Agency, 1980) in that MC removal is particularly sensitive to OH levels in the tropics, a region that accounts for about 70 percent of the global sink. Approximately 50 percent of the global sink occurs over the tropical ocean. By integrating MC loss over altitude and latitude, using current reaction rate constants for key reactions, Logan et al., (1981) calculated a global lifetime for MC of 5 years. It was emphasized that one-dimensional models are inappropriate for calculating the lifetime of a compound such as MC. The model of Logan et al., (1981) predicted a mean OH level in the northern hemisphere of 1×10^6 per cm^3. This value is somewhat higher than the level (2.5×10^5 per cm^3) calculated by Crutzen and Fishman (1977). In the model studies of Derwent and Eggleton (1981), a global lifetime for MC was calculated at 4.8 years, using a two - dimensional model. These investigations found that global or hemispheric models were inapproriate; in the case of MC, a lifetime of 12 years was calculated when OH was averaged over all altitudes, latitudes, and seasons. It was concluded that neglect of the variations of OH destruction with altitude, latitude, and season may lead to an under - or overestimation of the impact of MC on stratospheric O_3. Global and box models, as evaluated by Derwent and Eggleton, gave larger O_3 depletion estimates; 1-D models underestimate such impact.

The mass balance studies of Singh (1977a; 1977b) had predicted reduced OH levels (3×10^5 molecules cm^{-3}) to account for observed ambient levels of MC. These OH levels are in reasonable agreement with the OH values (3×10^5 to 4×10^6) determined by Campbell and coworkers (1979) during monitoring studies. From the hemispheric distribution of MC, OH abundance in the northern hemisphere was 1.5 to 3 times lower than in the southern hemisphere. Carbon monoxide (CO) levels were believed primarily responsible for the lower northern hemisphere levels of OH. However, Campbell (U.S. Environmental Protection Agency, 1980) has cautioned that, because of the combination of MC oxidation in the tropics and CO reduction in the northern hemisphere, there is a difficulty with using the N/S ratio of MC to obtain hemispheric means of OH. For example, a southern hemisphere OH concentration several times higher than northern hemisphere values requires the transition from the southern hemisphere value to the lower northern hemisphere value to occur within a few degrees of the equator. Based upon the observed tropospheric distribution of MC, atmospheric loading, and its rate of reaction (National Aeronautics and Space Administration, 1977) with OH, Singh (1977a; 1977b) computed a global average residence time between 8 and 11 years. This time span would be sufficient to allow 15 to 22 percent of the MC emitted to reach the stratosphere (National Aeronautics and Space Administration, 1977; Singh et al., 1979a). The National Research Council (1979a), using 1976 global release rates, estimated that about 12 percent reaches the stratosphere.

Singh and coworkers (1979b) have found that field measurements support a 6 to 8 year global average residence time. Measurements of MC between latitudes 35°N and 35°S indicated a global average concentration of 95 ppt. When estimates of other investigators are taken into account, the suggested range is 6 to 12 years (Singh et al., 1979b). This range would allow an estimated 12 to 25 percent of all MC emissions to enter the stratosphere (Singh et al., 1979b).

These latter estimates agree with McConnell and Schiff (1978), who used a one-dimensional model to compute a global average MC mixing ratio of 90 ppt, a value consistent with observed ambient levels at the time. The average tropospheric OH level needed to account for this computed MC level was 5×10^5 molecules cm^{-3}.

Based upon a MC residence time of 5.4 years, Derwent and Eggleton (1978) calculated that approximately 10 percent survives tropospheric removal processes to reach the stratosphere. Lovelock (1977b) estimated a 5 to 10 year residence time based on ambient measurements from 1971 to 1976.

Support for an 8 to 12 year residence time for MC can be found in the modeling results of Chang and Penner (1978). They computed an average residence time of 11.3 years (10 to 12.8 years) from a two-box model interrelating hemispheric abundance, release rates and interhemispheric transport time through continuity equations.

Neely and Plonka (1978), in contrast to Singh and coworkers (1977a; 1977b) and Crutzen and Eishman (1977), who compute an average tropospheric OH concentration of 2×10^5 to $4 \times 10^5 cm^{-3}$, find their computed time-averaged OH concentration of 4.8×10^5 molecules cm^{-3} compatible with a residence time for MC of 2.6 to 4.0 years. In their mass budget model, this OH concentration was required to reconcile emissions (based on Dow Chemical production data) with observed ambient MC levels. In contrast to Singh, who used a global ambient MC mixing ratio of 90 ppt, Neely and Plonka (1978) used 76 ppt. The emissions data were significantly higher than those data calculated by Singh.

In a recent review, Altshuller (1980) suggested an average OH concentration of 3×10^5 molecules cm^{-3} as the most reliable value at present. He cautioned, however, that uncertainty still exists about the extent to which MC reacts with OH. The residence time for MC was calculated to fall in the 8 to

13 year range. For example, a residence time of 13 years was calculated from the rate constant expression of Watson et al. (1977) at 265°K. With the rate constant expression derived by Chang and Kaufman (1977), a MC residence time of 8 years was computed.

Rasmussen and Khalil (1981b) reported that trospheric measurements of MC made at six locations in the northern and southern hemispheres, between January 1979 and June 1980 were consistent with an estimated lifetime in the range of 6 to 10 years. Average concentrations over both hemispheres were calculated from latitudinal profiles and indicated that the global atmospheric concentration (from January 1979 to January 1981) increased at 6.7 ± 2.0 percent per year. In a report submitted for publication, Khalil and Ramussen (1981) determined that the increase in concentration was smaller during 1980 than during 1979. It was concluded that a decrease in the emissions rate has occurred since 1975.

The World Meteorological Organization (1982) recently reviewed that data base and found that, given the uncertainties in release rates and absolute concentrations of MC, as discussed by Logan et al. (1981), the measurements of MC appear to be consistent with a lifetime of 5 to 10 years, and with globally averaged OH concentrations of $\simeq 7 \times 10^5$ molecules cm^{-3}. This estimate was, in part, based on redeterminations of the rate constant for reaction of HO with MC (Kurylo et al., 1979; Jeong and Kaufman, 1979) and the knowledge that release rates as given by Neely and Plonka (1978) do not account for release in Eastern Bloc countries.

Since distribution of OH has only been estimated through use of models, estimates for the atmospheric lifetime of MC should be cautiously viewed.

3.3.2 Impact Upon the Ozone Layer

As stratospheric ozone levels decrease, changes in the amount of light in the solar spectrum around 300 μm that reach the earth's surface may forecast an increased incidence of skin cancer (National Research Council, 1979b, 1982). Reduction in O_3 levels also increases the likelihood of adverse changes in weather and climate (National Research Council, 1979b, 1982). Reduced ozone concentrations could result from the following reaction mechanisms:

$$CH_3CCl_3 \xrightarrow{h\nu} CH_3CCl_2\cdot + Cl\cdot \qquad (1)$$

$$Cl\cdot + O_3 \longrightarrow ClO + O_2 \qquad (2)$$

$$ClO\cdot + O \longrightarrow Cl\cdot + O_2 \qquad (3)$$

$$ClO\cdot + NO \longrightarrow Cl\cdot + NO_2 \qquad (4)$$

The atomic chlorine produced in reaction (1) would react with O_3 to yield chlorine oxide. The subsequent chain reaction would result in a continual depletion of O_3. The importance of this cycle and other cycles in the stratosphere have recently been evaluated by Wuebbles and Chang (1981) and the NRC (National Research Council, 1982). These evaluations indicate that the efficiency of the chlorine oxide cycle is closely coupled with other cycles, principally the nitrogen oxides and hydroxyl radical cycles.

In a study (National Research Council, 1979a) of the impact of chloro and chloroflouro compounds on stratospheric O_3, the National Research Council (NRC) concluded that emissions of halocarbons represented the most immediate and serious threat to O_3. Based upon atmospheric measurement data available at that time, the NRC concluded that MC contributes one-quarter to one-half the number of chlorine atoms on a molecule-per-molecule basis that chlorofluorocarbons 11 and 12 contribute to the stratosphere. At the estimated 1976 global emissions rate of approximately 400,000 metric tons, MC was estimated

to destroy about 10 percent (Table 3-5) as much O_3 as both chlorofluorocarbons 11 and 12. The magnitude of the impact of MC was not delineated further due to a lack of reliable measurement data on OH abundance in the troposphere. The NRC cautioned, however, that continued increased usage of MC could result in the halocarbon becoming the largest source of stratospheric chlorine and, thus, the most serious threat to stratospheric O_3.

Preliminary results obtained using the Lawrence Livermore Laboratory one-dimensional vertical transport-kinetics model suggest that the relative efficiency of MC in destroying ozone is much less than chlorofluorocarbons (U.S. Environmental Protection Agency, 1980). Table 3-5 shows this relative efficiency.

The "best estimate" of the NRC for the eventual steady-state O_3 decrease due to chlorofluorocarbons 11 and 12 at 1977 release rates was 16.5 percent (National Research Council, 1979a). This estimate was about twice as high as the estimate reported by the NRC in 1976 (National Research Council, 1976). Due to the uncertainties in the modeling approach and data base, it was reported that there was a 95 percent probability that the true value of eventual O_3 reduction would be somewhere between 5 and 28 percent.

In their most recent report, the NRC (1982) revised their O_3 depletion estimates downward, principally due to refinements of the values of important reaction rates. The NRC now estimates that the steady-state ($\simeq$ 100 years) reduction in total global ozone, in the absence of other pertubations, could be between 5 and 9 percent. These estimates only considered release of chlorofluorocarbons 11 and 12 at the 1977 release rates.

The World Meteorological Organization (1982) assuming continued release at the current estimated emissions rate for MC and using the model of Wuebbles

(1981) and revised reaction rate kinetics, calculated an estimated steady-state depletion of the total O_3 column of 0.8 percent (Table 3-5). If other stratospherically -important halocarbons are considered (particularly chlorofluorocarbon 113, carbon tetrachloride, and methyl chloroform) at current release rates, the WMO estimates that the predicted column O_3 depletion of from 5 to 9 percent would be increased about one-third. In scenarios more representative of real-time conditions for example, considering variations in carbon dioxide and nitrogen oxides, the WMO derived other estimates of steady-state O_3 depletion. In each scenario, a continued increase in upper stratosphere O_3 depletion is predicted. As noted by the WMO the 5 to 9 percent depletion estimate due to FC-11 and FC-12, if correct, suggests that less than a 1 percent decrease in global average stratospheric O_3 should have occurred to date. This estimated 1 percent decrease is not estimable because state-of-the-art instrumentation and statistical methodology indicate that detection of global average stratospheric O_3 trends is limited to about a 2 percent change per decade.

In addition to the uncertainties and limitations of the models used to estimate the impact of MC on O_3, the complexity of rapidly-changing knowledge in atmospheric chemistry make it difficult to assess with confidence such impact in quantitative terms. Among the atmospheric reactions that can act to enhance or restrict O_3 depletion due to MC, the NRC (National Research Council, 1979a) cited those described in Table 3-6 as important determinants. An evaluation of the impact of MC upon stratospheric O_3 must take into account these and other atmospheric processes if realistic estimates of O_3 depletion are to be made.

TABLE 3-5. RELATIVE EFFICIENCY OF HALOCARBONS IN REDUCING STRATOSPHERIC OZONE
(U.S. Environmental Protection Agency, 1980)

Compound	Percent ozone depletion after 320 years*
F-11	-10.7
F-12	-8.5
F-113	-8.25
F-114	-5.38
MC	-0.93[a]
	-1.6[b]

*production rate assumed, for each species individually, at 1,000 million pounds annually

[a]based on 4.5 year lifetime

[b]based on 9 year lifetime

TABLE 3-6. IMPORTANT ATMOSPHERIC REACTIONS THAT AFFECT STRATOSPHERIC OZONE (National Research Council, 1979a)

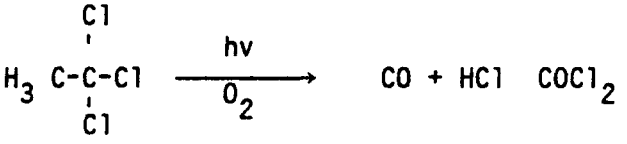
$Cl + O_3 \longrightarrow ClO + O_2$
$ClO + O \longrightarrow Cl + O_2$
$ClO + NO \longrightarrow Cl + NO_2$
$Cl + CH_4 \longrightarrow HCl + CH_3$
$HCl + OH \longrightarrow Cl + H_2O$
$ClO + NO_2 + M \longrightarrow ClONO_2 + M$
$ClONO_2 + h\nu \longrightarrow Cl + NO_3$
$ClO + HO_2 \longrightarrow HOCl + O_2$
$HOCl + h\nu \longrightarrow Cl + OH,\ ClO + H$

The British Department of the Environment (1979) also released a report on the effect of chlorofluorocarbons on stratospheric ozone. Based on annual production of 450,000 metric tons and an OH + MC rate constant of 19 x 10^{-15} cm^3 $molecule^{-1}$ $sec,^{-1}$ the estimated steady state ozone depletion was 1.0 percent, due to MC (Table 3-5).

3.3.3 Laboratory Studies

In experiments designed to characterize the UV absorption spectrum for MC in the wavelength and pressure ranges associated with the stratosphere, Vanlaethem-Meuree et al. (1979) found that photo-dissociation was the dominant sink process at altitudes above 25 kilometers.

In Spence and Hanst's (1978) photooxidation studies, when MC was irradiated at maximum intensities of 3100 Å and 3650 Å, one-fifth of the initial amount (10 ppm) was consumed after 6 minutes. The principal products observed were carbon monoxide (1.5 ppm), hydrochloric acid (6 ppm), and phosgene (2 ppm):



Of the halocarbons evaluated, methyl chloroform was the least reactive.

The recent reaction rate studies, involving MC and OH, by Jeong and Kaufman (1981) and by Kurylo et al. (1981), indicate that the rate of this key reaction is slower and more temperature sensitive than previously had been indicated. Jeong and Kaufman (1981) measured reaction rates using the discharge-flow method and MC which had been extensively purified. A reaction rate at 293°K was determined at 1.06 ± 0.09 x 10^{-14} cm^3 sec^{-1}. The Arrhenius expression, within 95 percent confidence limits but not including systematic errors, was 5.49 ± 1.40 x 10^{-12} exp [- (1832 ± 98/T] cm^3 sec^{-1}. The authors

indicated that the most recent rate (at 298°K) reported by JPL (Jet Propulsion Laboratory, 1979), 1.9 x 10^{-14} cm^3 sec^{-1} is too high by a factor of about 1.7 at this temperature, and by a factor of 1.9 at 265°K, the temperature used by Singh (1977) in deriving average OH concentrations.

The Arrhenius expression determined by Kurylo et al., (1979) was in close agreement with that determined by Jeong and Kaufman (1981). Kurylo et al. (1979) used the flash-photolysis method and also extensively purified the MC prior to use.

3.4 AMBIENT MIXING RATIOS

Modeling approaches for reconciling emissions of MC to ambient air mixing ratios have implied low (3 x 10^5 to 6 x 10^5 molecules cm^{-3}) atmospheric levels of hydroxyl radicals (OH), the principal scavenging species for MC. If verified, these OH levels would strongly suggest that MC and many other chemical species have a tropospheric lifetime sufficiently long to allow their significant transport to the stratosphere. These models, however, have relied on point measurements of MC mixing ratios determined at disparate sites, primarily in the northern hemisphere. Before 1977, reliable estimates of globally averaged MC concentration were not available. Recent measurements, however, indicate that the global average concentration is consistent with a long (5 to 11 years) tropospheric lifetime and that MC remains a serious threat to stratospheric O_3 levels.

3.4.1 Global Atmospheric Distributions

The global average background mixing ratio of MC has been determined by several laboratories, including SRI International and Washington State University. The field studies of Singh and co-workers at SRI have been reported in a number of publications (Singh, 1977a; Singh et al., 1977c; 1978a; 1978b; 1978c; 1979a; 1981). The global average for late 1977 was reported as 95 ppt (Singh et al., 1979a). This average was derived from measurements made in the

northern (average = 113 ppt) and southern (average = 77 ppt) hemispheres. Based on data collected at latitudes 30°N to 40°N from 1975 to 1978, MC presence in the atmosphere was increasing at the rate of 15 ppt (or 17 percent) per year.

Field studies by Singh et al. (1979a) were conducted during two oceanographic cruises between latitudes 64°N and 40°S (15 September to 30 October 1977; 20 November to 13 December 1977). Samples were collected in electropolished stainless steel and glass vessels and analyzed by GC-ECD, operated coulometrically. Samples were analyzed in situ as well as after storage. The northern temperate average mixing ratio was reported as 123 ppt. The latitudinal distribution is shown in Figure 3-1.

The vertical profile and latitudinal gradients of MC in the troposphere and lower stratosphere have been investigated by Cronn and coworkers in a series of high-altitude studies (Cronn and Robinson, 1979; Cronn et al.; 1976; 1977a; 1977b). Most recently, experiments conducted at the Panama Canal Zone (9°N latitude) and at 37°N indicated that MC tropospheric abundance was 18 percent lower at 9°N (Cronn and Robinson, 1979). Singh et al. (1979a) recorded a 17 percent difference between these latitudes (Figure 3-1). For July 1977, the average tropospheric background concentration (139 whole air samples were collected between ground level and 13.7 kilometers) was 97.3 ± 4.6 ppt at 9°N. At 37°N (Pacific Ocean west of San Francisco), an average mixing ratio of 116 ± 14 ppt was measured. Tropopause height at the Canal Zone was 15.7 kilometers. Methyl chloroform tropospheric mixing ratios did not vary significantly with increasing altitude at 9°N but there was a precipitous drop in the mixing ratio across the tropopause.

Analysis of pressurized tropospheric samples was performed by a dual GC-ECD. The detection limit for MC was 6 ppt and the precision of analysis

was ±4.2 percent. Analyses were performed on 5-ml aliquots. For the low-pressure stratospheric air samples, precision was ±7 percent with a detection limit of 2 ppt. Methyl chloroform was preconcentrated with a freezeout sample loop. Overall accuracy of analysis was estimated at about 10 percent.

In experiments conducted at 37°N (Cronn et al., 1977a), samples were collected at altitudes ranging from 6.1 to 14.3 kilometers with the tropopause height between 11 and 12 kilometers. Samples were analyzed by GC-ECD utilizing the freezeout concentration method. The average trospheric background mixing ratio for MC in April 1977 (excluding samples within 0.8 kilometer of the tropopause) was 116 ± 14 ppt. This value is consistent with the results of Singh et al., (1979a), who obtained a value of 117 ppt at this latitude during the fourth quarter of 1977 (Figure 3-1).

When this observed mixing ratio (116 ppt) was compared with that obtained in March 1976 at 48°N (Pacific Northwest), an annual atmospheric increase in MC of 23.7 percent was calculated. Cronn et al. (1976; 1977a) collected whole air samples at altitudes ranging from 4.6 to 14.6 kilometers (average tropopause height was 10.8 kilometers) during March 1976 over Western Montana and Idaho. The average tropospheric background mixing ratio for MC was 94.5 ± 8.2 ppt. Samples were analyzed by GC-ECD both isothermally with a 5-ml aliquot and with the freezeout concentration method. Precision of the overall method was ±4 percent.

The Washington State University (WSU) group has made several studies by aircraft of the latitudinal distribution of MC (Cronn, 1980a; Robinson, 1978; Robinson and Harsch, 1978). Interhemispheric differences of MC in the troposphere in June, 1976, were reported, with northern levels of 96 ppt and southern levels of 88 ppt (Robinson and Harsch, 1978). Lower stratospheric levels were 80 and 67 ppt, respectively. Work begun at WSU in 1976, and continuing

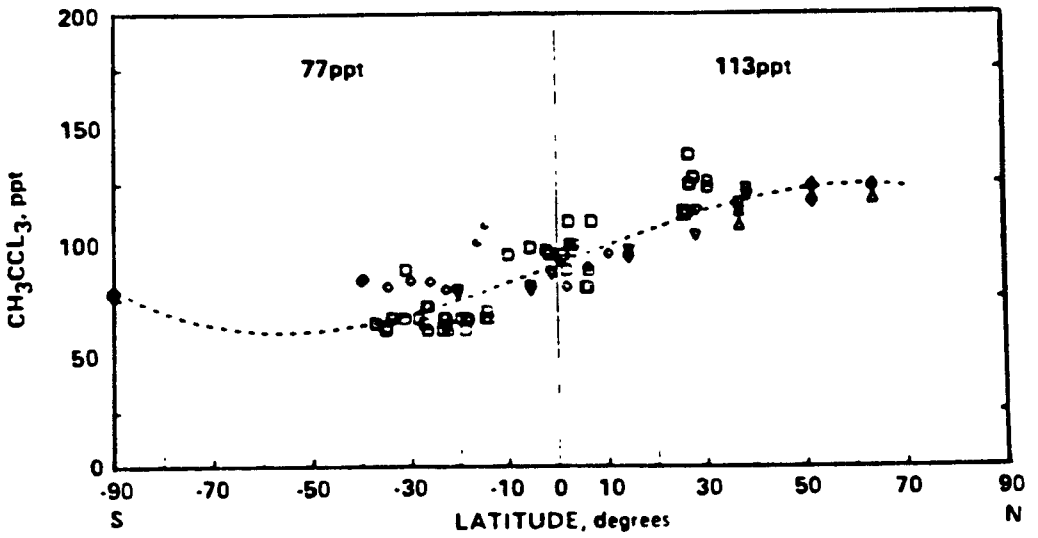


Figure 3-1. Global distribution of methyl chloroform (Singh et al., 1979a)

at both WSU and the Oregon Graduate Center, has provided annual measurements of interhemispheric differences of MC of 1.67, 1.72, 1.56, 1.40, and 1.45 for 1975, 1976, 1977, 1978, and 1979, respectively (Khalil and Rasmussen, 1980; Robinson, 1978). Time-trend monitoring has been conducted nearly continuously at a ground station in eastern Washington state since July 1977 (Cronn, 1980a). Increases have exceeded 12 percent per year since that time.

Rasmussen and Khalil (1981b), from 1979 to early 1981, measured tropospheric levels of MC at six locations, ranging from 70°N to 42°S, including several measurements at the south pole (90°S). Analysis was made by EC/GC. From these measurements, a global average concentration of 115 ppt was calculated along with an annual increase of 6.7 ± 2.0 percent. This global average is consistent with the values reported by others for previous years. In contrast, however, to the rate of increase reported by Singh et al. (1979a) for the period 1975 to 1978, the rate of increase appears to be declining, which Rasmussen and Khalil (1981b) attribute to an overall reduction in the rate of emissions. The hemispheric difference in concentration reported by Rasmussen and Khalil (1981b) is consistent with that reported by Singh et al., (1979b). During the period from January 1979 to December 1980, the northern hemisphere average was 130 ppt compared to the southern hemisphere average of 99 ppt (Rasmussen and Khalil, 1981b).

Intermittent monitoring of MC at various urban, nonbackground and rural locations has also been conducted by Cronn and coworkers (Cronn, 1980b; Cronn and Harsch, 1979b; Cronn et al., 1979; Harsch and Cronn, 1979). Levels greater than 5 ppb have been measured in Claremont, California, with an average of 1.2 ppb during September 1978 (Cronn et al., 1979; Harsch and Cronn, 1979). Evidence of regional pollution buildup was observed in the Smoky Mountains of Tennessee in September 1978, with levels averaging 50 percent greater than

background tropospheric levels typical at that time (Cronn and Harsch, 1979; Cronn et al., 1979). Values in the Caucasus Mountains of the Republic of Georgia, USSR, in July 1979, were identical to levels measured in rural eastern Washington (Cronn, 1980b).

A series of studies on the distribution and levels of MC and other halogenated hydrocarbons at various sites has been conducted by Pellizzari and coworkers (Pellizzari, 1977; 1978; Pellizzari and Bunch, 1979; Pellizzari et al., 1979). Methyl chloroform was detected in the ambient air at sites in New Jersey, New York, California, Louisiana, and Texas. Levels are included in Table 3-7.

Point measurements made by Lovelock (1977b) during 1972 to 1977 resulted in a lower global average background mixing ratio (73 ppt). Air samples collected at rural sites in the British Isles indicated that, during the 5 year period, MC mixing ratios increased from 31 ppt to 97 ppt. In the southern hemisphere (Africa and Antarctica), it increased from 12 ppt to 50 ppt. Absolute accuracy of the GC-ECD method was reported as ±30 percent.

In field measurements of ambient MC levels over North America (18°N to 65°N) from October 4 to 13, 1976, Pierotti and co-workers (1980) determined an average tropospheric mixing ratio of 145 ± 25 ppt for this region. The mixing ratio dropped sharply across the tropopause and in their stratosphere, suggesting a large sink at these altitudes. These investigators suggested that the data were consistent with a northern hemisphere background mixing ratio of about 100 ppt. Other point measurements of MC atmospheric mixing ratios in the troposhere are shown in Table 3-7.

TABLE 3-7. AMBIENT AIR MIXING RATIOS OF METHYL CHLOROFORM MEASURED AT SITES AROUND THE WORLD

Location	Type of site	Date	Maximum (ppb)	Minimum (ppb)	Average (ppb)	Reference
Alaska (70°N)		Aug. 1979 -Jan. 1981			≃ 0.155	Rasmussen and Khalil, 1981b
Antarctica						
South Pole	Remote	1/75			0.054	Robinson, 1978
South Pole	Remote	1/76			0.057	Ibid.
South Pole	Remote	1/77			0.070	Ibid.
South Pole	Remote	10/77 - 11/77			0.082	Ibid.
South Pole	Remote	1/78			0.083	Ibid.
South Pole	Remote	1/79			0.095	Khalil and Rasmussen
South Pole	Remote	Jan. 1979 - Jan. 1981	≃ 0.12	≃ 0.094		Rasmussen and Khalil, 1981b
South Pole	Remote	1/80			0.103	Ibid.
Arizona						
Phoenix	Urban	4/23-5/6, 1979	2.8136	0.1978	0.8235 ± 0.5974	Singh, et al., 1981
Arkansas						
Helena	Remote	11/30/76	≤ 1	≤ 1	≤ 1	Battelle, 1977
California						
Los Angeles	Urban	4/9-4/21, 1979	5.143	0.224	1.028 ± 0.646	Singh et al., 1981
Oakland	Urban	6/28-7/10, 1979	0.9672	0.1429	0.2909 ± 0.1606	Ibid.
San Jose	Urban	8/21-8/27, 1978	2.931	0.150	0.789 ± 0.649	Singh, et al., 1979a
Point Arena	Marine	8/30-9/5, 1978	0.158	0.115	0.132 ± 0.011	Ibid.
Claremont	Urban	9/78	5	0.3	1.2	Cronn, et al., 1979
Point Arena	Marine	5/23-5/30, 1977	0.150	0.083	0.111 ± 0.018	Ibid.
Badger Pass	High altitude	5/5-5/13, 1977	0.342	0.130	0.231 ± 0.056	Ibid.
San Francisco	Free tropo-sphere	4/77			0.12 ± 0.01	Cronn, et al., 1977a
Riverside	Urban	4/25-5/4, 1977	3.012	0.282	0.834 ± 0.560	Ibid.
Mill Valley	Background subject to urban transport	1/11-1/27, 1977	0.895	0.107	0.313 ± 0.130	Ibid.
Yosemite	High altitude	5/12-5/18, 1976	0.126	0.073	0.104 ± 0.009	Ibid.
Palm Springs	Suburban	5/5-5/11, 1976	0.545	0.075	0.159 ± 0.075	Ibid.
Los Angeles	Urban	4/28-5/4, 1976	7.663	0.100	1.545 ± 1.538	Ibid.
Badger Pass	High altitude	May 1976	---	---	0.988 ± 0.0097	Singh, et al., 1978c
Los Reyes	Marine	12/1-12/12, 1975	0.212	0.061	0.111 ± 0.027	Singh, et al., 1979a
Stanford Hills	Background subject to urban transport	11/23-11/30, 1975	0.565	0.070	0.141 ± 0.117	Ibid.
Los Angeles Basin	Urban-suburban	4/9-4/21, 1974	2.14	0.01	0.37 ± 0.05 (24-hour)	Simmonds et al., 1974
Delaware						
Delaware City	Urban	7/8-7/10, 1974	0.30	0.03	0.10	Lillian et al., 1975

TABLE 3-7. (continued)

Location	Type of site	Date	Maximum (ppb)	Minimum (ppb)	Average (ppb)	Reference
Hawaii						
Cape Kumakahi	Remote	Nov. 1979 - Jan. 1981			≃ 0.14	Rasmussen and Khalil, 1981b
Ireland						
Western Ireland	Remote	June/July 1974	---	---	0.048 ± 0.0172	Lovelock, 1974
Japan						
Tokyo	Urban	9/10 - 10/27, 1975	20.60	0.20	1.70 ± 1.70	Tada et al., 1976
Tokyo		May 1974-Apr 1974	---	---	0.800	Ohta et al., 1977
Kansas						
Jetmar	Remote	6/1-6/7, 1978	0.159	0.106	0.130 ± 0.016	Singh, et al., 1979a
Louisiana						
Baton Rouge, Geismar, Plaquemine	Urban	Jan/March 1977	1.6	trace	0.11	Pellizzari et al., 1979
Maryland						
Baltimore	Urban	7/11-7/12, 1974	0.21	0.044	0.12	Singh, et al., 1979a
New Jersey						
Seagirt	Marine	6/18-6/19, 1974	0.20	0.044	0.10	Lillian et al., 1975
Sandy Hook	Marine	7/2-7/5, 1974	0.33	0.030	0.15	Ibid.
Bayonne	Urban	March-December, 1973	14.4	0.075	1.59	Ibid.
Rathway/ Woodbridge, Boundbrook, Passaic	Urban	Sept. 1978	20.5	trace	11.4	Pellizzari et al., 1979
New York						
New York City	Urban	6/27-6/28, 1974	1.6	0.10	0.61	Lillian et al., 1975
Niagara/Falls/ Buffalo	Urban	July 1978	1.0	0.26	0.66	Pellizzari et al., 1979
White Face Mountains	High altitude	9/16-9/19, 1974	0.13	0.032	0.067	Lillian et al., 1975
Ohio						
Wilmington	Urban	7/16-7/26, 1974	0.35	0.030	0.097	Ibid.
Oregon						
Cape Meares	Remote	Jan. 1979 - Jan. 1981			≃ 0.155	Rasmussen and Khalil, 1981b
Panama	Remote tropo-sphere	7/77			0.97 ± 0.05	Cronn and Robinson, 1979
Samoa (14°S)	Remote	Feb. 1980 - Jan. 1981			≃ 0.155	Rasmussen and Khalil, 1981b

TABLE 3-7. (continued)

Location	Type of site	Date	Maximum (ppb)	Minimum (ppb)	Average (ppb)	Reference
Soviet Union						
Caucasus Mountains	Remote	7/79	0.12	0.15	0.13 ± 0.06	Cronn, 1980b
Tasmania						
Cape Grim	Remote	Oct. 1976 - March 1977 Jan. 1979 - June 1980	---	---	0.012 ± 0.003 ≃ 0.1	Fraser and Pearman, 1978 Rasmussen and Khalil, 1981b
Tennessee						
Smoky Mountains	Regionally polluted	9/78	0.32	0.11	0.19 ± 0.03	Cronn and Harsch 1979b
Texas						
Houston, Deer Park, Pasadena	Urban	July 1976	5.1	trace	0.44	Pellizzari, et al., 1979
Northern Mid-Latitudes	Remote troposphere	6/76	0.11	0.07	0.095 ± 13	Robinson and Harsch, 1978
Washington						
Pullman	Remote	1/75			0.090	Robinson, 1978
Pullman	Remote	1/76			0.098	Ibid
Pullman	Remote	1/77			0.109	Ibid
Pullman	Remote	10/77 - 11/77			0.115	Ibid
Pullman	Remote	1/78			0.120	Ibid
Pullman	Remote	1/79			0.135	Khalil and Rasmussen, 1980
Pullman	Remote	1/80			0.157	Ibid
Pullman	Remote troposphere	3/76			0.095 ± 0.008	Cronn et al., 1976
Spokane	Urban	4/78			0.5	Cronn et al., 1979

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4. METABOLIC FATE AND DISPOSITION

4.1 ABSORPTION, DISTRIBUTION, AND ELIMINATION

Methyl chloroform (MC; 1,1,1-trichloroethane) is currently one of the most widely used of the chlorinated aliphatic hydrocarbon solvents. Since the introduction in the mid-1950's as a cold cleaning solvent substitute for carbon tetrachloride, MC has gained recognition as being among the least toxic of the chlorinated aliphatic hydrocarbons and is increasingly replacing other supposedly more toxic chlorinated solvents such as trichloroethylene (Torkelson et al., 1958; Prendergast et al., 1967; Stewart, 1968). The fact that its isomer, 1,1,2-trichloroethane, is markedly more toxic than MC (Hardie, 1964; Irish, 1963; Browning, 1965; Carlson, 1973), is in agreement with the general observation that chlorinated ethanes having chlorines on both carbon atoms are considerably more soluble in water, blood, and lipid (Table 4-1). These physical properties are responsible in part for the manifestations of chlorinated hydrocarbon toxicity (Sato and Nakajima, 1979; Clark and Tinston, 1973).

4.1.1 Oral and Dermal Absorption

While limited absorption of MC vapor through the lungs is the common route of entry into the body, MC is also rapidly and completely absorbed from the gastrointestinal tract (Stewart, 1971). Stewart and Andrews (1966) reported an instance of non-fatal acute intoxication after oral ingestion of a liquid ounce of MC (0.6 g/kg body weight,BW). The concentration of MC in the expired air was measured serially and found equivalent to an inhalation exposure

TABLE 4-1. PARTITION COEFFICIENTS OF METHYL CHLOROFORM AND OTHER SOLVENTS AT 37°C

Compound	Vapor Press torr at 25C	Water / Air	Olive Oil / Air	Blood / Air	Olive Oil / Blood
1,1,1-Trichloroethane	125	0.93	356	3.3	108
1,1,2-Trichloroethane	25	17.1	2273	38.6	59
1,1-Dichloroethane	250	2.7	187	4.7	40
1,2-Dichloroethane	80	11.3	447	19.5	23
Trichloroethylene	436	1.3	718	9.5	76
Tetrachloroethylene	20	0.43	1917	13.1	146
Dichloromethane	400	7.6	152	9.7	16
Chloroform	250	3.5	401	10.3	39
Carbon tetrachloride	100	0.25	361	2.4	150

Adapted from Sato and Nakajima, 1979.

of experimental subjects to 500 ppm. On the other hand, MC vapor is poorly absorbed through intact skin and, unless it is trapped against the skin beneath an impermeable barrier, it is unlikely that toxic quantities can be absorbed (Stewart, 1971; Stewart and Dodd, 1964). Stewart and Dodd (1964) demonstrated, with continuous immersion for 30 min of the thumbs or hands of volunteers, that the solvent penetrates the skin, enters the blood circulation, and is excreted through the lungs in exhaled air. Fukabori and coworkers (1976, 1977) attempted a quantitation of cutaneous absorption in humans. Systemic absorption was evaluated by measurement of MC in blood and exhaled air and its biometabolites [trichloroethanol (TCE) and trichloroacetic acid (TCA)] in urine. After applications of the solvent to the skin of the forearm in a circumscribed area (12.5 cm^2) for 2 hr a day for 5 consecutive days, or immersion of the hands 11 times a dayfor 10 min periods, the MC concentrations in exhaled air and urinary metabolites corresponded roughly to a 2-hr inhalation exposure to 10-20 ppm MC in ambient air. The investigators concluded that absorption through the skin for workers in direct contact with liquid MC may significantly (5%) add to the absorption from vapor exposure.

4.1.2 Pulmonary Uptake and Body Burden

Possibly because of its reputation as an organic solvent with low human toxicity, few studies have been made of the pharmacokinetics of MC pulmonary uptake, concentration in the body, and metabolism after exposure to low inhalation concentrations approximating the accepted TLV-TWA concentration. Information available from these studies relate to single exposures in experimentally controlled conditions with animals or human volunteers. Little information is available regarding long-term exposure, such as may occur in

the workplace or in the environment. Recent studies have greater reliability than earlier studies because of the availability of gas chromatographic methods for the analytic determination of MC and its metabolites in alveolar air, body fluids, and tissues (Monster et al., 1979b; Monster and Boersma, 1975; Astrand et al., 1973; Eben and Kimmerle, 1974; Briemer et al., 1974; Humbert and Fernandez, 1976, 1977; Stewart et al., 1969), although spectrophotometric methods based on adaptations of the Fujiwara reaction are still widely used by many investigators for determining urinary excretions of trichloroethanol (TCE), trichloroacetic acid (TCA), or total urine chloro-derivatives of MC (Ogata et al., 1974; Imamura and Ikeda, 1973; Tanaka and Ikeda, 1968; Ikeda and Ohtsuji, 1972).

Inhaled MC rapidly equilibrates with arterial capillary blood across the lung alveolar endothelium (Astrand, et al., 1973). The rate of pulmonary uptake or absorption depends largely on the solubility of MC in blood (Ostwald solubility coefficient) and hence the blood/air partition coefficient (Table 4-1). Vapors with a high partition coefficient are absorbed into the body readily and achieves a high level of accumulation. Conversely, vapors with a low partition coefficient accumulate slowly because and, partition occurs more rapidly with venous blood and alveolar air, are more rapidly eliminated into expired air following exposure. In comparison with other common solvents in Table 4-1, MC possesses a relatively low blood/air partition coefficient of about 3.3 at 37°C.

The magnitude of MC uptake into the body (dose, burden) is directly related to the following factors: 1) concentration of MC in the inspired air; 2) duration of exposure; 3) pulmonary ventilation during exposure; 4) blood/air partition coefficient; 5) rates of diffusion into, and solubility in, the

body tissues; and 6) total body-lipid repository. Consequently, during exposure at a given inspired air concentration, pulmonary uptake and retention is initially large and gradually decreases to a minimum steady-state value as total body equilibrium (and body burden) with inspired air concentration, is reached. At this steady-state condition, pulmonary uptake balances the pulmonary and other routes of elimination, including metabolism. For any given breath cycle during exposure, the proportion of MC absorbed and retained by the body is equal to the inspired air concentration (C_I) minus the end alveolar air concentration (C_A) and, since pulmonary uptake is a function of inspired air concentration, the percent retention is:

$$\% \text{ retention of inspired air concentration} = \frac{C_I - C_A}{CI} \times 100 \qquad (1)$$

This value is large at the beginning of exposure, but gradually decreases to a constant minimum value as total body equilibrium is approached (Figure 4-1). The percent retention value at equilibrium is independent of the inspired air concentration at equilibrium. During experimental exposures of subjects to 70 and 140 ppm MC for 4 and 8 hr, both Monster et al. (1979b) and Humbert and Fernandez (1977) found retention to be 30 percent of inspired air concentration at an equilibrium reached after 4 hr of exposure.

The total amount (dose, Q) of MC retained in the body during an inhalation exposure can be estimated by multiplying percent retention by the volume of air inspired during the exposure period, or:

$$Q = (C_I - C_A) \dot{V} \cdot T \qquad (2)$$

where $\dot{V}$ is ventilation rate (ℓ/min) and T is exposure period (min). Since the retention value decreases exponentially during the exposure until equilibrium is reached (Figure 4-1), either experimental measurements of retention at frequent intervals during exposure (Monster et al., 1979b) or integration over

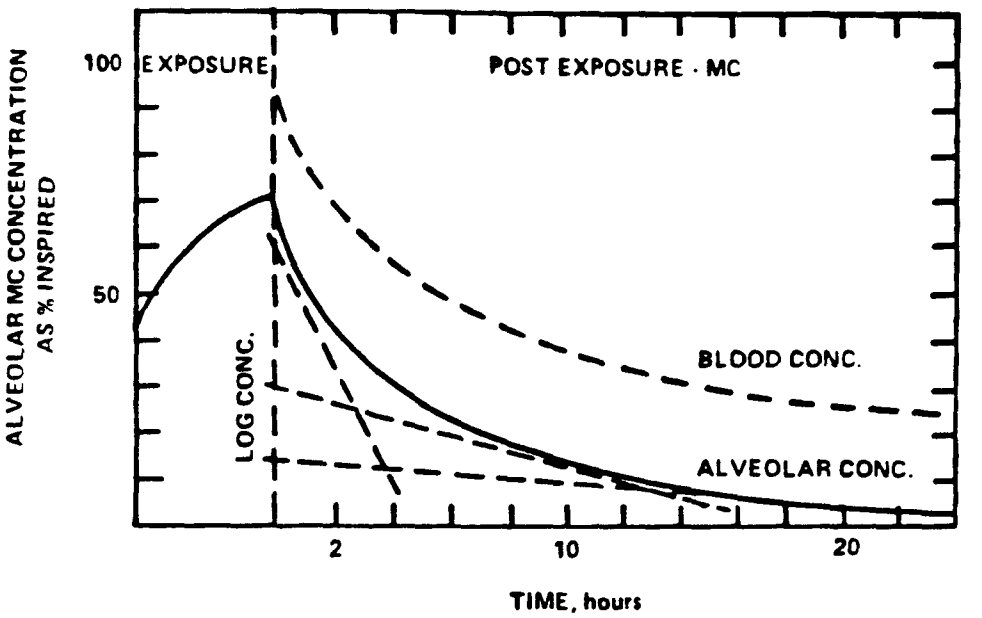

Figure 4-1. Absorption and pulmonary elimination of MC, and blood concentration (see text for explanation).

Source: Davidson (1980).

the experimentally determined retention function is required (Humbert and Fernandez, 1977). The exponential nature of the retention curve is due to first-order kinetics of saturation of body compartments with MC.

Table 4-2 shows the amounts of MC absorbed into the body during inhalation exposures for volunteers from the studies of Monster et al. (1979b) and Humbert and Fernandez (1977). Monster and his coworkers estimated pulmonary uptake of MC by multiplying the minute volume by percent retention during single 4-hr exposures to 70 ppm and 142 ppm. They observed a direct proportionality between uptake and inspired air concentrations of MC. Similar results were obtained by Humbert and Fernandez for volunteers exposed for 8 hr to 72 ppm and 213 ppm. Comparison of pulmonary uptake for 4-hr and 8-hr (Table 4-2) exposures indicates that the amount of MC retained is also proportional to duration of exposure, although the values for uptake determined by Humbert and Fernandez are 40 percent lower than those of Monster et al. This variation can be ascribed to differences in the experimental methodologies and average minute volume. Nonetheless, these experimental results indicate that the body burden resulting from an 8-hr inhalation exposure to 350 ppm (TLV-TWA) approximates 1.5 to 2 g of MC for a normal 70-kg man.

The body uptake of MC increases with the duration of inhalation exposure and with physical work or exercise. Monster et al. (1979b) found that during a 4-hr exposure to 142 ppm MC, with physical activity equivalent to light physical work (100 watts), pulmonary uptake increased from 429 mg to 538 mg MC, an increase of 25 percent (Table 4-2). This increase was primarily due to an increase of ventilation from 10.7 ℓmin^{-1} sedentary to 30.6 ℓmin^{-1} with work. While it might be expected from equation (2) that the increased uptake should be directly proportional to the ventilation rate increment, an increase

TABLE 4-2. ESTIMATED UPTAKE OF MC DURING A SINGLE 4-HR INHALATION EXPOSURE (AVERAGE BODY WEIGHT, 77 kg; 67 kg LEAN BODY MASS), MONSTER ET AL., 1979

Subject	Exposure Concentration		
	70 ppm (at rest*) Uptake, mg	145 ppm	142 ppm*, with work (100 watt) Uptake, mg
A	140	305	435
B	240	520	610
C	200	465	540
D	185	395	560
E	200	425	575
F	190	465	505
Av.	193	429	538

*Ventilation minute volume increased from average of 10.7 ℓ/min. at rest to 30.6 ℓ/min during light work.

ESTIMATED UPTAKE OF MC DURING A SINGLE 8-HR INHALATION EXPOSURE (AVERAGE BODY WEIGHT 74 kg), HUMBERT AND FERNANDEZ, 1977

Subject	Exposure Concentration*	
	72 ppm Uptake, mg	213 ppm
BH	293	921
JC	274	912
JO	277	--
Av.	281	917

*Average ventilation minute volume 5.7 ℓ/min.

in ventilation also tends to increase alveolar elimination of MC from pulmonary venous blood. Similar observations were made by Astrand et al. (1973) with volunteers exposed to an MC inhalation concentration of 250 and 350 ppm for 30 min at rest, alternating with identical exposure plus 50 watt of light work. Table 4-3 shows that their subjects responded to this work with a 3-fold increase of pulmonary ventilation, nearly a 2-fold increase in cardiac output, and a 50 percent increase in arterial blood concentration, which is an index of pulmonary uptake. Also, end alveolar concentration of MC increased while retention decreased from 50 to 33 percent with work. Therefore, physical activity during MC exposure increases the uptake and body burden, but the increase is not directly proportional to increased ventilation and is self-limited by a compensatory increase of pulmonary elimination. For solvents like MC, with a low blood/air partition coefficient, physical activity has a smaller effect on net pulmonary uptake and body retention than those solvents with a high blood/air partition coefficient (e.g., trichloroethylene, perchloroethylene, dichloromethane; Table 4-1; Monster, 1979).

During inhalation of MC, and in the elimination phase after exposure, the arterial blood concentration always is directly proportional to the alveolar concentration (Monster et al., 1979b; Humbert and Fernandez, 1977; Astrand et al., 1973; Gamberale and Hultengren, 1973; Eben and Kimmerle, 1974). Since at equilibrium the end alveolar air concentration is proportional to inspired air concentration, blood concentration of MC is also related to inspired air concentration (Monster et al., 1979b; Humber and Fernandez, 1977; Astrand et al., 1973). This fixed relationship between alveolar air and blood concentration is defined by the blood/air partition coefficient for MC. Figure 4-2 illustrates this linear relationship for a volunteer exposed for 30 min to

TABLE 4-3. MEAN VALUES AND SEM FOR 12 MALE SUBJECTS AT REST AND EXERCISE FOR 30 MINUTE PERIODS

MC	Ventilation BTPS ℓ/min	Cardiac output ℓ/min	Alveolar conc ppm	Blood arterial conc. µg/g
At rest				
250 ppm	6.6 ± 0.4	5.1 ± 0.4	125 ± 6	3.0 ± 0.2
350 ppm	6.6 ± 0.4		179 ± 13	5.0 ± 0.5
50 Watt				
250 ppm	22.5 ± 1.0	9.7 ± 0.6	168 ± 7	4.5 ± 0.2
350 ppm	21.8 ± 1.1		239 ± 17	7.2 ± 0.4

From Astrand et al. (1973).

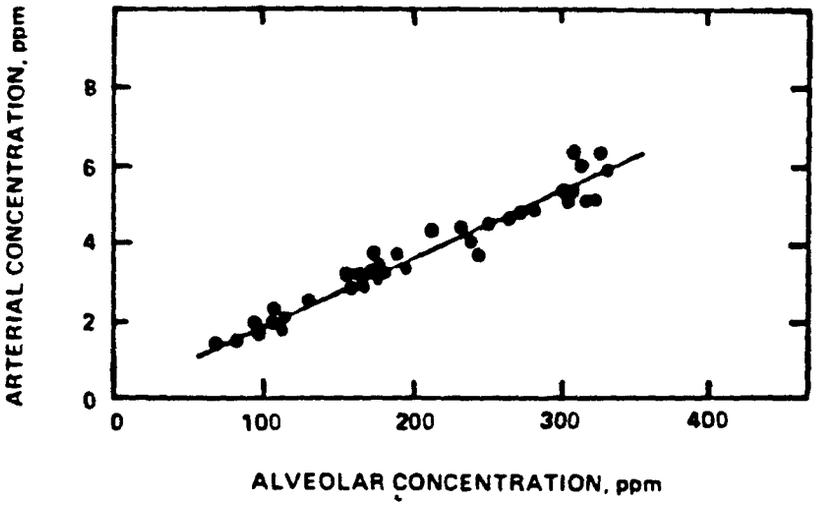

Figure 4-2. Relationship between methyl chloroform concentration in alveolar air and arterial blood. Data from one subject. Product moment correlation: r = 0.985. Data from one subject exposed to 30-min. periods of MC. Alveolar air samples and arterial blood samples.

Source: Gamberale and Hultengren (1973).

increasing increments of MC concentration in inhaled air. The relationship was independent of the duration of exposure over the time period studied. Eben and Kimmerle (1974) exposed rats to 204 ppm for 8 hr daily, 5 days a wk for 14 weeks and found that the blood concentration of MC determined immediately after daily exposure remained constant during the entire 3 mo period.

The blood/air partition coefficient, as determined from in vivo measures of alveolar air concentration and blood concentration of MC, agrees well with the in vitro value of 3.3 at 37°c determined by Sato and Nakajima (1979) (Table 4-1). Table 4-3 summarizes the data of Astrand et al. (1973) determined for sedentary men exposed to 250 and 350 ppm MC for 30-min periods alternating with 30-min periods of physical activity. The ratios of arterial blood concentration (μg/g) to alveolar MC concentration remain nearly constant over a 2-fold range of alveolar concentrations, with an average value of 5. Monster et al. (1979b) estimated from their study of men exposed to 70 and 142 ppm MC a blood/alveolar air concentration ratio of 6. In comparison to other solvents (Table 4-1), MC has a relatively small blood/air partition coefficient, and hence for equivalent ambient air exposure concentrations the blood concentration of MC is proportionally lower than for other solvents.

The amount of MC pulmonary uptake is influenced by total body weight and also by the total fat content of the body (average body fat = 8 percent of body weight). The capacity of adipose tissue to absorb MC in vivo is determined by the product of adipose tissue volume and the lipid solubility of MC. The lipid/blood partition coefficient for MC (108 at 37°C) is higher than for most other structurally related solvents (Table 4-1) and, therefore, the capacity of adipose tissue for MC is relatively high. However, because of the low rate of perfusion (5 percent cardiac output), the time needed to saturate

adipose tissue is large in comparison with that for other tissues. Also, since the blood/air partition coefficient for MC is lower than that of other solvents, the amount of MC in adipose tissue (concentration) at the end of an exposure of similar duration will be relatively lower. Monster (1979) suggests that because of the high solubility of MC in adipose tissue, accumulation may occur with repeated daily exposures, particularly in obese persons. This speculation is supported by the observations of Savolainen, Vainio and co-workers (1977, 1978), who exposed rats to MC (500 ppm) 6 hr daily for 5 days and determined MC concentrations in perirenal adipose tissue and in other body tissues. Their data, shown in Table 4-4, indicate that measureable amounts of MC remained in perirenal fat tissue 18 hr after the previous exposure of day 4, and markedly increased further with a 6-hr exposure on day 5. The adipose tissue/blood partition coefficient calculated from these data was 21, as compared to 1.6 for brain and liver tissues. On the other hand, Eben and Kimmerle (1974) exposed rats for 14 weeks (8 hr daily, 5 day per wk) to 204 ppm MC but failed to find MC in adipose or other tissues and concluded that MC did not accumulate with chronic exposure. However, the average exposure concentration for their rats was lower than that used by Savolainen et al. (500 ppm vs. 204 ppm).

4.1.3 Tissue Distribution

During exposure to MC, distribution of the compound throughout the body and the amount concentrated by each tissue is primarily governed by the blood concentration, the blood perfusion rate, and the affinity of MC for respective tissues, as determined by individual tissue/ blood partition coefficients. In comparison with other chlorinated hydrocarbon solvents that are known to be distributed widely in the body, MC has one of the highest lipid/ blood partition coefficients (108 at 37°C, Table 4-1) and would distribute into all

TABLE 4-4. TISSUE CONTENT (RAT) OF METHYL CHLOROFORM (MC) AFTER CHRONIC INHALATION EXPOSURE OF 500 ppm*

Exposure on 5th day hr.	Cerebrum	Cerebellum	Liver	Perirenal fat	Blood
	nmolMC/g wet weight ± range				
0	0.15 ± .03	0.17 ± .03	0.15 + .01	16.9 + .5	0.08 ± .01
2	14.6 ± 1.1	14.0 ± 2.2	14.7 ± .04	183.5 ± 10.7	11.5 ± 2.0
3	13.4 ± .60	13.2 ± .8	15.7 ± 3.3	218.9 ± 63.4	8.5 ± 1.0
4	12.2 ± .40	15.9 ± 1.5	16.2 ± 2.8	261.2 ± 19.1	12.7 ± 2.9
6	15.6 ± 4.6	21.3 ± 9.6	21.3 ± .4	276.0 ± 30.1	13.1 ± 1.9

*Measurements were performed on the 5th day of exposure after 4 previous daily exposures, 6 hr daily.

From Savolainen et al. (1977).

body tissues, particularly those high in lipid content, such as brain and adipose tissue (Holmberg et al., 1977). Table 4-4 shows the concentrations of MC in liver, brain, and adipose tissue of rats exposed to 500 ppm in their inspired air for 6 hr daily for 5 days (Savolainen et al., 1977). Adipose tissue appears to have a partition coefficient with blood of approximately 20, and brain tissue levels are also greater than blood concentration. In man, MC readily passes the blood-brain barrier, resulting in high concentrations in the brain (Caplan et al., 1976) and in the cerebrospinal fluid (Larsby et al., 1978). While it has not been demonstrated directly to cross the placental barrier into the fetus, it may be expected to do so (Laseter and Dowty, 1977) like other highly lipid-soluble haloalkanes. Trichloroethanol (TCE), a major metabolite of MC, is known to cross readily into the fetus (Bernstine, 1954, 1957). While there is no report of MC occurring in colostrum or milk of nursing mothers, it may be expected to distribute readily into these compartments because of their high lipid content.

4.1.4 Pulmonary Elimination

Figure 4-1 shows schematically the time-course of pulmonary elimination of MC after exposure. At termination of exposure, MC immediately begins to be eliminated from the body into the lungs with blood concentration and alveolar air concentration describing parallel exponential decay curves with three major components. These components represent first-order passive diffusions of MC from three major body compartments: (1) most rapidly from a vessel-rich group of tissues (VRG) with high blood flow and high diffusion rate constant (VRG: brain, heart, kidneys, liver, endocrine, and digestive system), (2) more slowly from the lean body mass (MG; muscle and skin) and (3) from adipose tissue (FG) (Fiserova-Bergerova and Holaday, 1979). The rate constants for

the passive diffusion from VRG, MG and FG compartments are dependent on both the arterial blood flow/tissue mass and the relative solubilities of MC in the tissues of these compartments (tissue/ blood partition coefficients). However, the ranking of half-times ($t_{1/2}$) of elimination of MC is VRG < MG < <G and is independent of the body burden. The areas under the alveolar or blood elimination curves in Figure 4-1 are proportional to the quantity of MC absorbed during exposure. The body burden can be obtained by integrating the exponential functions from the time immediately at the end of exposure to infinity.

The precise half-times of elimination of MC from the three major body compartments have not been well established. Monster et al. (1979b), who exposed subjects to 70 ppm and 145 ppm for 4 hr, estimated from decay curves of MC in blood and exhaled air half-times of elimination of 9.2 hr and 26 hr for the MG and FG compartments, respectively. Humbert and Fernandez (1977) determined the exponential decay of alveolar air concentration after 8 hr exposure of subjects to 72 and 215 ppm MC. These investigators calculated half-times of elimination for compartments VRG, MG, and FG as 0.8 hr, 7 hr, and 35 hr, respectively. From the postexposure alveolar concentration curves published by Stewart and his associates (Stewart and Andrews, 1966; Stewart et al., 1969; Stewart, 1971) for subjects singly and repeatedly exposed to various inhalation concentrations of MC, the half-time of elimination for MG and FG can be estimated as approximately 14 hr and 24 hr, respectively. The long half-time of elimination (24 to 35 hr) from the adipose tissue compartment observed by all investigators reflects the high lipid/blood partition coefficient of MC and indicates that complete elimination of MC from this compartment requires at least 4 to 5 days. Experimentally, both Monster et al.

(1979b) and Humbert and Fernandez (1977) observed that, after single controlled inhalation exposures, pulmonary elimination was not complete for 6 to 10 days as determined by the continued presence of MC in alveolar air. The possibility of significant accumulation with repeated daily exposures to this solvent (Laseter and Dowty, 1977), however, is offset in part by the low blood/air partition coefficient (Table 4-1), which for a given exposure concentration limits pulmonary absorption and body dose.

4.1.5 Elimination by Other Routes

There is no report in the literature of significant elimination of MC by any route other than pulmonary. MC is poorly soluble in water, even when compared with other chlorinated hydrocarbons (Table 4-1), and with its high lipid/water partition coefficient MC is unlikely to be excreted unchanged in the urine in any significant amounts. Studies of chlorinated compounds in the urine after exposure of animals and humans to MC have not reported its appearance in urine (Monster et al., 1979; Eben and Kimmerle, 1974; Humbert and Fernandez, 1977; Seki et al., 1975; Stewart et al., 1961; Hake et al., 1960). Since highly lipid soluble substances like MC readily cross into the intestinal lumen, some fecal and flatus excretion can be expected during inhalation exposures. After controlled inhalation exposures, Humbert and Fernandez (1977) were able to account for 88 to 100 percent of an estimated retained dose as unchanged MC in postexposure exhaled air and as metabolites of MC in urine. However, Monster et al. (1979b) could account for only 60 to 80 percent; furthermore, they noted that the percentage recovered decreased with higher exposure doses.

4.2 BIOTRANSFORMATION

MC has long been known to be metabolized to only a very limited extent by mammals. The generally accepted metabolites of MC -- trichloroethanol (TCE),

TCE-glucuronide, and trichloroacetic acid (TCA) -- are excreted primarily by the kidney, but very small amounts of TCE (<1 percent) are excreted by the lungs (Monster et al., 1979b). TCE-glucuronide is also excreted to an unknown extent in bile (Owens and Marshall, 1955). No other metabolites have been reported.

4.2.1 Magnitude of MC Metabolism

Only one balance study with isotopically labeled MC has ever been carried out. More than 20 years ago, Hake and his coworkers (1960), using ^{14}C-labeled MC, determined that less than 3 percent of MC is metabolized by rats. More recently, estimates of the extent of metabolism in man have been made from controlled inhalation exposures with unlabeled MC (Seki et al., 1975; Monster et al., 1979b; Humbert and Fernandez, 1977). From the experimentally determined retained dose and the amounts of MC metabolites excreted into the urine, the percent of the dose metabolized in man is estimated to be about 6 percent.

Hake et al. (1960) found that 98.7 percent of a dose of MC given to rats was eliminated unchanged via the lungs. These investigators injected ^{14}C-labeled 1,1,1-trichloroethane-1-^{14}C (700 mg/kg) intraperitoneally into 3 rats (170-183 g), which were then placed individually in a Roth metabolism unit with air traps for ^{14}C-MC (cold toluene), $^{14}CO_2$ (NaOH solution) and finally a trap for "metabolites" (quartz-tube furnace and halogen absorber that converted any halogenated hydrocarbon to inorganic halogen and CO_2, and absorbed the halogen). Each rat was kept in the unit for 25 hours, during which time urine and feces were collected. At necropsy at 25 hr, blood and tissue samples were analyzed for total ^{14}C-activity. The ^{14}C-MC used in the experiments was synthesized by the investigators and was determined by paper chromatography to be 99 percent pure, with possible contamination by 0.4 percent 1,1,2-trichloroethane isomer and 0.5 percent 1,1-dichloroethane. Their findings, summarized

in Table 4-5, indicate that metabolism of MC in the rat is limited to about 2 percent of a very large dose. However, only TCE-glucuronide was identified as a metabolite in the urine, and the source of the $^{14}CO_2$ in expired air could not be defined because of the presence of small amounts of ^{14}C-1,1,2-isomer and ^{14}C-dichloroethane in the dose.

Man also appears to possess a very limited capacity for metabolism of MC. Table 4-6 summarizes data taken from several investigative studies showing the amount of urinary metabolites excreted after exposure to various concentrations (4.3 to 213 ppm) of MC in inspired air. Seki et al. (1975) surveyed workers in 4 printing plants where MC was the sole organic solvent in use. The workers were exposed 8 hr daily, 5 1/2 days per wk, over a period of at least 5 years. Urine samples were collected in the latter half of the work week. Their data in Table 4-6 show a proportional increase of both TCE (as glucuronide) and TCA, and also total trichlorinated compounds (TTC) with increased ambient air concentrations of MC. Seki et al. expressed their data as a linear relationship between inspired MC concentration and urinary metabolite excretion, with an added constant increment presumably due to continued excretion from the previous day's exposure. From this observation and from evidence of continued excretion during exposure-free weekends, they suggested that MC accumulates in the body to a steady-state body burden defined by the air concentration of each daily exposure. Seki et al. also noted that the amounts of metabolites excreted daily in the urine of these workers were less than 5 percent of that observed with comparable exposures to trichloroethylene, of which 60 to 80 percent is metabolically degraded to TCE and TCA (Monster, 1979). This comparison suggests that about 5 percent or less MC is metabolized.

TABLE 4-5. HAKE ET AL. (1960) RECOVERY EXPERIMENT WITH RATS (3) INTRAPERITONEALLY INJECTED WITH ^{14}C-MC (700 mg/kg)

	Average % dose
Expired Air	
Unchanged MC (by isotopic dilution)	97.6
Unknown compound detected by furnace (assumed to be unchanged MC)	1.1
$^{14}CO_2$ (in NaOH) 70% within 4 hr; 100% within 12 hr	0.5
Urine	
TCE-glucuronide + other volatile compounds but no detectable TCA	0.85
Feces	
Uncharacterized	0.03
Tissues	
Uncharacterized except skin (90% unchanged MC)	0.18

The data (Table 4-6) of Monster et al. (1979b) and of Humbert and Fernandez (1977) were obtained from subjects given single 4-hr and 8-hr exposures to 70 and 145 ppm, and 72 and 213 ppm MC, respectively. Total urinary excretion of TCE (glucuronide) and TCA is observed to be proportional to the inspired air concentration of MC and to the expected body burden from these exposures (with duration of exposure also taken into account). Both these research groups attempted a balance study by estimating the retained body dose of MC either by measuring lung clearance during exposure (Monster et al., 1979b), or by integrating over the MC alveolar air decay curve to infinite time postexposure (Humbert and Fernandez, 1977). The percentages of the retained dose metabolized to TCE and TCA were 2.5 and 6.3 percent, respectively. The difference can be ascribed to the different methodologies used for estimating body dose and their inherent imprecisions. In both studies, the percentages of MC metabolized were found to be independent of the retained dose (Table 4-6). A similar observation with rats was made by Eben and Kimmerle (1974), who measured urinary excretion of TCE and TCA for 3 days after a 4-hr inhalation of MC at 221 and 443 ppm. The amounts of the metabolites excreted were proportional to the inspired concentration of MC. In rats, the urinary ratio of TCE/TCA was 20/1 rather than the 3/1 observed in humans (Table 4-6).

A reasonable conclusion from these studies is that MC is minimally metabolized by man on the order of 3 to 6 percent of the inhaled dose. The percentage of the dose metabolized is constant and independent of the body dose (at least up to 213 ppm), which suggests that some factor other than the capacity of the metabolizing system is the limiting one (e.g., hepatic extraction).

4.2.2 Kinetics of Blood and Urine Metabolites

The blood and urinary metabolites of MC (total amount, excretion ratios, and excretion time-course) are of interest as quantitative indices of exposure

TABLE 4-6. RELATION BETWEEN INHALATION EXPOSURE AND URINARY METABOLITES OF MC

Seki et al., 1975

Average concentration of metabolites in urine samples from workers daily exposed to MC.

Plant	Air conc. MC, ppm	No. Subjects	TCE* mg/ℓ	TCA mg/ℓ	TTC/g creatinine
A	0	30	0	0	0
B	4.3	10	1.2	0.6	2.1
C	24.6	26	5.5	2.4	6.8
D	53.4	10	9.9	3.6	15.0

Monster et al., 1979b

Averaged amounts of metabolites in total urine collected 70-hr post single exposure (4 hr).

Air Conc. MC, ppm	No. Subjects	TCE* mg	TCA mg
72	6	5.5	1.5
145	6	11.5	2.8
Estimated as % retained dose		2%	0.5%

Humbert and Fernandez, 1977

Averaged amounts of metabolites in total urine collected for 12 days post single exposure (8 hr).

Air cond. MC, ppm	No. Subjects	TCE* mg	TCA mg
72	3	15.2	5.2
213	2	30.7	13.0
Estimated as % retained dose		4.6%	1.7%

*TCE found as glucuronide.

and body burden. However, the known metabolites of MC--TCE, TCE-glucuronide, and TCA -- are not pathognomonic of MC, but are also metabolites of other chlorinated hydrocarbons, e.g., trichloroethylene.

From studies of men exposed to 70 and 145 ppm MC inhaled for 4 hr, Monster et al. (1979b) found that the TCE concentration in blood was proportional to both the inspired concentration and the blood concentration of MC. TCE blood concentration was about 4 percent that of MC (0.2 mg ℓ^{-1} and 0.09 mg ℓ^{-1} TCE for 145 and 70 ppm MC inspired, respectively). After termination of exposure, blood TCE concentration declined exponentially with a half-life of 10 to 12 hr. Urinary appearance of TCE and TCE-glucuronide paralleled the disappearance of blood TCE, and daily excretion decreased with a half-time of renal elimination of 10 to 12 hr. This value is in agreement with that observed after ingestion of TCE itself (Briemer et al., 1974; Muller et al., 1974). In contrast to the first-order blood decay kinetics of TCE, blood concentrations of TCA progressively increased after the end of MC exposure for about 40 hr before declining exponentially with a half-life of 70 to 85 hr. Consequently, TCA appeared in the urine in almost equal daily amounts for 3 days before decreasing. Exogenous TCA administered to men has a similarly long half-time of renal elimination of 50 to 82 hr, presumably because of very tight non-covalent binding to plasma proteins (Paykoc and Powell, 1945; Muller et al., 1974). Therefore, the rise in plasma concentration of TCA during the 24 to 48 hr period following exposure is due to a rate of formation of TCA from TCE greater than the rate of renal elimination of TCA. Similar observations on daily urinary excretion of TCE, TCE-glucuronide, and TCA following acute MC inhalation exposure have been made in man by Humbert and Fernandez (1977), and in rats by Eben and Kimmerle (1974).

Stewart et al. (1969) investigated urinary metabolite excretion in men repeatedly exposed to MC inhalation (500 ppm, 7 hr per day for 5 days). The daily ratio TCE/TCA during exposure remained relatively constant (about 2.8), but rapidly decreased within several days after exposure (5th day, 0.4), indicating that the daily urinary TCE excretion decreased while the TCA excretion decreased at a lesser rate or may have gradually increased. Eben and Kimmerle (1974) also chronically exposed rats for 14 wk (8 hr daily, 5 days per week) and measured blood levels of MC, TCE, and TCA, as well as daily urinary excretion. Blood concentrations of MC and TCE (determined immediately after daily exposure) remained essentially constant during the entire 14 week period, with a concentration ratio of MC:TCE of 10:1. Weekly urinary excretion of TCE reached a plateau within 3 to 4 wk, whereas TCA weekly excretion was constant throughout the entire 14-wk period. The urinary excretion ratio TCE/TCA was thus initially low, but after 3 to 4 wk exposure reached a constant value of approximately 18.

These findings show that the daily urinary ratio of TCE/TCA (mg/day) during chronic MC exposure of both man and rats is determined by the relative rates of metabolic formation and by the differences in renal elimination of TCE (rapid, half-time 10 to 12 hr) and TCA (slow, half-time 50 to 70 hr). In blood, both metabolites achieve steady-state plateau concentrations (TCE more rapidly than TCA) related to the inspired air concentration of MC and its metabolites. In urine, the TCE/TCA ratio, initially low, rises to a constant daily value. After termination of either acute or chronic exposure, the ratio of the amounts of daily urinary metabolites, TCE/TCA (mg/day), is highest 24 hr after exposure. Thereafter, its progressively decreases daily to less than unity by the 5th or 6th day postexposure because of the relatively rapid renal

elimination of TCE and the slow renal elimination of TCA (Stewart, 1969; Eben and Kimmerle, 1974; Monster, 1979).

The profile of TCE and TCA urinary excretion during and after MC exposure is similar to that observed for trichloroethylene (Nomiyama and Nomiyama, 1971; Muller et al., 1974; Sato et al., 1977; Monster et al., 1976, 1979a; Fernandez et al., 1977). However, the ratio of TCE/TCA excreted is 2-fold greater for MC than for trichloroethylene, suggesting differences in the pathways and rates of metabolism to TCE and TCA for these two chlorinated hydrocarbons. Trichloroethylene, a chlorinated olefin, is metabolized by hepatic microsomes to an epoxide, then to chloral hydrate, and thence to TCE and TCA (Liebman and Ortiz, 1977; Henschler, 1977; Van Duuren, 1977). However, neither epoxide nor chloral hydrate have been identified as metabolites of MC. Comparison of the percentage of the body dose metabolized to TCE and TCA (MC, 3-6 percent vs. trichloroethylene, 80-90 percent) explains the 25- to 30-fold difference in the total amounts of these metabolites (mg/day) excreted into urine for comparable body doses retained after inhalation exposure (Seki et al., 1975; Stewart, 1968; Stewart et al., 1969; Monster, 1979; Ikeda and Ohtsuji, 1972; Ikeda et al., 1972). In a comparative study of rats exposed to 200 ppm MC or its 1,1,2-isomer, Ikeda and Ohtsuji (1972) reported that the urinary excretion of total chlorinated metabolites was substantially less for the 1,1,2-isomer, indicating that the 1,1,2-isomer is metabolized to an even smaller extent than MC. These workers determined the urinary metabolites of the 1,1,2-isomer as TCE and TCA by a spectrophotometric method based on the Fujiwara reaction. However, the MC isomer requires a shift of a chlorine atom from one carbon to the other in order to form TCA or TCE, an unlikely reaction in vivo for a saturated aliphatic, and it is probable that dichlorometabolites were actually measured.

4.2.3 Enzyme Pathways of Methyl Chloroform Metabolism

The metabolic pathways and enzyme mechanisms for the metabolism of halogenated hydrocarbons assume considerable importance for understanding and assessing cellular toxicity. Compounds that in the course of their metabolism form intermediates reactive with cellular macromolecules, e.g., epoxides or free radicals, are associated with enhanced cellular toxicity and carcinogenic potential (Van Duuren, 1977). In comparison with other halogenated hydrocarbons, MC is not extensively metabolized by mammalian systems; this may explain in part its lower toxicity and carcinogenic potential (Weisburger, 1977). Unfortunately, these same attributes may also have contributed to the current inadequate state of knowledge of the pathways of MC biotransformation and the enzyme systems involved.

Figure 4-3 summarizes the presently postulated enzyme steps in the biotransformation of MC to TCE and TCA, the only known metabolites appearing in the plasma and urine of animals and man (Table 4-6). It is assumed that metabolism occurs principally in the liver, although in vitro experiments that directly demonstrate and evaluate MC metabolism by the liver have only been reported for TCE production (Ivanetich and Van Den Honert, 1981).

In view of the absence of MC-labeled or unlabeled balance studies with methodologies of current sophistication, the possibility of the existence of unknown minor metabolites of secondary pathways is real. Hake et al. (1960), in the only reported study using labeled MC, found that about 0.5 percent of the dose (of the 2 percent metabolized; see Table 4-7) was converted to $^{14}CO_2$, following 1,1,1-trichloroethane-1-^{14}C administration (intraperitoneal) to rats, suggesting carbon-carbon cleavage to chloroform. Chloroform is extensively metabolized to CO_2 in man (50 percent) and to glutathione-conjugated

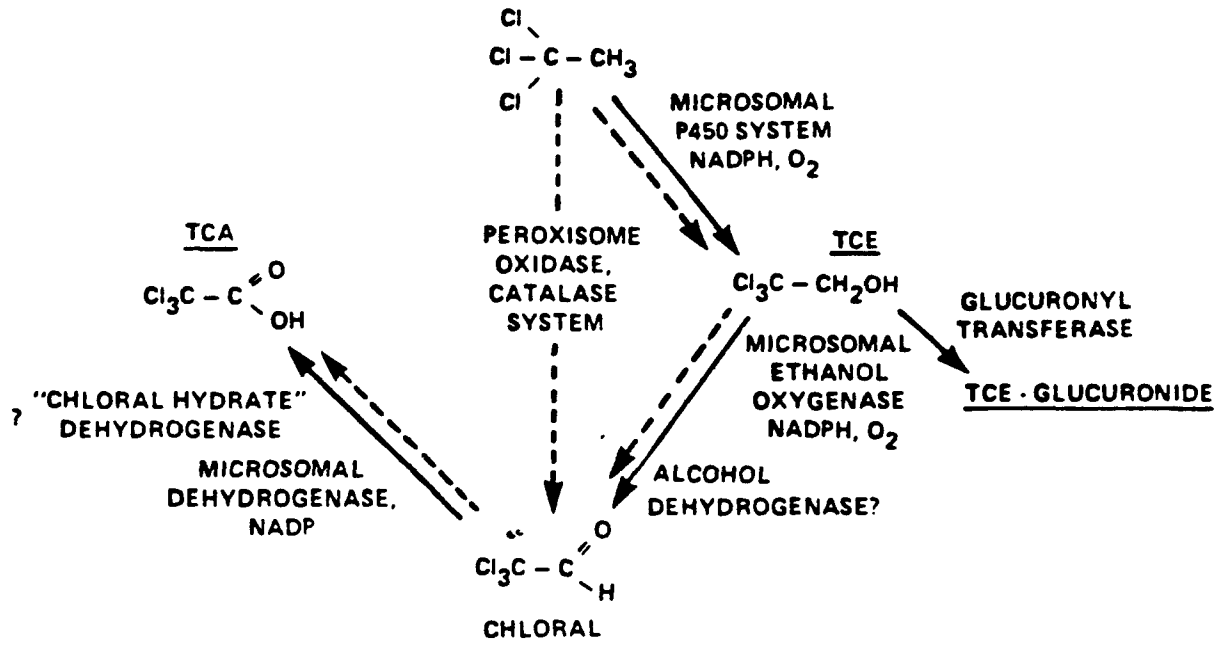

Figure 4-3. Postulated pathways of hepatic biotransformation of MC.

Source: Davidson (1980) and Ivanetich and Van Den Honert (1981).

chloromethyl derivatives (Fry et al., 1972). During these conversions, free radicals or reactive intermediates are produced which contribute to chloroform toxicity (Brown et al., 1974). However, the origin of the $^{14}CO_2$ is an open question since Hake et al. did not identify chloroform as a metabolite of MC; also, the ^{14}C-MC used was contaminated with trace amounts of the MC isomer 1,1,2-trichloroethane-1-^{14}C (0.4 percent) and 1,1-dichloroethane-1-^{14}C (0.5 percent). Both of these compounds were reported by Van Dyke (1971, 1977) to be readily dechlorinated by the rat liver microsomal P450 system. The optimal configuration for dechlorination was a dichloromethyl group. Hence, 1,1,2-trichloroethane, the more toxic isomer, was readily dechlorinated but 1,1,1-trichloroethane was not. For the isomer 1,1,2-trichloroethane, the products were identified as mono-and dichloroethanol and mono- and dichloroacetic acid (Van Dyke and Wineman, 1971), which are known to be metabolized to CO_2 or to form glutathione conjugates (Yllner, 1971a,b). Carlson (1973) found that pre-treatment of rats with phenobarbital, but not methylcholanthrene, potentiated hepatotoxicity (measured as serum SGOT and SGPT) of both inhaled MC and its 1,1,2-isomer, but the toxicity of the isomer was increased to a far greater extent. These several observations suggest that 1,1,2-trichloroethane, but not MC, may be extensively metabolized by the oxidative dechlorination system of Van Dyke and Wineman (1971).

Figure 4-3 shows that the initial pathway of MC transformation is hydroxylation of MC to TCE by the microsomal P450 mixed function oxidase system (Ivanetich and Van Den Honert, 1981). There are several other observations which support this finding.

First, when MC is incubated aerobically with rat liver microsomes plus NADPH, it produces a P450 type I binding spectrum with peaks at 452 nm and 420 nm, and a reduced spectrum with a peak at 420 nm only (Cox et al. 1976; Pelkonen and Vainio, 1975).

Secondly, MC inhalation induces the P450 drug metabolizing system (Fuller et al., 1970; Lal and Shah, 1970). Rats exposed to inhaled MC (2500 to 3000 ppm) for 24 hr exhibited decreased hexobarbital sleeping time, and decreased duration of effect of meprobamate and zoxazolamine. Furthermore, liver microsomes from MC-pretreated rats exhibited increased in vitro metabolism of hexobarbital, zoxazolamine, and aminopyrine, type I substrates. Livers from pretreated rats had increased cytochrome P450 and NADPH cytochrome C reductase activity, preventable by cycloheximide or actinomycin D. This induction of hepatic microsomal drug metabolism in the reports of Fuller et al. (1970) and Lal and Shah (1970), suggests the possibility that MC might induce its own metabolism with repeated daily exposure. Stewart et al. (1969) observed that men experimentally exposed to 500 ppm MC 7 hr for 5 days excreted in their urine progressively increased daily amounts of TCE and TCA although the daily ratio TCE/TCA remained relatively constant (2.8). Eben and Kimmerle (1974) found that rats exposed daily to 204 ppm MC (8 hr/day 5 day/wk) for 14 weeks excreted progressively increasing amounts of TCE for the first few weeks. The TCE/TCA ratio increased to a maximum (about 20) that was maintained for the remainder of the 14-wk exposure period.

Thirdly, MC can interact with pathways of drug metabolism. Plaa et al. (1958) and Shah and Lal (1976) found that MC given intraperitoneally to mice (1 mg/kg) potentiates pentobarbital sleeping time and reduces hexobarbital metabolism by liver microsomes. This observation, in contrast to induction of metabolizing enzymes by inhalation exposure or by intraperitoneal administration in oil, is explained on the basis of different amounts of MC reaching the liver by the various routes and methods of administration. Van Dyke and Rikans (1970) added MC directly to rat liver microsomes incubated in vitro.

They observed no effect on N-demethylation of aminopyrine, but a 50 percent increase of aniline 4-hydroxylation, a type II substrate. The 1,1,2-isomer produced similar results.

The origin of TCA as a plasma and urinary metabolite of MC is postulated to occur from enzymic oxidation of TCE. TCE-glucuronide, also present in plasma and urine, is presumed to be formed by glucuronyl transferase. TCE, exogenously administered to man, yields TCA as a metabolite (Marshall and Owens, 1954; Owens and Marshall, 1955a,b; Muller et al., 1974). Marshall and Owens (1954) also observed TCA formation during TCE incubation with rat or dog liver slices. The most likely reaction for the oxidation of TCE to TCA would involve the enzyme alcohol dehydrogenase (Figure 4-3). However, in vitro studies with alcohol dehydrogenase purified from horse liver, and with rat liver cytosol fractions, have shown that TCE is a poor substrate for alcohol dehydrogenase and that significant conversion to trichloroacetaldehyde (chloral) does not occur (Sellers et al., 1972; Friedman and Cooper, 1960; Marshall and Owens, 1954). The reverse reaction --reduction of chloral to TCE -- proceeds rapidly with a K_m of 2.7×10^{-3}M for horse liver enzyme (Butler, 1948, 1949; Marshall and Owens, 1954, 1955a,b; Friedman and Cooper, 1960; Sellers et al., 1972). Also, chloral hydrate has been sought, but not detected, as an intermediate metabolite in plasma of rats and man exposed by inhalation to MC (Monster et al., 1979; Eben and Kmmerle, 1974). On the other hand, chloral hydrate exogenously administered is very rapidly metabolized in vivo with a half-life of only a few minutes, yielding both TCE and TCA as metabolites in plasma and urine (Butler, 1948; Marshall and Owens, 1954, 1955a,b; Breimer et al., 1974; Muller et al., 1974; Cole et al., 1975).

The conversion of chloral to TCA is usually ascribed to so-called "chloral hydrate dehydrogenase," a substrate-specific NAD-dependent enzyme described by Cooper and Friedman (1958). This enzyme was obtained from rabbit liver acetone powders. Cooper and Friedman reported that acetaldehyde was not a substrate, but rather a markedly effective inhibitor; they did not demonstrate a normal endogenous substrate. Human cytosolic acetaldehyde dehydrogenase does not convert chloral hydrate to TCA (Kraemer and Deitrick, 1968; Blair and Bodley, 1969; Sellers et al., 1972). Grunnet (1973) reported that chloral hydrate is not a substrate for mitochondrial NAD-dependent acetaldehyde dehydrogenase. Microsomal NADP-dependent acetaldehyde dehydrogenases with broad substrate specificity have been described, but whether chloral hydrate is a substrate has not been determined (Tottmar et al., 1973).

In short, there is little evidence which precisely defines the enzymatic pathways for the metabolism of MC to TCE by P450 mixed function oxidase system, and TCE to TCA by classical alcohol dehydrogenase and acetaldehyde dehydrogenase enzymes. Although as yet uninvestigated, it is possible that TCE may be a substrate for the microsomal P450 ethanol oxidative system (MEOS) described by Lieber and his coworkers for ethanol and other alcohols (Lieber and De Carli, 1969; Teschke et al., 1977). TCE has been shown by Uehleke et al. (1976) to give a binding spectrum with rat microsomes. An alternative pathway also uninvestigated is afforded by the peroxisomal oxidase-catalase system (Figure 4-3), which is known to readily oxidize ethanol and a broad spectrum of other substrates (Masters and Holmes, 1979; Chance et al., 1977). Indeed, peroxisomes may perhaps be involved in the initial oxidation of MC to TCE and other halogenated hydrocarbons as well.

4.3 SUMMARY AND CONCLUSIONS

The pharmacokinetics and metabolism of MC in man have been studied less than other chlorinated aliphatic solvents, both in controlled experimental conditions and in the workplace. Like other solvents of this group, inhalation and lung absorption of MC vapor in the air is the most important and rapid route of absorption into the body. Absorption through the skin by direct liquid contact is slow and adds less than 5 percent to total body dose. At the accepted TWA value (350 ppm) for an 8-hr exposure, less than 2 g may be expected to be absorbed into the body of a normal 70 kg man. This is because pulmonary absorption is directly related to the blood/air partition coefficient, which for MC is less than that of most other structurally related solvents. MC total body dose increases in direct proportion to inspired air concentration and duration of exposure; it is also increased by physical activity during exposure. MC distributes throughout the body, readily crossing the blood-brain barrier and probably the placental barrier as well. It can be assumed that MC also distributes into the colostrum or milk of nursing mothers, although no specific data are available. Relative body tissue concentrations are not known, but there is a high affinity for adipose tissue due to the higher lipid/ blood partition coefficient of MC compared with that of other related solvents. Blood and tissue concentrations achieved during exposure are directly proportional to inspired air concentration and total body dose.

MC is metabolized in man to a very limited extent--about 6 percent of the total body dose. Metabolism appears to occur principally in the liver, and to an unknown extent in other tissues, yielding only trichloroethanol (TCE) and trichloroacetic acid (TCA) as identified metabolites. Urinary excretion of these metabolites is proportional to inspired air concentration and the total

body dose of MC. Detailed information concerning the enzymatic pathways of metabolism is lacking. The importance of greater knowledge of the biochemical mechanisms and pathways of metabolism relates to awareness that "reactive intermediate" metabolites may contribute to tissue and organ toxicities as well as carcinogenic potential. The mechanism(s) of the initial biotransformation of MC to TCE, where "reactive intermediates" may occur, are speculative, although present evidence suggests a microsomal cytochrome P450 oxidative reaction. However, specific covalent binding studies which would confirm reactive intermediates have not been carried out. Also, other minor pathways and unidentified metabolites cannot be excluded because of the lack of definitive studies. Metabolism is enhanced by microsomal inducers such as phenobarbital and possibly MC itself. The interaction of MC metabolism and toxicity with other common drugs, including ethanol, has not been adequately investigated.

During post-exposure, more than 80 percent of MC is excreted unchanged by the lungs. Alveolar air concentration and blood concentration decline in a parallel exponential fashion exhibiting three major components of elimination with half-times of approximately 1, 9, and 30 hr. The long half-time of elimination (30 hr) is associated with elimination from adipose tissue and indicates that accumulation may occur with repeated daily exposures, particularly in obese persons. Further research on the disposition and fate of MC after low chronic vapor exposures would be helpful, particularly with respect to bioaccumulation, enzyme mechanisms of biotransformation, and interactions with common drugs.

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5. TOXIC EFFECTS

Since its commercial introduction in 1954, methyl chloroform has been used increasingly as an industrial solvent and in consumer products. Usually the most important path of entry into the body is by inhalation. The health hazards of MC inhalation in the work place or public environment, as well as exposure by other routes, are pointed out by human and animal studies indicating that MC has significant adverse biological effects on the central nervous (CNS) and cardiovascular systems. In addition, MC may cause organ tissue damage generally associated with chlorinated hydrocarbon solvent toxicity. Like some of these other structurally related compounds, it may also have a teratogenic, mutagenic, and/or carcinogenic potential. The available literature on the possible toxic effects of MC is reviewed in this chapter.

5.1 HEALTH EFFECTS IN HUMANS

5.1.1 Experimental Studies

Experimental studies in humans have centered around three general areas: clinical experiences with MC as an anesthetic; the kinetics of MC absorption and excretion after exposure via the inhalation and cutaneous routes; and the impairment of psychophysiological functions in humans exposed to MC.

Dornette and Jones (1960) administered MC to 50 patients undergoing elective surgery. Nitrous oxide-oxygen (4:1) was used as the vehicle and as a supplemental anesthetic agent. The concentration of MC required for induction

of surgical plane anesthesia varied from 10,000 to 26,000 ppm, and for maintenance of light anesthesia from 6,000 to 22,500 ppm. Rapid induction and recovery, analgesia, and the absence of disagreeable odor, respiratory depression, postoperative depression, nausea and vomiting were listed as advantages in the use of MC. A definite disadvantage was depression of blood pressure during anesthesia of moderate depth. The tendency to develop ventricular arrhythmias during hypoxia was also observed. (This effect was reversed when effective oxygenation was reestablished).

Cardiac sensitization by halogenated hydrocarbons, with resultant increased susceptibility of the heart to catecholamine-produced arrhythmias, e.g., ventricular fibrillation or ventricular tachycardia, is a well-known phenomenon recently reviewed by Aviado et al (1976). Clark and Tinston (1973) believe that cardiac sensitization caused by these relatively inert, lipid soluble hydrocarbons is very likely to be a structurally non-specific action on myocardial membranes by solution and distribution within these membranes, and is, therefore, an example of "physical toxicity" (see Sect. 5.2.3). From an evaluation of 14 halogenated hydrocarbons in dogs, Clark and Tinston (1973) found that the cardiac sensitizing potencies, as determined by the partial pressure in inhaled air needed to sensitize the heart to epinephrine, was directly related to their saturated vapor pressures. In a similar way, the anesthetic potency or narcotic action of the halogenated hydrocarbons, a structurally nonspecific action, is directly related to the blood/air or lipid/air partition coefficient for these compounds (Table 4-1) (Miller et al., 1972; Eger et al., 1965; Sato and Nakajima, 1979).

Siebecker et al. (1960) reported that electroencephalographic patterns during MC anesthesia showed little change before circulatory depression and that the changes were similar to those during halothane anesthesia. The

investigators found MC to be less potent clinically than either chloroform or halothane in supplementing nitrous oxide-oxygen for anesthesia.

Stewart et al. (1961) evaluated the acute effects of increasing concentrations (0 to 2,600 ppm) of MC over a 15 min exposure period. The commercial grade of MC used was chlorothane. Table 5-1 shows the subjective and physiological responses during exposure to MC. In another experiment in which 6 subjects were exposed to MC at 500 ppm for 78 min or 186 min, no eye irritations or dizziness occurred, nor were balance or coordination affected. Exposure at 900 to 955 ppm for 73, 35, and 20 min produced a number of psychophysiological effects which are listed in Table 5-2.

In another study, Torkelson et al. (1958) exposed humans to MC (Chlorothane) vapors. Exposure to 550 ppm for 90 minutes had no measureable effect on the vital signs being monitored. Exposure to 500 ppm for 450 minutes produced no significant changes in pulse, respiration, blood pressure, reflexes, or equilibrium; liver function tests were also negative. Exposure to 1000 ppm for 30 minutes was also without effect. However, exposure to 900 to 1000 ppm for 75 min resulted in slight eye irritation and a feeling of lightheadedness, and the Flanagan and Romberg tests revealed a slight but definite loss of coordination and equilibrium. ECG and liver function tests were normal. Exposure to 1900 ppm for 5 minutes resulted in an obvious disturbance of equilibrium and a positive Romberg test.

In 1969, Stewart et al. reported that exposure to 500 ppm for periods of 6.5 to 7 hours/day for 5 consecutive days resulted in mild subjective responses (sleepiness, eye irritation, and mild headache). The only untoward physiological response was an abnormal Romberg test. None of the clinical tests performed during or following the exposure were abnormal.

TABLE 5-1. SUBJECTIVE AND PHYSIOLOGICAL RESPONSES TO A CONSTANTLY INCREASING METHYL CHLOROFORM VAPOR CONCENTRATION OVER A PERIOD OF 15 MINUTES

Concentration (ppm)	Responses to Exposure
0 to 1000	Increasing awareness of a slightly sweet, not unpleasant odor.
1000 to 1100	Mild eye irritation noted in 6 of 7 subjects.
1900 to 2000	6 of 7 subjects aware of throat irritation.
2600	1 subject very lightheaded.
2650	2 subjects unable to stand. 3 subjects very lightheaded, but able to stand. 2 subjects were not lightheaded, and one of these was able to demonstrate a normal Romberg test.

Source: Stewart et al. (1961).

TABLE 5-2. SUBJECTIVE AND PHYSIOLOGICAL RESPONSES TO METHYL CHLOROFORM VAPOR CONCENTRATIONS OF 900 TO 1000 PPM

Average Concentration	Responses to Exposure[a]
900 ppm for 20 minutes (3 subjects)	Positive Romberg in one subject. Greater effort required to perform a normal Romberg in two subjects after 10 minutes of exposure. Heel-to-toe walking normal. Two subjects experienced lightheadedness above 900 ppm.
910 ppm for 35 minutes (2 subjects)	Greater mental efforts required to perform a normal Romberg test after 10 minutes of exposure. All heel-to-toe walking performed well. One subject experienced persistent lightheadedness above 900 ppm.
951 ppm for 73 minutes (3 subjects)	Greater mental effort required to perform a normal Romberg test after 10 minutes of exposure. After 15 minutes of exposure one subject had consistently positive Romberg. Heel-to-toe walking performed well by all during exposure. No lightheadedness.

[a]Mild eye irritation was noted by all subjects when vapor concentrations rose above 1000 ppm.

Source: Stewart et al. (1961).

In 1975, Stewart et al. reported an experiment in which 20 subjects were exposed to 500 ppm MC or less for 7.5 hours per day, 5 days per week for 3 weeks. No serious deleterious effects upon health or performance were detected, and the health of the subjects remained unimpaired during the inhalation studies. The blood chemistries, hematologies, urinalyses, electrocardiograms, and pulmonary function tests remained normal. There was a slight increase in the number of reported negative subjective responses (Table 5-3).

Twelve subjects were exposed to 250, 350, 450, and 550 ppm of MC in inspired air during four continuous 30 minute periods in an experiment reported by Gamborale and Hultengren (1973). 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 the tests were of perceptual speed and the others were tests of simple reaction time, choice reaction time, and manual dexterity. The same subjects were also studied under control conditions in which inspired air contained no MC but in which all operations and measurements were the same as during exposure to the solvent. The presence or absence of MC was completely disguised by the use of menthol crystals. To balance the training effects between experimental and control conditions, the order of conditions was reversed for half the subjects.

The change in mean performance level during exposure to the increasing concentrations of MC differed systematically from the change in performance under control conditions. The level of performance in the manual dexterity test and two perceptual tests were affected by training; however, the training effect was less pronounced during exposure to MC. 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. However,

TABLE 5-3. NUMBER OF SUBJECTIVE RESPONSES TO METHYL CHLOROFORM EXPOSURE

	10 Males																								10 Females					
	0 ppm			100 ppm			350 ppm			350 ppm			500 ppm			0 ppm		350 ppm												
Lightheadedness	0	0	0	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Syncope	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mild sleepiness	0	0	0	1	1	1	0	0	1	3	0	0	0	2	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Mild eye irritation	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mild nose or throat irritation	0	0	0	1	1	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Mild headache	0	0	0	0	1	0	0	1	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	1	1	1	0
Nausea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fatigue	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Objectionable odor	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	9	9	9	9

Source: Stewart et al. (1975).

this study contained several drawbacks: e.g., the substance used to disguise the MC odor may itself have had a toxic effect, and the introduction of a breathing tube may have induced stress in the subjects. Nevertheless, statistically significant performance differences between experimental and control conditions were obtained for all tests with exposures at 350 ppm or more.

Salvini et al. (1971) evaluated psychophysiological effects after exposing six male university students to an average vapor concentration of 450 ppm MC for two periods of 4 hours, separated by a 1.5 hour interval. Each subject was examined on two different days using a crossed-scheme analysis. The psychophysiological tests included a perception test with tachistoscopic presentation, the Wechsler Memory Scale test, a complex reaction time test, and a manual dexterity test. After two exposures, no disturbances in motor function, coordination, equilibrium, or behavior patterns were observed in any of the subjects. However, there were some complaints about eye irritation. The only factor that was reported to be statistically significant was the association between exposure to MC and perception of mental strain. Under stress conditions, exposure to 450 ppm MC decreased perceptive capabilities. A small reduction in performance was also observed but was not statistically significant.

Savolainen et al. (1981) evaluated various psychophysiological functions in 9 male students exposed for 4 hours/day, at 6-day intervals, to MC (200 and 400 ppm) and m-xylene (200 ppm) and MC (400 ppm) in combination. Exposure to MC or MC and xylene together were without effect on reaction time, body balance, and critical flicker fusion thresholds.

5.1.2 Occupational Studies

Chronic occupational exposure to other chlorinated solvents has been associated with adverse neurological and behavioral effects. However, it has

not been specifically determined whether relatively low level exposures to MC are clearly associated with such effects.

A recent attempt to assess the central and peripheral nervous system effects of MC in occupational situations was undertaken by Maroni and co-workers (1977). They studied a very small group (22 subjects) of female workers exposed to MC vapors at concentrations ranging from 110 to 990 ppm. When compared to workers who were reportedly unexposed, no differences were found in clinical symptoms or measures of nerve conduction velocity and psychometric function.

In another study, Seki et al. (1975) surveyed 196 male workers employed in four Japanese printing factories where MC was the sole organic solvent in use. The four groups of workers were exposed to average concentrations of 4, 25, 28, and 53 ppm. The workers participated in a medical interview coupled with a test for sense of vibration (studied at the distal joints of the thumbs and great toes using a 128 Hz tuning fork) as well as routine laboratory examinations, including peripheral hemograms, determination of blood specific gravity, and urinalysis for urobilinogen and protein. These examinations revealed no consistent dose-related adverse effects among the four groups of workers.

In the most recent study, Kramer et al. (1978) measured numerous physiological 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 been exposed to MC (and other solvents), in varying concentrations, for up to 6 years. The concentration range was 11 to 838 ppm, with a mean of 115 ppm MC. It is questionable whether this period of exposure would result in toxic symptoms. Because 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 accumulative, long term effects. The control group was only minimally exposed to nonchlorinated solvents.

Pairs were matched with regard to age, race, sex, work shift, job description and socioeconomic status, and examined within a 10 week period. Subject height, weight, blood pressure and pulse were obtained, and electrocardiograms were recorded. Laboratory blood determinations included hematocrit, hemoglobin, red blood cell count (RBC), white blood cell count (WBC), mean corpuscular hemoglobin (MCH), 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. 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 in charcoal tubes, except in a few locations where area sampling was more practical, 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 explaining that some data were eliminated on the basis of subjects' smoking habits, high blood pressure, or prior illness, the authors presented statistical findings but no individual data. MC 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 in SGPT and albumin. These differences were not discussed at length and the authors concluded that no health impairment was suffered by workers exposed to an average daily concentration of 115 ppm MC.

Nine women washing brass frames in open containers of pure MC were studied from the onset of their exposure and were the subject of a report in 1965 by Weitbrecht. Air measurements were made during the summer with methyl bromide indicator tubes (of questionable validity for measuring MC). An average of 10 ppm of MC was found in the general room air and 20 ppm in the worksite air. In addition to vapor exposures, the women's hands were immersed in liquid MC 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 and/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 MC; however, 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 exposure was continuous.

After the windows were closed in the fall, the women complained of loss of appetite, pressure sensation in the stomach, vomiting, tiredness, headache, and insomnia. The author 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 MC exposure from the possible suggestive effect of the safety signs, and did not 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.

5.1.3 Accidental Exposure

Accidental exposure to MC can lead to death. Table 5-4 lists the signs and symptoms of a number of cases in which the patients survived. These

TABLE 5-4. SIGNS AND SYMPTOMS OF PATIENTS SURVIVING INTOXICATION WITH METHYL CHLOROFORM

Reference	Patient	Amount	BP[a]	HR[b]	SGPT[c]	SGOT[d]	AP[e]	BUN[f]	ECG[g]	Comments
Stewart and Andrews, 1966	47 M	1 oz. orally	120/80	84	N[h]	N	NR[i]	N	N	No abnormal neurologic findings; proteinuria was 1+; hematocrit 53%; hemoglobin level 18 gm/100 ml
Stewart, 1971	44 WM	Inhalation	140/74	78	N	N	NR	N	N	Neurologic examination revealed abnormal Romberg's sign upon admission; hematocrit 46%; hemoglobin level 14.6 gm/100 ml
Stewart, 1971	55 WM	Inhalation	160/96	84	N	N	NR	N	N	No abnormal neurologic findings
Stewart, 1971	47 WM	Inhalation	160/90	76	N	N	N	N	N	No abnormal neurologic findings
Litt and Cohen, 1969	5 teen-age M	Inhalation	NR	NR	NR	340-100 μ	7-30 μ	NR	NR	Nervous system symptoms including paresthesia, tinnitus, ataxia, and headache

[a] Blood pressure (mmHg)
[b] Heart rate (beats/min)
[c] Serum glutamic-pyruvic transaminase
[d] Serum glutamic-oxaloacetate transaminase
[e] Alkaline phosphatase
[f] Blood urea nitrogen
[g] Electrocardiogram
[h] N = normal
[i] NR = not reported

results suggest that MC has only a minimal potential for producing liver or kidney injury in man. The primary toxic effect appears to be a reversible depression of the CNS, typical of an anesthetic agent. In addition, cardiovascular parameters may be altered by exposure to MC.

Two fatal cases in which the subjects intentionally inhaled cleaning fluids containing MC were reported by Hall and Hine (1966). A 19-year-old woman who was observed sniffing cleaning fluid over several days and acting irrationally was later found dead. 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; brain ventricles contained clear cerebrospinal fluid; vascular markings were prominent, and there was acute, passive congestion throughout the brain.

There were indications of chronic, intentional inhalation of a cleaning fluid containing MC in the other fatal case studied by Hall and Hine (1966). On autopsy, pathologic findings were confined to the respiratory system and the kidneys. The lungs were congested and edematous, the vessels dilated, and small hemorrhagic areas were present. The kidneys showed marked vascular congestion around the pyramids, especially on the periphery.

In neither of these cases were drugs or solvents detected in the stomach contents, and no barbiturates were found in the blood. Blood levels of MC were 72.0 and 13.0 mg percent, respectively.

Twenty-nine cases of sudden death from sniffing MC during 1964 to 1969 were reported by Bas (1970). These were among 110 cases of sudden death

attributed to sniffing volatile hydrocarbons and halocarbons summarized by the author. In 18 of the 110 cases, death followed sniffing coupled with some form of exercise. No anatomical abnormalities were found from gross or microscopic post mortem examinations that could explain the sudden deaths. The author discussed the possibility that resulted from cardiac sensitization to endogenous catecholamine.

Six fatal cases were reported by Stahl et al. (1969). In the first case, a 20-year-old man was found dead in a closed space in which he had been working with a "paint remover." Gas chromatographic analysis revealed MC in all tissues. Upon autopsy, the lungs were found to be congested and moderately edamatous; the liver, spleen, kidneys, and brain were also congested. Microscopic examination of the brain suggested anoxia as the cause of death.

In the second case, a 17-year-old man was found dead in a room in which he was cleaning an air vent with MC. Gas chromatographic analysis revealed the presence of MC although blood levels were only 0.15 mg percent. At autopsy, the skin was moderately cyanotic, the brain, liver, kidneys, and spleen were moderately congested, and the lungs were markedly edematous with evidence of aspiration of gastric contents. Blood lactic acid levels were high. The authors concluded that death was probably due to O_2 deprivation.

In the third case, an obese 24-year-old man was found dead in bed after having cleaned electrical equipment with MC. At necropsy, marked cyanosis of the head and neck were noted; the lungs were congested and edematous. The brain, spleen, and kidneys were also congested.

In the fourth, fifth, and sixth cases, three males were found dead in an unventilated 4 x 5 ft. compartment where they had been cleaning electrical equipment with MC. Autopsies revealed congestion and edema of the lungs. Blood levels of MC were 12.0 mg percent, 6.2 mg percent, and 6.0 mg percent in these victims.

Hatfield and Maykoski (1970) reported on a 27-year-old who was found dead in an aircraft tank that he had been cleaning with MC. Upon autopsy, the lungs showed some passive congestion and some edema. The kidneys showed some passsive congestion and there appeared to be some slight edema of the brain. Microscopic examination disclosed a pulmonary parenchyma with considerable acute passive congestion and focal extravasations of red blood cells into alveolar spaces. Upon section, the renal parenchyma was intensely congested and of a dark red color. Microscopically, there was intense, acute passive congestion. There appeared to be marked congestion of the small vessels within the white matter of the brain. The diagnosis was acute passive congestion of the viscera with petechial hemorrhages in the lung and brain. Hatfield and Maykoski estimated the concentration level of MC to which this worker was exposed at 62,000 ppm.

Caplan et al. (1976) reported a fatal intoxication in which a 40-year-old female was apparently overcome while painting a bathroom. On external examination, the only significant abnormality was in the respiratory system. The bronchi contained frothy fluid. On section, the lungs exuded moderate amounts of frothy fluid. Histologically, the lungs showed acute edema and congestion, and the liver showed a mild fatty change. MC was identified in tissue samples.

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

5.2 EFFECTS ON ANIMALS

5.2.1 Acute and Subacute Effects

The LD_{50}'s of MC for various species are found in Table 5-5. Administration of single oral doses yielded LD_{50}'s for laboratory animals ranging from 8.6 gm/kg for guinea pigs to 14.3 gm/kg for rats (Torkelson et al.,

TABLE 5-5. ACUTE TOXICITY OF METHYL CHLOROFORM

Reference	Species	Route	Sex	LD_{50} mg/kg	95% confidence limits
Torkelson et al., 1958	rats	oral	M	14,300	12,100 to 17,000
Torkelson et al., 1958	rats	oral	F	11,000	9,500 to 13,000
Torkelson et al., 1958	mice	oral	F	9,700	
Torkelson et al., 1958	albino rabbits	oral	mixed	10,500	9,700 to 11,300
Torkelson et al., 1958	guinea pigs	oral	mixed	8,600	6,100 to 12,200
Takeuchi 1966	SM mice	i.p.	?	2,568	
Priestly and Plaa 1976	CF-1 Swiss mice	i.p.	M	4,008	3,558 to 4,522
Klaassen and Plaa 1969	Sprague-Dawley rats	i.p.	M	5,054	4,389 to 5,586
Torkelson et al., 1958	albino rabbits	dermal	mixed	15,800	
Adams et al., 1950	rats	inhalation	mixed	18,000[1]	
Plaa et al., 1958	Princeton mice	i.p.	M	16,000	12,700 to 21,400
Klaassen and Plaa 1967	Swiss-Webster mice	i.p.	M	5,080	4,140 to 6,010
Klaassen and Plaa 1967	dog	i.p.	M	4,140	
Gehring 1968	Swiss-Webster mice	i.p.	F	4,700	4,320 to 5,110

[1] LC_{50} in ppm for 3 hr exposure; 7 hr exposure resulted in a LC_{50} of 14,250 ppm (12,950 to 15,675).

1958). The solvent caused slight transitory irritation in the eyes. The toxicity from skin absorption was found to be low, as doses of 4 gm/kg failed to kill any rabbits exposed for 24 hrs. Repeated multiple daily application of 500 mg/kg to the skin of rabbits caused no effect other than reversible local irritation. In other experiments, laboratory animals were exposed repeatedly to 500, 1000, 2000, and 10,000 ppm in order to establish conditions safe for repeated exposure. Rats, guinea pigs, rabbits, and monkeys were unaffected after 6 months of repeated 7 hr exposures 5 days/wk to 500 ppm. Female guinea pigs, which were found to be the most sensitive in previous experiments, were able to tolerate 1000 ppm for 0.6 hr/day for 3 months and 2000 ppm for 0.1 hr/day with no detectable adverse effects. Male rats tolerated exposure to 10,000 ppm for 0.5 hr per day with no organic injury. The effects of MC were shown to be primarily anesthetic, with only a slight capacity to cause reversible injury to the lungs and liver. Based on this work, Torkelson et al. (1958) suggested that the maximum allowable concentration for MC be 500 ppm.

In another study, Eben and Kimmerle (1974) exposed rats acutely (4 hr) and subacutely (8 hr/day, 5 times/wk for 3 months) to 220 and 440 ppm and 200 ppm, respectively. During the periods of exposure, the animals did not differ in any way from their controls in behavior, appearance, or body weight gain. Hematologic examination performed at the end of the exposure period did not reveal any pathologic abnormalities. Liver and renal function tests and blood glucose were normal. At autopsy, the organs of the exposed rats were normal; organ weights did not deviate significantly from those of the control animals.

Prendergast et al. (1967) repeatedly exposed 15 Sprague-Dawley rats, 15 Hartley guinea pigs, 3 squirrel monkeys, 3 New Zealand albino rabbits, and 2 beagle dogs (8 hr/day, 5 days/wk for 6 weeks) to 2200 ppm MC. The same number

of animals were exposed continuously for 90 days to 135 ppm and 370 ppm. The repeated exposure to 2200 ppm did not result in any deaths or visible signs of toxicity, although weight loss was observed in rabbits and dogs. The continuous exposure at 370 ppm did not cause any deaths, visible toxic signs, significant growth depression or biochemical, hematologic or pathologic changes. Continuous exposure to 135 ppm resulted in three deaths but no visible toxic signs or impaired growth in any of the survivors. Autopsy and subsequent histopathologic examination of the experimental animals revealed lung congestion and pneumonitis which may have been severe enough to have caused the deaths of the two rats and the rabbit, but which were not attributed to the exposure.

Because chlorinated hydrocarbons are known to produce a specific hepatotoxicity, the effects of MC on hepatic function have been studied by a number of different investigators. Lal and Shah (1970) exposed Swiss-albino, random-bred male mice to 3000 ppm for either 24 hr or for 4 or 8 hr/day for several days. Hexobarbital (80 mg/kg)[sic], barbital sodium (275 mg/kg)- or chloral hydrate (350 mg/kg)-induced sleeping time was measured at predetermined times after exposure. In addition, hexobarbital oxidizing activity, nitro-group reducing activity, and the protein content of the liver supernatant fraction were also determined. Inhalation of MC at a concentration of 3000 ppm for 24 hr produced a maximum reduction in the duration of hexobarbital sleeping time but had no effect on hypnosis produced by barbital or chloral hydrate. Hypnosis returned to the control level at 48 hr after the termination of exposure. Repeated short exposures, 4 or 8 hr/day for several days, had a cumulative effect, but a single 8 hr exposure did not. The supernatant fraction isolated (9000 g) from livers of mice previously exposed to MC oxidized hexobarbital more efficiently, but the ability to reduce p-nitrobenzoic acid remained

unaffected. The protein content of this liver supernatant fraction was also unaltered.

Fuller et al. (1970) made further observations on Lal and Shah's investigations of the inductive effect of MC on hepatic drug metabolism. Male Sprague-Dawley rats and Swiss-albino, random-bred mice were exposed to MC (2500 to 3000 ppm) in a dynamic chamber for 24 hr. Loss of righting reflex due to hexobarbital (120 mg/kg), meprobamate (300 mg/kg), or zoxazolamine (80 mg/kg) administration and in vitro activity of hexobarbital oxidase, zoxazolamine hydroxylase, aminopyrine demethylase, reduced nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome c reductase, and CO-binding pigment (cytochrome P-450) were then measured. Pretreatment with inhibitors of protein synthesis (cycloheximide and actinomycin D) were used to block the effect of MC on the hepatic drug-metabolizing system. Inhalation of MC (2500 to 3000 ppm) for 24 hr decreased the duration of action of hexobarbital, meprobamate, and zoxazolamine. This was accompanied by an increase in the metabolism of hexobarbital, zoxazolamine and aminopyrine in vitro by hepatic microsomal enzymes. Cytochrome P-450 and cytochrome c reductase were also increased; however, liver weight and liver microsomal protein were not enhanced. Pretreatment of rats with protein synthesis inhibitors prevented the MC induced decrease in hexobarbital sleeping time and the increase in hepatic drug metabolism. The authors concluded that MC may be inducing the production of a new enzyme protein and that this protein may be used as a "prepathologic" measure of MC toxicity.

Savolainin et al. (1977) investigated the effects of MC on rat brain and liver after intermittent inhalation. Ten male Sprague-Dawley rats were exposed to 500 ppm MC for 4 days, 6 hr daily. The right cerebral hemispheres were homogenized and analyzed for protein, RNA, glutathione, and for the activity

of acid proteinases. Liver microsomes were analyzed for the amount of protein and for cytochrome P-450 content. During exposure, the behavior of the exposed animals was analyzed in an open field test and did not differ significantly from that of the controls. Brain protein content was not affected; however, the amount of RNA was lower than in the controls. MC decreased the liver microsomal cytochrome P-450 content after cumulative exposure to the material for 5 days. The authors explained the decrease in cytochrome P-450 by the previously observed (Pelkonen and Vainio, 1975) affinity of MC for the type I binding site.

McNutt et al. (1975) demonstrated hepatic lesions in mice after continuous inhalation exposure to MC. CF-1 mice were exposed to 0, 250, or 1000 ppm MC continuously for up to 14 weeks with a weekly serial sacrifice. At 1000 ppm, from 1 to 14 weeks, significant changes in centrilobular hepatocytes were observed. Moderate liver triglyceride accumulation was evident in the 1000 ppm group and peaked at 40 mg/gm of tissue after 7 weeks of exposure (by 14 weeks the triglyceride level had not decreased to 16 gm). Electron microscopic evaluation revealed that cytoplasmic alterations were most severe in centrilobular hepatocytes in the 1000 ppm group and were mild to few in the 250 ppm group. The alterations consisted of vesiculation of the rough endoplasmic reticulum, with loss of attached polyribosomes, and increased smooth endoplasmic reticulum, microbodies, and triglyceride droplets. Necrosis of individual hepatocytes occurred in 40 percent of the mice exposed to 1000 ppm for 12 weeks. This necrosis was associated with an acute inflammatory infiltrate and hypertrophy of Kupffer cells. This study concluded that the effects of MC were similar to carbon tetrachloride, but they appeared to be much less severe.

TABLE 5-6. THE RELATIVE HEPATOTOXIC EFFICACY OF CHLORINATED SOLVENTS

Compound	Relative hepatotoxic efficacy
1,1,1-trichloroethane	1
Tetrachloroethylene	3
Trichloroethylene	8
Sym-tetrachloroethane	12
1,1,2-trichloroethane	40
Chloroform	60
Carbon tetrachloride	190

Adapted from Plaa et al., (1958).

Table 5-6 shows the relative hepatotoxic effect of MC in comparison to other chlorinated solvents. MC, according to Plaa et al., (1958), was judged to be the least hepatotoxic of the seven solvents investigated.

5.2.2 Central Nervous System Effects

The most notable pharmacologic effect of methyl chloroform following pulmonary vapor absorption is its action upon the central nervous sytem. Table 5-7 shows the occurrence of neurological signs of toxicity associated with progressively increasing inhalant concentrations of MC in a variety of species. At higher than anesthetic concentrations (approx. 10,000 ppm), severe respiratory depression develops and cardiac arrest may occur.

5.2.3 Cardiovascular Effects

The cardiovascular effects produced by exposure to MC have been extensively studied in recent years. Halogenated alkanes have been shown to sensitize the heart to catecholamines and at the same time produce cardiac depression.

TABLE 5-7. PROBABLE RESULT OF SINGLE EXPOSURE TO THE VAPORS OF METHYL CHLOROFORM

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 equilbrium (H)
	1,000	Possible beginning loss of equilibrium (H)
30	10,000	Pronounced loss of coordination (R)
	5,000	Incoordination (R, M)
	2,000	Loss of equilibrium (H)
	1,000	Mild eye and nasal discomfort; possible slight loss of equilibrium (H)
60	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.

From Stewart, (1968, 1971), Torkelson et al. (1958), and Toxicology Committee, Am. Ind. Hgy. Assoc., 1964.

Krantz et al. (1959) were the first to observe the cardiac depression produced by MC. Rats were deeply anesthetized with MC for 1 hr, at which time the hearts were immediately removed. Cardiac ventricular slices were promptly prepared and the oxygen uptake over the 1 hour period was measured. MC anesthesia was associated with a significant diminution (33.3 percent) in oxygen uptake of the myocardium. Blood pressure studies in dogs also revealed that anesthesia with MC elicited a depressed response. At the point of respiratory arrest, the blood pressure was reduced to approximately one-half its normal value. Ether anesthesia under similar conditions results in only a slightly depressed blood pressure. Six dogs and two rhesus monkeys were anesthetized and electrocardiograms recorded. The pattern of the electrocardiogram was essentially unaltered; the heart rate was increased and the T-wave was either flattened or inverted. At the point of respiratory arrest, a depressed S-T segment was observed; however, tachycardia was absent.

Herd and co-workers (1973, 1974) confirmed the initial observations of Krantz et al. (1959). They exposed dogs to MC (10^4-4 x 10^4 ppm/min) and observed a dose-dependent biphasic decline in arterial blood pressure. Since cardiac output increased initially, the initial decline in pressure (within 10 to 15 seconds after introduction of MC) was due to a decrease in total peripheral resistance (TPR). Injection of phenylephrine (pure alphaagonist) reversed the peripheral vascular effects, indicating that MC does not act directly on the vascular musculature. The second phase of blood pressure decline was found to be associated with a decrease in myocardial contractility, reflected by a decline in both heart rate and stroke volume. Exogenous Ca^{++} reversed the MC induced decline in myocardial contractility, but had no effect on the initial phase of peripheral vasodilation.

Taylor et al. (1976) exposed New Zealand white rabbits to a series of haloalkane chemicals. The animals were first anesthetized with sodium pentobarbital, then fitted with various cannulas allowing for the measurement of mean arterial pressure, left ventricular pressure, left ventricle dP/dt, cardiac output, stroke volume, heart rate, left ventricular end-diastolic pressure, central venous pressure, and peripheral vascular resistance. Table 5-8 lists the left ventricular and hemodynamic effects of 50,000 ppm MC. There was no effect on heart rate, left ventricular end-diastolic pressure, central venous pressure, or peripheral vascular resistance. During exposure, no cardiac arrhythmias were observed nor was there a significant change in pH, oxygen, or carbon dioxide tensions. As a cardiac depressant, MC appeared to be as potent as halothane and fluorocarbon 11.

Numerous hydrocarbon compounds have been shown to sensitize the myocardium to catecholamines. In humans, for example, several unexplained deaths have been associated with solvent abuse or overexposure; ventricular fibrillation due to cardiac sensitization has been suggested as the underlying mechanism. The cardiac sensitization potential of MC has been investigated under various circumstances. In an early study, Rennick et al. (1949) reported MC and epinephrine induction of idioventricular rhythms in dogs. Attempts to induce MC anesthesia resulted in the sudden death, presumably of cardiac origin, of two animals. Ventricular extrasystoles and ventricular tachycardia were seen in five dogs under barbital anesthesia when epinephrine was injected after "repeated small doses" of MC. Maximum sensitization of the heart to epinephrine occurred after the administration of 0.25 to 0.4 ml/kg of MC. Further administration of this compound produced severe hypotension. Somani and Lum (1965), Lucchesi (1965), and Hermansen (1970) administered MC

TABLE 5-8. LEFT VENTRICULAR AND HEMODYNAMIC EFFECTS OF METHYL CHLOROFORM

	Mean Arterial Pressure (mmHg)	Left Ventricular Pressure (mmHg)	Left Ventricle dP/dt (mmHg/sec)	Cardiac Output (ml/min)	Stroke Volume (ml)
Pre-exposure	69±5	97±3	3792±325	423±31	1.47±0.09
1 minute post exposure[a]	45±4	70±5	1433±163	266±26	0.92±0.07

[a]All values at 1 minute exposure are significantly different from pre-exposure values at $p < 0.05$.

Source: Taylor et al. (1976).

to dogs or mice as a method for induction of cardiac arrhythmias in studying and characterizing the sensitivity and specificity of adrenergic blocking agents.

Clark and Tinston (1973) evaluated the cardiac sensitizing potencies of 14 halogenated hydrocarbons in conscious beagle dogs. During the last 10 seconds of a 5 min exposure, epinephrine (5 mg/kg) was injected intravenously (bolus). As a control, epinephrine was given prior to exposure and also 10 min after the end of exposure. The electrocardiogram (lead II) was monitored continuously during this procedure. Several dose levels of the chemical being tested were used, each differing by a factor of two. The concentration at which 50% (EC_{50}) of the animals could be sensitized was calculated by a moving average interpolation. The mean concentration of MC which produced cardiac sensitization in 50% of the animals tested was 7,500 ppm (4,000 to 11,000). The authors found that they could directly predict the EC_{50} for cardiac sensitization by knowing the vapor pressure at 37°C and the partial pressure at the EC_{50}. Table 5-9 lists the EC_{50} for a number of different halogenated hydrocarbons. MC appears to be a highly potent sensitizing agent, with tetrachlorodifluoromethane being the most potent in the series. The authors concluded that cardiac sensitization was probably a structurally nonspecific action and that it was physically toxic.

Reinhardt et al. (1973) investigated five commonly used industrial and household solvents, including MC, to assess their cardiac-sensitization potential. The investigators conducted experiments on unanesthetized, healthy male beagle dogs that had been trained to breathe through a one-way face mask while supported in a standing position by a sling. The dog inhaled house air for 7 minutes and the test compound for 10 minutes. Epinephrine (8 µg/kg in 1 ml of normal saline) was injected i.v. in 9 seconds as a control dose after 2 minutes

TABLE 5-9. CONCENTRATION OF CHEMICALS CAUSING CARDIAC SENSITIZATION AND THEIR PHYSICAL PROPERTIES (IN PPM)

hemical	EC_{50}	Vapor pressure at 37°C (mmHg) P_s	Partial pressure at EC_{50} (mmHg) P_{cs}	Relative saturation for cardiac sensitization P_{cs}/P_s
etrachlorodifluoromethane	1,200	99	2	0.02
arbon tetrachloride	5,000	190	4	0.02
richloroethane	7,500	210	6	0.03
alothane	20,000	480	15	0.03
richlorotrifluoroethane	10,000	524	8	0.02
ethylene chloride	24,000	661	18	0.03
richlorofluoromethane	12,500	1,186	10	0.01
ichlorofluoromethane	25,000	2,052	19	0.01
ichlorotetrafluoroethane	100,000	2,310	76	0.03
inyl chloride	50,000	4,218	38	0.01
ropane	200,000	9,538	153	0.02
romotrifluoromethane	200,000	15,276	153	0.01
hlorotrifluoromethane	800,000	40,698	610	0.02

ource: Clark and Tinston (1973).

of breathing air, and as a challenge dose after 5 minutes of breathing the test compound. The 10-minute interval between the two doses was found to be adequate to prevent additive effects when tested in 13 control dogs subjected to the same procedures, but with air substituted for the test compound. A positive response was considered to be either cessation of cardiac output (ventricular fibrillation) or the development of an arrhythmia that was not observed following the control dose and that was considered to pose a serious threat to life (multiple, consecutive beats of ventricular origin). The concentration of the test compound being delivered to the animal was determined by gas chromatography at 2-minute intervals.

The results obtained for MC indicated no response in 12 dogs at a nominal concentration of 0.25 percent (V/V) and a marked response in 3 of 18 dogs exposed at a nominal concentration of 0.5 percent (V/V); 12 of 12 responded at a nominal concentration of 1.0 percent (V/V). However, unlike the other substances, MC-induced ventricular fibrillation in the animals from the 1.0 percent group reverted to multiple consecutive ventricular beats within a matter of seconds and eventually recovered to a normal cardiac rhythm. The results confirm earlier reports that MC is capable of sensitizing the dog heart to epinephrine.

Trochimowicz and co-workers (1976) were concerned with the problem of haloalkane-induced cardiac sensitization in patients who had survived myocardial infarction. They induced myocardial infarction in beagle dogs and tested for cardiac sensitization to epinephrine after exposure to MC (2500, 3700, and 5000 ppm). Myocardial infarction failed to significantly lower the threshold for cardiac sensitization. There was no greater potential for cardiac sensitization among dogs having recovered from myocardial infarction as compared to normal healthy animals.

At sufficiently high levels (in the thousands of ppm, for durations of exposure of the order of minutes), MC can cause significant alterations in cardiovascular function in a variety of experimental animals, including mice, rabbits, dogs, and possibly monkeys. The concentration levels reported for these effects are generally more than an order of magnitude greater than the current TLV for humans of 350 ppm (0.035 percent) and are likely to be lethal to the experimental animals if the exposure is continued for more than several minutes. Indeed, some experimenters appeared to find it necessary to increase the oxygen content of the inspired gas/air mixture to 40 percent to prevent asphyxia of the exposed animals. That they appeared unable to find effects at lower exposure levels is noteworthy. Also noteworthy is the fact that many of the investigators reported complete recovery of the animals if the exposure was stopped. This was the case, for example, with the dog experiments of Reinhardt et al. (1973), and Trochimowicz et al. (1976). At necropsy following sacrifice of several of the animals several months after exposure, there was no pathology attributable to the exposure per se. Delayed cardiotoxicity from acute exposure has not yet been demonstrated or ruled out.

5.3 TERATOGENICITY, MUTAGENICITY, AND CARCINOGENICITY

It has been proposed that the susceptibility of individuals to cancer is related to their ability to metabolize carcinogenic compounds to benign molecules and, conversely, to their capacity to metabolize benign compounds to carcinogens (Kellerman et al., 1973). Susceptibility may be partly explained by genetic differences involving enzymatic pathways, repair mechanisms, and immune response mechanisms. An assessment of the carcinogenic potential of MC must therefore take into account tissue concentrations of MC during typical exposures (e.g., TLV-TWA, 350 ppm), as well as the extent and nature of MC

metabolism. Both these aspects have been extensively reviewed in Chapter 4. While our knowledge is still limited in these areas, it can be concluded that MC is metabolized in humans to a very small extent. About 6 percent of the body dose is converted by a hepatic microsomal oxidase system to trichloroethanol. The mechanism of this overall reaction is unknown, as is the potential for generation of "reactive intermediate compounds" which may contribute to organ toxicity and/or carcinogenesis. Until further research is done, particularly studies to determine how and whether intermediate reactive compounds from MC metabolism bind to cellular macromolecules, an evaluation of mutagenicity and carcinogenicity must be made solely on the biological effects of MC in various direct mutagen and carcinogen tests. Unfortunately, MC has not been subjected to extensive and thorough testing. The available studies are summarized in Table 5-10.

5.3.1 Teratogenicity, Embryotoxicity, and Reproductive Effects

5.3.1.1 Overview--This review subscribes to the basic viewpoints and definitions of the terms "teratogenic" and "fetotoxic" as summarized and stated by Chernoff (1980):

> Generally, the term "teratogenic" is defined as the tendency to produce physical and/or functional defects in offspring in utero. The term "fetotoxic" has traditionally been used to describe a wide variety of embryonic and/or fetal divergences from the normal which cannot be classified as gross terata (birth defects) -- or which are of unknown or doubtful significance. Types of effects which fall under the very broad category of fetotoxic effects are death, reductions in fetal weight, enlarged renal pelvis edema, and increased incidence of supernumary ribs. It should be emphasized, however, that the phenomena of terata and fetal toxicity as currently defined are not separable into precise categories. Rather, the spectrum of adverse embryonic/fetal effects is continuous, and all deviations from the normal must be considered as examples of developmental toxicity. Gross morphological terata represent but one aspect of this spectrum, and while the significance of such structural changes is more readily evaluated, such effects are not necessarily more serious than certain effects which are ordinarily classified as fetotoxic--fetal death being the most obvious example.
>
> In view of the spectrum of effects at issue, the Agency suggests that it might be useful to consider developmental toxicity in terms of three basic subcategories. The first subcategory would be embryo or fetal lethality.

TABLE 5-10. ONCOGENIC TERATOGENIC TESTING OF METHYL CHLOROFORM

Test System	Species	Reference	Results
Teratogenicity			
Organogenesis	Chick embryo	Elovaara et al., 1979	Positive; high toxic dose, skeletal abnormalities
Mammalian gestation	S/D rat, S-W mice	Schwetz et al., 1975	Negative
Carcinogenicity			
NCI bioassay - 2 yr	Osborne-mendel rats, and $B_6C_3F_1$ mice and oral gavage; 750 and 1500 mg/kg (rat)	NCI, 1977; NCI Clearinghouse on Environmental Carcinogens, 1977	Inconclusive; high animal mortality
NTP bioassay - 2 yr	Rat and mouse gavage		In progress
Industry bioassay - 1.5 yr	S/D rats, inhalation 875 and 1750 ppm		Negative

NOTE: See appendix for discussion of chemical purity.

This is, of course, an irreversible effect and may occur with or without the occurrence of gross terata. The second subcategory would be teratogenesis and would encompass those changes (structural and/or functional) which are induced prenatally, and which are irreversible. Teratogenesis includes structural defects apparent in the fetus, functional deficits which may become apparent only after birth, and any other long-term effects (such as carcinogenicity) which are attributable to in utero exposure. The third category would be embryo or fetal toxicity as comprised of those effects which are potentially reversible. This subcategory would therefore include such effects as weight reductions, reduction in the degree of skeletal ossification, and delays in organ maturation.

Two major problems with a definitional scheme of this nature must be pointed out, however. The first is that the reversibility of any phenomenon is extremely difficult to prove. An organ such as the kidney, for example, may be delayed in development and then appear to "catch up". Unless a series of specific kidney function tests are performed on the neonate, however, no conclusion may be drawn concerning permanent organ function changes. This same uncertainty as to possible long-lasting after effects from developmental deviations is true for all examples of fetotoxicity. The second problem is that the reversible nature of an embryonic/fetal effect is one species might, under a given agent, react in another species in a more serious and irreversible manner.

It is not possible, on the basis of limited available data, to define the full potential of MC to produce adverse teratogenic or reproductive effects. Human epidemiology studies have not been conducted to evaluate the effects of MC on the exposed population. The available mammalian studies were not properly designed to evaluate the ability of MC to produce a teratogenic response over a wide range of doses, which should include doses high enough to produce signs of maternal toxicity and lower doses which do not produce this effect. The teratology studies which were performed with laboratory animals used rats and mice and only single doses of MC which produced signs of maternal toxicity. Other studies in chicken embryos have indicated that MC disrupts embryogenesis in a dose-related manner. However, since administration of MC directly into the air space of chicken embryo is not comparable to administration of a dose to animals with a placenta, it is not possible to interpret this result in relationship to the potential of MC to cause adverse human reproductive effects.

In summary, although several studies have been conducted to evaluate the ability of MC to cause adverse teratogenic, embryotoxic and reproductive effects, the limitations of the available data does not allow for a full assessment of these effects. A better assessment of these effects could be performed if the available studies met criteria similar to those suggested for teratogenicity and reproductive testing (U.S. EPA, 1978).

5.3.1.2 Human Studies--No clinical reports associate maternal exposure to methyl chloroform with congenital malformations in offspring. No epidemiological studies have been performed.

5.3.1.3 Animal Studies--All studies performed to date in mammals have been done in rats and mice. On the basis of these studies, it does not appear that short- or long-term exposure to MC results in teratogenic effects in rats, or that short-term exposure to MC results in such effects in mice. Delays in fetal development have been observed in both species, but this may be a reversible effect. It should be noted, however, that these studies evaluated only one dosage level per animal species, which included dosages twice the maximum excursion limit for short-term exposures of rats and mice and six times the maximum excursion limit for long-term exposures of rats. Another study in chicken embryos indicates that MC may have teratogenic potential in this species. However, since it is not known how comparative studies in chicken embryos are to those in other mammalian species, the teratogenic potential of MC in chickens cannot be related to other animals without additional data. In addition, no multi-generational studies of mammalian reproductive performance have been performed.

5.3.1.3.1 Rats--Schwetz et al. (1975) report results from Sprague-Dawley rats exposed via inhalation to 875 ppm of MC for 7 hours daily on days 6 through 15 of gestation (Day 0 = the day sperm were observed in smears of vaginal contents).

Control rats were exposed to filtered air. Dams were evaluated for body weight gain, food consumption and various organ weights. Maternal carboxyhemoglobin level determinations were performed on blood samples collected via orbital sinus puncture immediately following the third and tenth (last) exposure. One-half of the fetuses in each litter were examined for soft-tissue malformations (free-hand sectioning), and one-half were stained and examined for skeletal malformations. One fetus in each litter was randomly selected and evaluated using histological techniques following serial sectioning.

Twenty-three litters from dams exposed to 875 ppm of methyl chloroform were evaluated. No effect was observed on maternal body weight or food consumption. The mean absolute liver weight was increased as compared with control, however the mean relative liver weight was unchanged. No embryotoxic or teratogenic effects were observed which were attributable to maternal MC exposure.

York et al. (1981) exposed Long-Evans rats by inhalation to dosages of 2100 ± 200 ppm MC for 6 hours daily, 5 days per week, in the following regime: (1) two weeks prior to mating through day 20 of gestation; (2) two weeks prior to mating only; (3) throughout gestation only; (4) controls which were exposed to filtered air before and during pregnancy. Day 1 of pregnancy was designated as the day spermatozoa were observed in smears of vaginal contents. One-half of each group was sacrificed on day 21 and assessed for signs of maternal toxicity, embryotoxicity or teratogenicity. The other one-half were allowed to deliver young naturally. When possible, litters were culled to four pups of each sex on day 4 postparturition and to two pups of each sex at 21 days postpartum. Pups were evaluated for behavioral effects (open field activity, running wheel activity, amphetamine challenge) and carcinogenicity. Surviving rats were sacrificed and necropsied at 12 months of age.

York et al. (1981) reported that both total fetal body weight and male fetal body weight were significantly depressed in litters exposed during pregnancy. Delayed ossification was more frequent in fetuses which had been exposed before and during pregnancy, and a delay in the development of the kidney was a more frequent observation in fetuses in all exposed groups. These effects are thought to be indicative of a slight, but possibly reversible delay in development. No treatment-related behavioral effects were observed in the pups, nor were significant signs of maternal toxicity observed.

5.3.1.3.2 Mice--Schwetz et al. (1975) exposed Swiss-Webster mice to 875 ppm of MC, twice the maximum excursion limit, for 7 hours daily, on days 6 through 15 of gestation (day 0 = day a vaginal plug was observed). Dams were Caesarean sectioned on day 18 of gestation and thirteen litters were evaluated. Methodology similar to that described previously (Schwetz et al. 1979) in rats was used, with the exception that food consumption was not monitored.

Mean and relative maternal liver weights in the exposed rats were slightly but not statistically decreased. Also, fetuses from the exposed group were slightly but not statistically smaller (both the crown-rump length and the body weight). This type of observation is thought to indicate a slight, but perhaps reversible delay in fetal development. No increased soft tissue or skeletal variations of the fetuses were attributable to maternal exposure to MC.

5.3.1.3.3 Chicken embryos--Elovaara et al. (1979) evaluated the effects of a number of aliphatic hydrocarbons on the development of chick embryos and reported the toxicity and teratogenic potential of MC in relationship to those of other aliphatic chlorinated hydrocarbons. MC was injected into the air space of fertilized chicken eggs at 2, 3, and 6 days of incubation and the rate of survival or death after 14 days of incubation was used as a measure of

embryotoxicity. The approximate LD_{50} value of MC varied between 50 and 100 μM/egg, depending upon time of injection. The types of abnormalities reported were absence of eye(s), upper beak deformations, exencephaly, brain hemorrhages, paleness (anemia), profound edemas either in the rump sacs or other areas, defects in external viscera and musculoskeletal defects of lower extremities. The spontaneous background level of malformations in vehicle-injected controls included only eye and skeletal abnormalities. This study indicates that MC has possible teratogenic potential when evaluated in chicken embryos, and that additional experiments should be performed for further evaluation. A scientific basis for the comparison of developmental toxic effects in various animal species is needed before results in chickens can be compared with other mammalian animal species.

5.3.2 Mutagenicity

Methyl chloroform has been tested for its mutagenic potential in several systems (bacteria, yeast, and rats), but sufficient data are not presented for evaluating the results presented in three papers (the Dow 1978 rat cytogenetic study, the Henschler et al. 1977 testing in Salmonella, and the Loprieno et al. 1980 testing in yeast). Of the remaining papers, only two described the results of mutagenicity testing conducted in such a manner as to prevent evaporation of MC and to ensure exposure of the indicator organisms. Both of these tests (Simmon et al. 1977 and Snow et al. 1979) were conducted in Salmonella and a weak positive response was reported for both.

On the basis of the available evidence, it is concluded that MC is mutagenic in bacteria. If the metabolism and pharmacokinetics of this compound in humans results in metabolic products which can interact with DNA as is the case for bacteria, it may cause mutagenic effects in humans as well. However, additional testing in other organisms (e.g., mammalian cells in culture) is

necessary to confirm the mutagenicity observed in bacteria. Careful attention should be given to the design and conduct of these studies to prevent the evaporation of MC, overcome its low solubility in aqueous media, and to ensure exposure of the indicator organisms.

Results from a joint study sponsored by Imperial Chemical Industries and the Medical Research Council in the United Kingdom and the National Institute of Environmental Health Sciences in the USA, conducted to assess the ability of short-term tests to predict carcinogenicity, have recently been published (8/6/81). EPA has not received a copy of this report to evaluate these data. Although preliminary indications are that MC tested negative, no information was available concerning which, if any, precautions were taken to ensure exposure of the organisms to the compound in these preliminary reports. These data will be evaluated critically in the near future when the Agency receives a copy of the final report.

Price et al. (1978) exposed Fischer rat embryo cell cultures (F1706, subculture 108) to 1,1,1-trichloroethane liquid at concentrations of 9.9×10^{1} and 9.9×10^{2} μM for 48 hours. 1,1,1-trichloroethane was diluted with growth medium to yield the appropriate doses. The 1,1,1-trichloroethane sample obtained from the Fisher Scientific Company was purportedly $\geq$ 99.9 percent pure, but a personal communication from Carlson of the Fisher Scientific Company revealed that methyl chloroform supplied by them to Dr. Price was really the product of the Dow Chemical Company which is about 95 percent pure. The cells were grown in Eagles minimum essential medium in Earle's salts supplemented with 10 percent fetal bovine serum, 2 mM L-glutamine, 0.1 mM nonessential amino acids, 100 μg pencillin, and 100 μg streptomycin per ml. Quadruplicate cultures were treated at 50 percent confluency with each dose.

After treatment, cells were cultured in growth medium alone at 37°C. Transformation of cells treated with either dose level of 1,1,1-trichloroethane was observed by 23 and 44 days of incubation and was characterized by progressively growing foci composed of cells lacking contact inhibition and orientation. There was no transformation of cells grown in medium alone or in the presence of a 1:100 acetone concentration. Fifty-two and 55 microscopic foci per three dishes with low and high 1,1,1-trichloroethane dose, respectively, were found in dishes inoculated with 50,000 cells from cultures treated four subcultures earlier and held for four weeks at 37°C in a humidified CO_2 incubator prior to staining.

5.3.3 Carcinogenicity

[NOTE: Refer to Carcinogen Assessment Group's assessment of MC attached to this document as Appendix I.]

At this time, direct animal bioassays for MC carcinogenicity have been carried out but are inconclusive. Table 5-11 gives the results of National Cancer Institute (NCI) animal bioassays of congeners of MC. The isomer 1,1,2-trichloroethane is carcinogenic in mice, inducing liver cancer and pheochromocytoma in both sexes. Di- and tetrachloroethanes and hexachloroethane also produce liver carcinomas in mice.

The initial NCI bioassay of MC (1977) was carried out in both sexes of Osborne-Mendel rats and $B_6C_3F_1$ mice by oral gavage at two dose levels (rats, 750 and 1,500 mg/kg, 5 days/wk; mice, 2,807 and 5,615 mg/kg time weighed average) for 78 weeks. Animals were observed for another 12 weeks for a total of 90 weeks in the experiment. In male rats, 64 percent given the low dose and 72 percent given the high dose died within the first year, while 48 percent of females given the low dose and 42 percent given the high dose died

TABLE 5-11. SUMMARY OF NCI CHLOROETHANE BIOASSAY RESULTS AS OF JULY 1978 (Parker, et al., 1979)

Compound	Species/sex	Tumor site	Statistically significant tumors
monochloroethane	no testing planned		
1,1-dichloroethane	retesting recommended because initial results inconclusive		
1,2-dichloroethane	rats/female	mammary gland	adenocarcinomas
	rats/male	forestomach	squamous cell carcinomas
		circulatory system	hemangiocarcinomas
		subcutaneous tissue	fibromas
	mice/female	mammary gland	adenocarcinomas
		endometrium	stomal sarcomas
		lungs	adenomas
	mice/male	lungs	adenomas
1,1,1-trichloroethane	retesting in progress		
1,1,2-trichloroethane	mice/female	liver	hepatocellular carcinomas
	mice/male	liver	hepatocellular carcinomas
	mice	adrenal glands	pheochromocytomas
1,1,1,2-tetrachloroethane	testing in progress, no report available		
1,1,2,2,-tetrachloroethane	mice/male	liver	hepatocellular carcinomas
	mice/male	liver	hepatocellular carcinomas
pentachloroethane	testing in progress, no report available		
hexachloroethane	mice/female	liver	hepatocellular carcinomas
	mice/male	liver	hepatocellular carcinomas

within a year. Similar mortality was observed in mice. The high mortality and symptoms of other toxic effects indicate that the maximum tolerated dose may have been exceeded. These high doses may also alter metabolism.

However, mortality was also high in untreated control rats (30 percent) and control mice (50 percent). It should be noted that MC bioassay animals were housed with animals receiving a variety of other chlorinated hydrocarbons. Although a variety of neoplasms were found in both treated and control rats and mice (Table 5-12), there was no dose-related increased incidence of tumors in either sex or species. The NCI Report (1977) does not comment on whether the failure to demonstrate carcinogenicity for MC is due to lack of carcinogenic potential for this compound or due to the bioassay design and obviously poor experimental conditions. NCI is currently testing MC in rats and mice by gavage at lower doses.

Table 5-13 summarizes the results of an industry sponsored chronic bioassay (Quast et al., 1978; Rampy et al., 1977) by inhalation exposure to MC. Male and female rats were exposed 6 hours/day, 5 days/week to 875 ppm and 1,750 ppm over a period of 52 weeks or about one-half their lifetime. The actual amount of MC absorbed via the lungs by the rat and by the tissues was not determined and cannot be estimated without metabolism and pharmacokinetic data for the rat. Based on the tumor incidence in the treated rats, which was similar in classification to those of the control animals, MC exposure did not result in a carcinogenic outcome. On the other hand, the inhalation dose of MC was only two- to threefold higher than that allowed in the workplace and only one species was tested.

In recent years, a great deal of attention has been focused on the role of MC in the destruction of stratospheric ozone (O_3). Because O_3 absorbs most of the ultraviolet (UV) radiation in the 290 to 320 nm wavelength range before

TABLE 5-12. SUMMARY OF NEOPLASMS IN RATS AND MICE INGESTING METHYL CHLOROFORM

Species	Sex	Number of Animals	Dose[a]	Total number of tumors	Number of tumors observed						
					Liver, spleen	Lung	Kidney, bladder	Integumentary system	Heart, vasculature	Brain, pituitary	Other
Rat	Male	20	-	3	1	-	-	1	-	-	1
		50	750	6	1	-	-	-	1	1	3
		50	1500	4	-	-	1	-	1	-	3
	Female	20	-	14	-	-	-	-	-	3	11
		50	750	6	-	-	-	-	-	2	4
		50	1500	12	1	-	-	1	1	1	8
Mouse	Male	20	-	5	2	1	-	-	-	-	2
		50	2807	2	1	1	-	-	-	-	-
		50	5615	9	8	1	-	-	-	-	-
	Female	20	-	5	2	-	2	-	-	1	5
		50	2807	2	1	-	-	1	-	-	-
		50	5615	3	-	1	-	1	-	-	1

[a]Compound administered in corn oil by stomach tube five days per/week. Concentration is a time-weighted average expressed in mg/kg/day.

Source: National Cancer Institute, 1977.

TABLE 5-13. SUMMARY OF NEOPLASMS IN RATS INHALING METHYL CHLOROFORM

Sex	Number of Animals	Concentration (PPM)	Total number of tumors	Number of tumors observed						
				Liver, spleen	Lung	Kidney, bladder	Integumentary system	Heart, vasculature	Brain, putuitary	Other
Male	189		200	2	1	2	36		39	120
	94	875	77	1	-	2	11	-	13	50
	92	1750	103	-	-	1	21	1	21	60
Female	189	-	561	2	1	2	328	2	102	124
	94	875	264	1	-	1	177	-	28	57
	92	1750	300	3	-	1	223	-	35	38

Source: Quast et al., 1978.

it reaches the earth's surface, a decrease in O_3 concentration could be deleterious to biological processes. It is known that nucleic acids and proteins absorb significantly in this wavelength range, with molecular disruption that results in genetic mutations. Alteration of nucleic acids by UV irradiation of tissues leads to an increased prevalence of skin cancer (National Research Council 1976, 1979).

Depletion of stratospheric O_3 levels have been correlated with an increase in the incidence of skin cancer (National Research Council, 1976; 1979; 1982). Accelerated usage of MC would be expected to cause a further increase in O_3 depletion, thus resulting in higher incidence of skin cancer. Preliminary information from an ongoing epidemiological study of skin cancer suggest that the incidence of nonmelanoma skin cancer in the United States may even be greater (NCI, unpublished results, August 1979).

5.4 SUMMARY OF ADVERSE HEALTH EFFECTS AND LOWEST OBSERVED EFFECTS LEVELS

5.4.1 Inhalation Exposure

The high volatility of methyl chloroform (MC), the extensive use of this compound as an industrial solvent, and the early interest in MC as an anesthetic has resulted in many reports in the scientific literature of human exposure to MC. Human experimental studies have been performed using acute and subchronic exposures to MC. Although these studies provide precise information on exposure levels, they are limited by the small numbers of subjects employed in the studies and the restricted number of physiological and behavioral parameters which were assessed. While information on human chronic inhalation exposure to MC is available from studies of occupationally exposed groups, there is uncertainty in these studies as to the exact extent of exposure; some studies are complicated by simultaneous exposure to other chemicals used in the workplace. Although these human studies have deficiencies which preclude

any individual study from being used for human risk assessment, the combined information presented in these studies does provide dose-response relationships which give a relatively clear description of the toxic effects of MC. Studies in experimental animals are available for acute and subchronic exposure to MC, but the uncertainty of extrapolation from animals to humans and the relatively large number of controlled human studies of acute exposure makes this animal data useful only in a supportive role for human risk assessment. No adequate chronic studies using experimental animals are available and although the reports of human occupational experience with MC are not ideal, they provide the best information on the effects of chronic exposure to MC.

5.4.1.1 Effects of Single Exposures--Lethal effects of acute exposure to MC have been reported after accidental exposure and abuse, with death resulting from CNS depression followed by respiratory and cardiac failure (Hall and Hine 1966; Bas, 1970; Stahl et al., 1969; Bonventre et al., 1977; Klienfeld and Feiner, 1966; Halfield and Mayroski, 1970; Caplan et al., 1976). From the levels of MC in the blood and brain of cadavers, estimates have been made of the concentration of MC present in the air during the time the victim was exposed. These estimates range from 200 to 102,900 ppm, with the majority of values being between 6,700 and 18,600 ppm (Table 5-14). However, these estimates are extremely crude and probably low since it is not known to what degree the MC had dissipated from the victims' body prior to obtaining tissue samples. Also, some of the observed deaths which occurred at relatively low MC concentrations may have resulted from aspiration pneumonia prior to extensive involvement of the CNS. A clearer indication of the levels of MC needed to produce narcosis is available in the study of Dornette and Jones (1960) investigating the use of MC as an anesthetic in humans. Although this study

TABLE 5-14. HUMAN FATALITIES ASSOCIATED WITH METHYL CHLOROFORM

Case No.	Sex	Material or Product Inhaled	Condition of Lungs at Autopsy	1,1,1-Trichloroethane Concentrations		Remarks	Source
				Blood mg%	Air ppm[X]		
1	F	Energine	passive congestion	72	102,900		Hall and Hine, 1966
2	M	1,1,1-trichloroethane	no autopsy	--	--	75,000 ppm in work space; collapsed after leaving work area	Kleinfeld and Feiner, 1966
3	M	"degreaser"	acute congestion and edema	30.0	42,900		Bonventre et al., 1977
4	M	Chlorothene®	heavy, edematous	13	18,600	possible aspiration, pneumonia	Hall and Hine, 1966
5	M	1,1,1-trichloroethane	heavy, edematous	12.0	17,000		Stahl et al., 1969
6	M	"	heavy, edematous	6.3*	9,000		Stahl et al., 1969
7	M	"	heavy, edematous	6.2	8,900		Stahl et al., 1969
8	M	"	heavy, edematous	6.0	8,600		Stahl et al., 1969
9	M	"	moderately edematous	6.0	8,600		Hatfield and Maykoski, 1970
10	M	"paint remover"	moderately edematous	4.7*	6,700		Stahl et al., 1969
11	F	"paint thinner"	acute edema & congestion	2.0	2,900	ethanol conc. in blood was 0.04%	Caplan et al., 1976
12	M	1,1,1-trichloroethane	markedly edematous	0.15	200	possible aspiration, pneumonia	Stahl et al., 1969

[X]Calculations based on assumption from Stewart et al., 1969, of one hour exposure correlating to 0.07 mg percent in blood per 100 ppm in air.
*Estimated from brain concentration.

study gives an indication of the levels of MC which cause CNS depression, presumably a higher concentration would be needed to cause depression severe enough to result in respiratory or cardiac failure. From these data and the LC_{50} concentrations of 14,250 ppm obtained by Adams et al. (1950) for rats, it can be estimated that a single exposure to concentrations of MC less than 5,000 ppm are probably not potentially life threatening in humans, while higher concentrations may produce narcosis and possibly death.

The effects of exposure of human volunteers to MC for single short term periods were reported for MC levels far below the levels which cause narcosis (Table 5-15). Stewart et al. (1961) exposed 7 subjects to vapors of MC which were increased from 0 to 2,600 ppm in increments of 15 minutes each. The progress of observed effects is presented in Table 5-1, with 6 of 7 subjects complaining of throat irritation at 1,900 ppm and lightheadedness and incoordination occurring between 2,600 and 2,650 ppm. The progressive exposure method used in this study and the small number of subjects makes the results difficult to interpret. However, in a second experiment in which subjects were exposed to 900 MC for periods of 20, 35, or 73 minutes, difficulty was observed in the performance of the Romberg tests, and some lightheadedness was experienced. No effects were observed in subjects exposed to 500 ppm for MC for 78 or 186 min. In both of these experiments, commercial grade MC was used which contained the inhibitors dioxane (2.4-3.0%), butanol (0.12-0.3%) and small amounts of 1,2-dichloroethane. These compounds may have also had some effect on the subjects. In support of the above findings, Torkelson et al. (1958) obtained similar results with 2 groups of 4 subjects each exposed to 900 or 500 ppm of pure MC for 75 to 90 minutes. Subtle changes in perceptive capability were observed following exposure to 350 and 450 ppm of MC by Gamborale and Haltengren (1973) and Salvini et al. (1971). However, these

TABLE 5-15. NON-LETHAL EFFECTS OF METHYL CHLOROFORM ON HUMANS

Study	Dose/Species	Effect
Dornette & Jones, 1960	10,000-26,000 ppm 6,000-22,500	Induction of anesthesia Maintain light anesthesia Depressed BP during mod. anesthesia Tendency to develop ventricular arrhythmias during hypoxia (reversed by oxygenation)
Siebecker et al., 1960	Anesthesia	Little change in EEG-similar halothane anesthesia
Stewart et al., 1961	0-2,650 ppm for 15 min 500 ppm 900-1000 ppm	See Table 5-1 No effects See Table 5-2
Torkelson et al., 1958	900-1,000 ppm for 75 min 1,900 ppm for 5 min	Slight eye irritation and lightheadedness; Flanagan and Romberg test showed slight loss of coordination and equilibrium Equilibrium disturbed, positive Romberg test
Torkelson et al., 1958 Stewart, 1968; 1971 Am. Ind. Hyg. Assoc.	Results of single exposures	See Table 5-7
Stewart et al., 1969	500 ppm 6.5-7 hr/day for 5 days	Mild subjective complaints; abnormal Romberg
Stewart et al., 1975	500 ppm	See Table 5-3

TABLE 5-15. (continued)

Study	Dose/Species	Effect
Gamborale and Hultengren, 1973	250, 350, 450, 550 ppm for 4-30 min periods	Change in manual dexterity and perceptual tests in exp. vs. control groups
Salvini et al, 1971	450 ppm for 2-4 hr periods	Decreased perceptive capability under stress, eye irritation
Maroni et al., 1977	110-990 ppm	No effects
Seki et al., 1975	4, 25, 28, 53 ppm	No effects
Kramer et al., 1978	11-838 ppm → x = 115	No effects, although SGPT and albumin were different in exposed vs. control group.
Weitbrecht, 1965	10-20 ppm, hands immersed in MC	Transient irritation of conjunctiva, upper respiratory tract; burning sensation in tongue; teeth felt dull (rhubarb effect) feeling of ice-cold fingers when placed in liquid MC; hypertension; positive urobilinogen; automatic dystrophy; circulatory dystrophy; psychasthenia
Stewart and Andrews, 1966 Stewart, 1971 Litt & Cohen, 1969		See Table 5-4

last two observations are questionable since the effects of mentol used to mask the odor of MC in the first study wre not evaluated, and in the second study the control subjects were not matched for all intervening variables such as food and drinking habits.

Although a precise dose-response gradient of effects produced by MC exposure cannot be derived, it is possible to establish a crude relationship between exposure and effects from a compliation of the human data available. A summary of the estimated dose-response relationships for acute effects of single short-term exposures is presented below:

>5,000 ppm	Onset of narcosis, possible life threatening
2,650-1,900 ppm	Lightheadedness, irritation of the throat
1,000 ppm	Disturbance of equilibrium
500-350 ppm	Slight changes in perception, obvious odor
100 ppm	Apparent odor threshold

The approximate concentrations of MC which elicit a particular adverse effect have greater uncertainty at the two extremes that is, life threatening levels (>5,000 ppm), and the lowest observed adverse effect level (LOAEL)* (500-350 ppm). This results from the inherent difficulties in obtaining exact exposure values in the cases of accidental overexposure to MC, and the difficulty in the acquisition of either quantitative or qualitative data on slight behavioral changes at the lower exposure levels. Acute overexposure to MC may be limited by the low odor threshold in humans of 100 ppm. Others report that an obvious odor is present at 500 ppm. It also should be noted that there are no reports of residual adverse effects from a single exposure to MC.

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*LOAEL: is defined as the lowest exposure level in a study or group of studies which produces statistically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

A major uncertainty in the dose-response relationship estimated for MC from the compilation of the available human reports is the lack of information on the length of exposure in accidental exposure, and the short duration (less than 2 hours) in most of the studies in which controlled exposures of human volunteers were used. Although inhaled MC is retained in the lungs in proportion to the concentration in the air, the time to reach pulmonary steady-state conditions is relatively long (4 hours). Since the maximum body burden from a given exposure to MC was probably not reached in any of these studies, it is likely that exposures for longer times would result in a greater body burden and more severe effects at a given concentration. In the studies of the inhalation toxicity of MC, there are insufficient data to predict the results of the increased body burden of MC obtained by extending the exposure until steady-state conditions are obtained. However, from the pharmacokinetic data presented in Figure 4-1, it can be reasonably concluded that the effects observed in the dose-response table would not shift by more than 30%. From the above discussion, it should be evident that these approximations are crude estimates and contain several areas of uncertainty.

5.4.1.2. Effects of Intermittent or Prolonged Exposures

There is very limited information from either animal or human studies on the effects of subchronic or chronic inhalation exposure to MC. As discussed below, the only experimental study of humans involved repeated exposure to MC 5 days per week for 3 weeks and is of such a short duration that no information can be extrapolated from this study as to the long term effects of MC exposure (Stewart et al., 1976). Observations of occupationally exposed workers are limited to reports where the exposure estimates are imprecise and comparable control populations were not studied. The paucity of chronic

toxicity data adds additional uncertainty in deriving human risk assessment based upon inhalation exposure to MC.

There are, however, three subchronic experimental animal studies with exposures continuing for approximately 90 days which provide some information on the effects of repeated exposures to MC. The study of Torkelson et al. (1958) using rats, guinea pigs, rabbits, and monkeys, and the study of Eben and Kimmerle (1974) using rats established a no observed effect level (NOEL)* for subchronic exposure to MC for 7 to 8 hours a day, 5 days per week for 3 months at 500 and 440 ppm, respectively. Similarly, a NOEL of 370 ppm was obtained by Pendergast et al. (1967) in a variety of species (15 guinea pigs, 3 squirrel monkeys, 3 New Zealand rabbits, and 2 beagle dogs) exposed continuously to MC for 6 weeks. In this study there were 3 deaths in the low exposure group (135 ppm), but these were attributed to lung infections. These three studies would indicate that subchronic exposure to MC in the range of 370 to 500 ppm produces no gross signs of toxicity. However, the report of McNutt et al. (1975) indicates that exposure below this range may alter some biochemical parameters in the liver and brain.

McNutt et al. (1975) observed alterations in the rough endoplasmic reticulum, detachment of polyribosomes, microbodies, and triglyceride droplets in the livers of mice exposed to 250 ppm of MC continusously for 24 weeks. At 1000 ppm, the extent of these changes had increased and some individual hepatocyte necrosis was observed. Although it is unclear whether the early biochemical and histologic changes observed at exposures of 250 ppm adversely affected liver function, they may represent the first stages in the sequence of events which leads to the hepatocellular necrosis observed at 1000 ppm.

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*NOEL: is defined as the exposure level at which there are no statistically significant increases in frequency or severity of effects between the exposed population and its appropriate control.

The NOEL of 370 to 500 ppm discussed previously may reflect the insensitivity of the parameters investigated in the other studies.

The only study involving multiple experimental exposures of humans was that of Stewart et al. (1975), in which 20 subjects were exposed to 500 ppm of MC for 7.5 hours a day, 5 days per week for 3 weeks. There were no effects on the clinical chemistry of the blood or urine, nor on pulmonary function tests. However, the subjects did have an increased number of subjective complaints, including sleepiness, irritation, and headaches. Again, these tests would probably not be sensitive enough to detect the slight changes in the liver observed in mice at exposures to 1000 or 250 ppm by McNutt et al. (1975). The combined evidence from the human and animal studies would indicate that only minimal effects are produced by multiple exposure to 250 ppm of MC and that the pathologic importance of these effects are unknown.

Reports of occupational exposure have major deficiencies which add to the uncertainty of a NOEL derived from these studies. The study by Weitbrecht (1965), which reported on the exposure of 9 women to MC at a workroom concentration of 10 ppm, is unacceptable for human risk assessment. The number of workers surveyed was too small to obtain an adequate data base, and the measurements of MC in the general workroom air were irrelevant for establishing individual expsoure of workers operating over open vats of a compound as volatile as MC. Also, the workers had their hands immersed in the solvent for varying lengths of time, and it has been determined by Fukabori et al. (1976, 1977) that significant amounts of MC can be absorbed through unbroken skin. Therefore, while no reliable estimate of exposure concentration can be made, it was probably considerably higher than the 10 ppm reported.

The studies of Maroni et al. (1977), Seki et al. (1975) and Kramer et al. (1978) reported a NOEL for workers occupationally exposed to MC of between 53

and 350 ppm. The short duration of exposure, averaging less than 1 year, of the work population in the report of Kramer et al. (1978) precludes the use of this study in human risk assessment. The study of Seki et al. (1975) provides information on 196 male workers exposed to MC for at least 5 years at concentrations of 4, 25, 28, and 53 ppm. The number of workers exposed at each concentration was relatively small, with only 42 people exposed to the highest concentration. While no dose related effects were observed, the exposed groups were only compared among themselves and not with a control population. The reported details of the analytical procedures were insufficient to determine whether the analytical data represented measurements over the entire time period (5 years) of exposure of the study population, or whether the concentrations reported were the concentrations in the breathing zone. Most of the deficiences in this study would probably result in an underestimation of the exposure levels, hence, it is reasonable to assume that 53 ppm is a NOEL concentration for MC. Maroni et al. (1977) looked for neurophysiological abnormalities in a population of 21 women who had been exposed for 6.5 years to an average concentration of MC between 110 and 345 ppm. No neurotoxicity was observed in exposed workers, as compared to a control population of 7 unexposed women. The small size of the exposed and control populations, and the limited number of physiological measurements made makes the NOEL obtained from this study extremely uncertain. However, the data of Maroni et al. (1977) do provide greater confidence that long term occupational exposure to 53 ppm of MC produces no adverse effects.

5.4.2 Oral Exposure

There is little information on the toxicity of MC by the oral route. As summarized in Table 5-5, the acute LD_{50} for MC has been determined in rats, mice, guinea pigs, and rabbits by Torkelson et al. (1958) and the values range

from 8,600 to 14,300 mg/kg body weight. These LD_{50} values could theoretically be used to calculate an approximate human lethal dose using the cubed root of the body weight ratios for interspecies conversion (U.S. EPA, 1980; Freireich et al., 1966; Rall, 1969). However, the data obtained from the species studied in the report of Torkelson et al. (1958) do not show a relationship between MC toxicity and body weight. Therefore, without further information, it would not be justified to place much reliance on an approximate human lethal dose calculated using the above approach. However, as a crude indication of a lethal oral dose of MC, the values were calculated from each species with the range for a human lethal dose falling between 770 and 3940 mg of MC/kg. Also, there is no information from human exposure to MC to indicate whether values obtained from a calculated lethal dose are applicable to human toxicology. For the above reasons it is considered inappropriate to attempt to predict an approximate human lethal dose from the present data available.

There are no subchronic studies on oral exposure to MC, and only one chronic study, an NCI bioassay. In the NCI (1977) bioassay, rats and mice were treated by gavage with MC in corn oil 5 days/week for 78 weeks at a level of 750 and 1500 mg/kg body weight for the low and high dose group rats, and 2807 and 5615 mg/kg body weight for the low and high dose group mice. Early deaths were observed in both rats and mice, with a statistically significant dose-related trend observed in male and female rats, and in female mice. The control animals also had poor survival and the early mortality in this group would suggest that MC contributed only partly to the early deaths of the treated animals. Another difficulty with this study is that treatment of animals by gavage is not identical to exposure through food or water since the daily dose of the compound is administered at a single time, resulting in high body levels immediately after treatment. As a result of the poor survival of

the control animals and the inappropriateness of the route of administration, the relevance of this study to human risk assessment is questionable.

5.4.3 Dermal Exposure

There is insufficient information available for quantitative risk assessment of dermal exposure to MC. The pharmacokinetic data of Fakabori et al. (1976, 1977) would indicate that absorption of MC through intact skin can contribute significantly to the levels of MC in the body. The extent of dermal absorption was estimated to be 5 percent of respiratory absorption in humans in direct contact with the liquid. The high vapor pressure of MC would preclude dermal contact with this solvent for sufficient periods of time to allow toxic quantities to be absorbed, except in some industrial situations. Even so, the greater efficiency of absorption by inhalation would make this the route of greatest concern.

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7. Appendix

THE CARCINOGEN ASSESSMENT GROUP's CARCINOGEN ASSESSMENT OF METHYL CHLOROFORM

EXTERNAL REVIEW DRAFT
January 16, 1981

THE CARCINOGEN ASSESSMENT GROUP'S

CARCINOGEN ASSESSMENT

OF

METHYL CHLOROFORM

Roy E. Albert, M.D.
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CONTENTS

I. Summary 1

II. Introduction 2

III. Metabolism 2

IV. Mutagenicity and Cell Transformation 4

Cell Transformation

V. Toxicity 14

VI. Carcinogenicity 15

Rats
Mice
Carcinogenicity of 1,4-Dioxane

VII. Unit Risk Estimate 23

VIII. References 26

I. SUMMARY

There is no adequate basis for the evaluation of the carcinogenicity of methyl chloroform. A lifetime animal bioassay using both rats and mice, currently in progress under the National Toxicology Program (NTP), will be completed in May 1981. An earlier National Cancer Institute (NCI) study was inconclusive due to the poor survival of treated animals. An inhalation study in rats by the Dow Chemical Company showed no evidence of carcinogenicity, but the doses were given for only half of the lifetime of the animals and the highest dose did not appear to be the maximum tolerated dose.

Technical grade methyl chloroform has been shown to be weakly mutagenic and to transform animal cells in vitro using Fisher rat embryo cell line F1706. Technical grade methyl chloroform contains about 3% of the stabilizing substance dioxane which shows evidence of being a carcinogen (Kociba et al. 1974; Argus et al. 1965, 1973; NCI 1978).

Therefore, because of the inconclusive results of the NCI gavage bioassay in rats and mice, the dosage inadequacies in the negative Dow inhalation test and the possible contribution of dioxane to the positive mutagenic and cell transformation tests, a final judgment on the carcinogenicity of methyl chloroform will have to be deferred until the results of the NTP bioassay, which has a very low percentage (0.002%) of dioxane, are available.

II. INTRODUCTION

Methyl chloroform (1,1,1-trichloroethane, CH_3CCl_3) is used primarily as a cleaning or degreasing agent for metals. It is increasingly being used as a substitute for chlorinated ethylenes. An estimated 630 million pounds were produced in the United States in 1976; of this, dispersive uses of methyl chloroform (primarily metal degreasing and aerosols) comprise at least 300 million pounds. Methyl chloroform escapes into the environment primarily into the air. It is soluble (2 gm in 100 ml) in water and has a boiling point of the 74°C. The National Institute for Occupational Safety and Health (NIOSH) judges that 2.9 million workers may be exposed (Parker et al. 1979).

III. METABOLISM

Only a small percentage of methyl chloroform is metabolized; most is excreted unchanged by the lungs. Using rodent liver *in vitro*, Van Dyke and Wineman (1971) showed that dechlorination of chloroethanes was carried out by the microsomal mixed-function oxidases and required molecular oxygen. However, methyl chloroform was a poor substrate for this reaction compared to other chloroethanes and less than 0.5% of the chlorine was enzymatically removed. Metabolism was not increased when rats were pre-exposed to methyl chloroform for 3 days.

In humans, Monster et al. (1979) have estimated that 60 to 80% of inhaled methyl chloroform was exhaled unchanged from the lungs. Only a small part of the retained methyl chloroform was excreted in urine as trichloroethanol (2%) and trichloroacetic acid (1.5%). The authors had no explanation for the unaccounted methyl chloroform.

Hake and coworkers (1960) injected one female and two male rats (170 to

IV. MUTAGENICITY* AND CELL TRANSFORMATION

Methyl chloroform has been tested for its ability to cause point mutations in bacteria, point mutations and gene conversion in yeast, and for cytogenetic abnormalities in rats. The studies presently available for review are summarized in Table 1.

Five reports have been prepared about the mutagenicity of methyl chloroform in bacteria; all were conducted using the Salmonella/S9 system. Two of the reports, Henschler et al. (1977) and Taylor (1977) were reported to be negative. The report by Henschler cannot be evaluated because no data are presented. In the report by Taylor, actually an interoffice memo describing results generated from testing performed by a contract laboratory, 0, 50, 100, 200, 300, and 500 ul/plate doses of methyl chloroform (source and purity not reported) were administered in plate incorporation tests using TA 1535, TA 1537, TA 98, and TA 100. Different concentrations of S9 activation were also tested. The high doses of methyl chloroform (300 and 500 ul/plate) were reported to be toxic for all strains in tests conducted without activation. The 500 ul/plate dose level was reported to be toxic for either TA 1537 or TA 98 in the various tests conducted with metabolic activation, but not for the other strains. The criteria for determining toxicity were not reported. Although special precautions were not reported to have been taken to prevent evaporation of methyl chloroform, it appears that the test agent did enter the cells at the highest doses because of the toxicity reported.

*Prepared by the Reproductive Effects Assessment Group.

183 g) intraperitoneally (i.p.) with 700 mg/kg of ^{14}C-methyl chloroform. About 50% of the urinary radioactivity occurred as 2,2,2-trichloroethanol in the form of glucuronide conjugate. The remaining urinary radioactivity volatilized at room temperature and was probably the parent compound. It was suggested that methyl chloroform metabolized by an initial oxidation to trichloroethanol and subsequent oxidation to small quantities of trichloroacetic acid. In this study, 98.7% of the injected radioactivity was exhaled unchanged, and 0.5% as $^{14}CO_2$. Only 0.85% of the injected radioactivity was recovered in urine, and only half of that was identified as a metabolite (Figure 1).

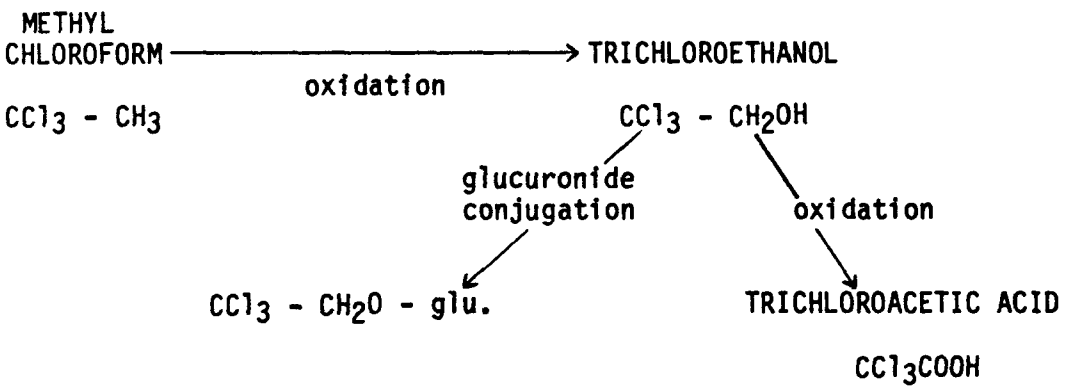

Figure 1. Metabolic route suggested for methyl chloroform.
Source: Hake et al. 1960, Ikeda an Ohtsuji 1972

Ikeda and Ohtsuji (1972) compared the quantities of metabolites in urine (trichloroethanol and trichloroacetic acid) in Wistar rats exposed by inhalation and by intraperitoneal injection. The quantity of metabolites was essentially equivalent for exposure to 200 ppm for 8 hrs and 2.78 mmol/kg body weight. These metabolites are the same metabolites formed from trichloroethylene. However, the concentration of trichloroethanol in the blood of volunteers exposed to methyl chloroform is only 1/35th that found in volunteers exposed to equivalent amounts of trichloroethylene (Monster 1979, Monster et al. 1979, Monster and Houtkooper 1979).

TABLE 1. MUTAGENICITY TESTING OF METHYL CHLOROFORM

A. BACTERIA

Reference	Test System	Strain	Activation System	Concentration	Result	Comment
Litton 1975	Salmonella/S9: spot test and plate incorporation	TA 1535 TA 1537 TA 1538	PCB induced liver, lung and testes S9 mix from adult male animals: ICR random bred mice, Sprague-Dawley rats and Macaca mulatta monkeys.	Formulation / % 99+ / 5.0 2.5 96 / 2.0 1.0 95.65 / 1.0 0.5 93.75 / 0.5 0.25	99+% formulation reported positive with TA 1535. Result was reported to be repeatable. The other formulations were reported to be negative.	1. All formulations reported to be not soluble at test concentrations. 2. Toxicity reported to be variable (In many tests, 25/48, as many or more survivors were observed at the high dose compared to the low dose). 3. Strains TA 98 and TA 100 not tested (not available at time test conducted). 4. No information about the identity of the stabilizers and other components. 5. No special precaution taken to prevent evaporation of the compound, but test reported to be conducted in suspension.
Henschler et al. 1977	Salmonella/S9	TA 100	PCB induced rat liver microsome S9 mix.	Not reported.	Reported negative.	1. No precautions taken to prevent evaporation reported. 2. No data presented, therefore, cannot evaluate. 3. Only one strain tested.
Simmon et al. 1977	Salmonella/S9: conducted in sealed desiccator	TA 1535 TA 1537 TA 1538 TA 98 TA 100	PCB induced rat liver microsome S9 mix.	(Extrapolated from figure 21) 0, 100, 200, 300, 400, 500, 750, 1000 ul/9-liter desiccator.	TA 100 Dose / +S9 / -S9 0 / 125 / 125 100 / 130 / 145 200 / 125 / 180 300 / 175 / 185 400 / 145 / - 500 / 200 / 220 750 / 260 / 210 1000 / 280 / 225	1. Results indicate ability of methyl chloroform to mutate bacteria when precautions are taken to ensure exposure of test organisms. 2. Data were presented for TA 100 only. 3. Exact purity of test compound not given, but reported to be high.

(continued on the following page)

TABLE 1. (continued)

A. BACTERIA

Reference	Test System	Strain	Activation System	Concentration	Result	Comment
Taylor 1977	Salmonella/S9: plate incorporation tests	TA 1535 TA 1537 TA 98 TA 100	Aroclor-activated rat liver microsome S9 mix. Different amounts tested (0, 10, 20, 30, 40, and 50 ul/plate).	0, 50, 100, 200, 300, and 500 ul/plate	Reported negative.	1. No precautions reported to have been taken to prevent evaporation of the test material. 2. Protocol not adequately described. 3. No positive controls reported to have been run. 4. The purity of the test chemical not reported.
Snow et al. 1979	Salmonella/S9: conducted in sealed chambers	TA 100	Methyl chloroform induced Syrian golden hamster liver S9 mix.		Aldrich Sample / PPG Sample	1. Only one strain tested. 2. Results indicate ability of methyl chloroform to mutate bacteria when precautions are taken to ensure exposure of test organisms. 3. Linear dose responses obtained with no significant differences found between Aldrich or PPG samples at any concentration tested. 4. Protocol not completely described. 5. Purity of Aldrich sample not reported. Purity of the PPG sample reported to be high but information about composition not provided.
					(without activation)	
				0*	144,115,130 / 144,115,150	
				500	234,251,235 / 225,232,233	
				750	271,271,274 / 263,301,262	
				1000	315,270,310 / 307,283,268	
				1500	355,336,340 / 398,360,336	
					(with activation)	
				0	122,143,119 / 122,143,119	
				500	324,281,312 / 266,291,297	
				750	365,346,351 / 359,333,348	
				1000	384,402,393 / 373,372,407	
				1500	485,432,430 / 471,467,430	
					Linear Regression Analysis (y = ax +b)	

Chemical Source		B	y	r
Aldrich	+S9	.21	168	.94
	-S9	.14	152	.96
PPG	+S9	.22	157	.97
	-S9	.15	143	.97

*ul/5.6-liter Billups-Rothenberg Modular Incubator Chamber

(continued on the following page)

TABLE 1. (continued)

B. YEAST

Reference	Test System	Strain	Activation System	Concentration	Result	Comment
Litton 1975	Saccharomyces cerevisiae: gene conversion	D4	PCB induced Sprague-Dawley rat liver S9 mix.	Formulation % 99+ 4.5 2.25 96 2.0 1.0 95.65 2.0 1.0 93.75 5.0 2.5	Reported negative.	1. All formulations reported to be not soluble at the test concentrations employed. 2. Toxicity reported to be variable (in many cases as many or more survivors observed at the high dose as at the low dose). 3. No information about stabilizers or other chemical substances in the formulations. 4. No special precautions taken to prevent evaporation of methyl chloroform but tests reported to be conducted in suspension.
Loprieno et al. 1979	Schizosaccharomyces pombe forward mutation	ade 6-60/ rad 10-198/ h-	Host mediated assay B6C3F1 mice.	0 or 5000 mg/kg administered by gavage to mice. Yeast exposed for 3, 6, or 16 h.	Reported negative.	1. Preliminary results; protocol not fully presented. 2. MTD may not have been employed. 3. Unclear if negative and positive controls performed concurrently. 4. Unclear if test compound was absorbed from GI tract and exposed test organisms. 5. No *in vitro* testing performed.

C. MAMMALIAN *IN VIVO* CYTOGENETICS

Quast et al. 1978	Chromosome aberrations in rat marrow cells	Sprague-Dawley, spartan substrain		0, 875, and 1750 ppm inhalation 5 days/week 6 hr/day for one year.	Reported negative.	1. Protocol and data not presented. Cannot evaluate conclusions. 2. Reported that data from female rats insufficient for clear interpretation of the results. 3. Treatment had no effect on body weight of rats. MTD may not have been employed.

No special precautions were reported to have been taken to prevent evaporation of methyl chloroform in the tests conduced by Litton-Bionetics (1975) for Dow Chemical Company either. Various formulations of methyl chloroform (99+%, 96%, 95.65%, and 93.75%) were assayed for mutagenic potential in Salmonella strains TA 1535, TA 1537, and TA 1538, both with and without metabolic activation. No information was provided concerning the stabilizers or other components of the formulated samples tested. Preliminary toxicity testing was conducted to determine the appropriate test doses. The test doses decided upon differed for each formulation and are presented in Table 1. It was reported by the contractor that the chemicals tested were not soluble in the aqueous testing environment, and it was stated, for the 99+% formulation at least, that "the toxicity from test to test was quite variable depending upon the ability to effectively disperse the compound in the testing medium." The low solubility of methyl chloroform coupled with its high volatility raise the concern that, in the tests conducted by Litton-Bionetics, exposure of the test organisms to it may have been minimal. Salmonella strain TA 1535 was reported to exhibit a repeatable mutagenic response to the 99+% formulation, but it is stated in the report that "the mutagenicity of this chemical for indicator strain TA 1535 must be considered presumptive for the following reasons:

A. The positive response is only evident at high dose levels which generally result in low population survivals (high toxicity). Thus one cannot exclude some type of selection.

B. The data from activation plate tests does (sic) not indicate any activity. The activation plate tests were repeated and were negative in those tests as well."

With respect to point A, an examination of the computer print-outs summarizing the mutagenicity of methyl chloroform for strain TA 1535 both with and without activation reveals that the population of cells in the high dose group was equal to or greater than the cells in the low dose group in two out of

four cases, including the experiment in which the highest mutation frequency was observed. In other words, there does not seem to be significant cytotoxicity at the high dose level which could possibly result in a spurious positive result.

With respect to point B, the plate activation tests performed in this experiment were spot tests. The proper conduct of a bacterial spot test requires that the compound be soluble in an aqueous environment, dissolving through the agar from point of placement outward, forming a concentration gradient. Since methyl chloroform is volatile and was not soluble in the testing performed by Litton-Bionetics, the negative results of the plate tests cannot be considered evidence supportive of the nonmutagenicity of methyl chloroform: therefore, the study by Litton-Bionetics (1975) is considered to be an inadequate assessment of the mutagenicity of methyl chloroform.

Two tests of the mutagenic potential of methyl chloroform in bacteria were reported to have been conducted using protocols designed to prevent evaporation of methyl chloroform and thereby ensure exposure of the indicator organisms. Both tests were reported to yield positive results (Simmon et al. 1977 and Snow et al. 1979). The testing performed by Simmon and coworkers was conducted using the standard battery of Salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100, both with and without PCB-induced rat liver microsome S9 mix for metabolic activation. The concentrations used for testing (extrapolated from figure 21) were 0, 100, 200, 300, 400, 500, 750, and 1000 ug/9-liter desiccator. A weak dose-related response was observed for TA 100 both with and without metabolic activation. These results indicate that methyl chloroform does possess mutagenic activity in Salmonella. The exact purity of the methyl chloroform sample tested was not given but was reported to be high.

In their studies, Snow et al. (1979) tested two samples of methyl chloroform in Salmonella strain TA 100 both with and without metabolic activation. Testing

conducted with metabolic activation employed an S9 mix obtained from methyl chloroform induced Syrian golden hamster liver microsomes. Similar to the study performed by Simmon et al. (1977), precautions were reported to have been taken to prevent evaporation of methyl chloroform. Doses of 0, 500, 750, 1000, and 1500 ul/5.6 liter Billups-Rothenberg Modular Incubator Chamber were employed, and repeatable, nearly identical, linear dose-responses were observed for TA 100 (see result column, Table 1) to the two samples of methyl chloroform tested. One of the samples was from Aldrich (97% methyl chloroform stabilized with 3% p-dioxane) and the other was from PPG Industries (reported to be a purified sample). The results of Snow and coworkers strengthen the observations by Simmon et al. (1977) that methyl chloroform is a weak mutagen in Salmonella. The nearly identical responses achieved after testing these two samples of methyl chloroform obtained from different sources support the conclusion that methyl chloroform is a mutagen.

Testing of methyl chloroform for mutagenicity employing yeast as indicator organisms has been conducted by two laboratories (Litton-Bionetics 1975 and Loprieno et al. 1979). Both reported negative results. The Litton-Bionetics yeast study was conducted at the same time as was the testing of methyl chloroform in bacteria, and many of the deficiencies noted above concerning the bacterial tests apply to the yeast testing as well. No special precautions were reported to have been taken to prevent evaporation of the test compound; the compound was not soluble under the condition of test, and the toxicity results were reported to be variable. In many cases (i.e., 5/11 for the various formulations) as many or more survivors were observed at the high dose as were observed at the low dose. As was the case for the bacterial results, the testing by Litton-Bionetics of methyl chloroform with respect to its ability to induce gene conversion in Saccharomyces cerevisiae with and without rat liver S9

mix metabolic activation is considered to have resulted in a "no-test." The volatility and insolubility of methyl chloroform raise the likelihood that the cells on test were simply not adequately exposed.

Based on preliminary testing using the host-mediated assay in B6C3F1 hybrid mice, Loprieno et al. (1979) have reported that methyl chloroform administered by gavage at 500 mg/kg did not increase the incidence of forward mutations in Schizosaccharomyces pombe measured after treatment times of 3, 6, and 16 hours. No information was provided concerning the ability of methyl chloroform to be absorbed and transported to the peritoneum, thereby effectively exposing the yeast cells, and no information is provided concerning whether or not testing was conducted to determine the ability of methyl chloroform to induce mutations in vitro. Furthermore, no data are presented concerning a determination of the toxicity of the substance to mice after acute exposure to arrive at a maximum tolerated dose for conducting the host-mediated assay. Besides the concerns that the indicator organisms may not have been exposed to methyl chloroform, the report does not provide adequate information concerning the design and conduct of the testing and this in turn, makes it impossible to assess the significance of the results. (It is not clear what protocol was followed to plate the yeast after harvest; it is not clear if concurrent positive and negative controls were performed, etc.)

The reported lack of chromosome aberrations produced after chronic exposure to Sprague-Dawley rats (Quast et al. 1978) also cannot be evaluated based on the data provided to EPA at the time of writing this report. Details concerning the protocol employed are very sketchy. The conclusions are forwarded unsupported by the presentation of experimental data.*

*A written request has been made to Dow to obtain these data.

A joint study sponsored by Imperial Chemical Industries and the Medical Research Council in the United Kingdom, and the National Institute of Environmental Health Sciences in the U.S.A. entitled the International Program for Evaluating Short-Term Tests for Carcinogenicity (IPESTTC) was recently conducted to assess the ability of short-term tests (including mutagenicity tests) to predict carcinogenicity. Forty-two chemical substances of high purity were tested blind in 23 different assays, (e.g., gene mutation tests in bacteria, yeast, and mammalian cells in culture; SCE formation in vitro and in vivo; chromosome aberrations in vitro, etc.) some of which were conducted in more than one laboratory. The results of the IPESTTC testing have recently been published (8/6/81). EPA has not yet received a copy of this report to evaluate the data, but preliminary indications are that methyl chloroform tested negative in a majority of the experiments (apparently only 9 weak positive responses were obtained out of 38 test systems). When EPA receives these data, they will be evaluated with respect to the mutagenicity of methyl cloroform. Since preliminary reports of the IPESTTC study do not note which, if any, precautions were taken to ensure exposure of the test organisms to the compound, and the data are not yet releasable for complete review, the preliminary indication that methyl chloroform tested negative in the IPESTTC study needs to be further evaluated.

In summary, methyl chloroform has been tested for its mutagenic potential in several systems (bacteria, yeast, and rats), but sufficient data are not presented for evaluating the results presented in three papers (the Dow 1978 rat cytogenetic study, the Henschler et al. 1977 testing in Salmonella, and the Loprieno et al. 1980 testing in yeast). Of the remaining papers, only two described the results of mutagenicity testing conducted in such a manner as to prevent evaporation of methyl chloroform and to ensure exposure of the indicator organisms. Both of these tests (Simmon et al. 1977 and Snow et al. 1979) were conducted in Salmonella and a weak positive response was reported for both.

On the basis of the available evidence, it is concluded that methyl chloroform is mutagenic in bacteria. If the metabolism and pharmacokinetics of this compound in humans results in metabolic products which can interact with DNA as is the case for bacteria, it may cause mutagenic effects in humans as well. However, additional testing in other organisms. (e.g., mammalian cells in culture) is necessary to confirm the mutagenicity observed in bacteria. Careful attention should be given to the design and conduct of these studies to prevent the evaporation of methyl chloroform, overcome its low solubility in aqueous media, and to ensure exposure of the indicator organisms.

CELL TRANSFORMATION

Price et al. (1978) exposed Fischer rat embryo cell cultures (F1706, subculture 108) to 1,1,1-trichloroethane liquid at concentrations of 9.9×10^1 and 9.9×10^2 uM for 48 hours. 1,1,1-Trichloroethane was diluted with growth medium to yield the appropriate doses. The 1,1,1-trichloroethane sample obtained from the Fisher Scientific Company was purportedly $\geq$ 99.9% pure, but a personal communication from Carlson of the Fisher Scientific Company revealed that methyl chloroform supplied by them to Dr. Price was really the product of the Dow Chemical Company which is about 95% pure. The chemical composition of Dow's methyl chloroform is given in Table 4, as reported by Quast et al. (1978) of the Dow Chemical Company. The cells were grown in Eagles minimum essential medium in Earle's salts supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 0.1 mM nonessential amino acids, 100 ug pencillin, and 100 ug streptomycin per ml. Quadruplicate cultures were treated at 50% confluency with each dose. After treatment, cells were cultured in growth medium alone at 37°C. Transformation of cells treated with either dose level of 1,1,1-trichloroethane was observed by 23 and 44 days of incubation and was characterized by

progressively growing foci composed of cells lacking contact inhibition and orientation. There was no transformation of cells grown in medium alone or in the presence of a 1:1000 acetone concentration. Fifty-two and 55 microscopic foci per three dishes with low and high 1,1,1-trichloroethane dose, respectively, were found in dishes inoculated with 50,000 cells from cultures treated four subcultures earlier and held for four weeks at 37°C in a humidified CO_2 incubator prior to staining.

Subcutaneous injection of cells treated with 9.9×10^{1} uM 1,1,1-trichloroethane two subcultures earlier produced local fibrosarcomas in 8/8 newborn Fischer 344 rats within 68 days following treatment. The ability of cells grown in growth medium alone to induce local fibrosarcomas was not determined; however, this tumor type did not develop in rats given cells grown in the presence of a 1:1000 concentration of acetone. Exposure of cells to 3.7×10^{-1} uM 3-methylcholanthrene produced 124 microscopic foci per three dishes in the inoculation test described above by 37 days of incubation and local fibrosarcoma in 12/12 rats by 27 days following subcutaneous injection of cells. The exposure of 3-methylcholanethrene was attained by initial dilution in acetone to 1 mg/ml followed by further dilution in growth medium to 0.1 ug/ml (personal communication, Dr. Price). It is understood that this cell line contains the genome of the Rausher leukemia virus, but there is no basis for minimizing the positive results since the mode of action of 1,1,1-trichloroethane is not known i.e., due to activation of the virus.

V. TOXICITY

The toxicity of methyl chloroform has been recently reviewed (Parker et al. 1979). Experiments were performed with various species and strains of animals at different concentrations. The most harmful effects of methyl chloroform are

central nervous system problems including anesthesia, disturbed equilibrium, and impairment of perceptual speed and dexterity. The effects of methyl chloroform on the heart include bradycardia, hypotension, and cardiac arrhythmias. Exposure can also cause inflammatory changes in the lungs, cellular damage and fatty changes in the liver, and damage to the kidneys. Methyl chloroform is reportedly teratogenic to chick embryos (Elovaara et al. 1979).

VI. CARCINOGENICITY

RATS

Two rat bioassays have been completed and one is in progress. The completed studies include an NCI bioassay and an inhalation study by the Dow Chemical Company. A 2-year carcinogenesis bioassay by gavage is now underway by the NTP in the mouse and rat with 1,1,1-trichloroethane, which has a very low percentage of dioxane. The animals will be sacrificed in May 1981. In the previous NCI bioassay, technical grade 1,1,1-trichloroethane was used. This was purchased from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin. The purity was checked by Hazleton Laboratories of America, Inc., Vienna, Virginia using gas-liquid chromatograph (glc) and infrared spectrophotometry. Analyses by glc showed that it contained 95% 1,1,1-trichloroethane and 3% p-dioxane, an inhibitor routinely added to commercial preparations of 1,1,1-trichloroethane. The remaining 2% of the glc peak area contained several minor impurities, two of which may have been 1,1-dichloroethane and 1,1-dichloroethylene. In this study, Osborne-Mendel rats were treated with 750 mg/kg and 1500 mg/kg of methyl chloroform in corn oil 5 times a week for 78 weeks by gavage (NCI 1977). The rats were observed an additional 32 weeks with the experiment ending at 110 weeks. Both males and females were used with 20 untreated males and 20 untreated females and 50 of each sex at each dose. The study was inadequate because only 3% of the treated rats survived to the end of the experiment.

The survival of both sexes of dosed rats was less than that of the matched control groups, which was also inadequate in the males. In male rats 6/20 (30%) of the controls, 32/50 (64%) of the low-dose group, and 36/50 (72%) of the high-dose group died within a year of the start of the study. The Tarone statistical test of survival showed a dose-related positive trend ($P < 0.001$) in the proportions of deaths over the period of the experiment, although this differential mortality is not reflected in the survival at 78 weeks. In female rats, 1/20 (5%) of the matched controls, 24/50 (48%) of low-dose group, and 21/50 (42%) of the high-dose group died in the first year. As in male rats, the statistical test for positive dose-related trend was significant ($P < 0.04$). In both sexes, the early mortality in the 1,1,1-trichloroethane-treated rats may have affected the incidence of late-appearing tumors; this is especially true in the males, since none survived to the scheduled termination of the study.

Fewer of the rats receiving 1,1,1-trichloroethane survived at both 78 and 110 weeks than did the positive control rats receiving the known carcinogen carbon tetrachloride (see Table 2).

TABLE 2. COMPARISON OF SURVIVAL OF CONTROL GROUPS, 1,1,1-TRICHLOROETHANE-TREATED, AND CARBON TETRACHLORIDE-TREATED (POSITIVE CONTROL) RATS

	1,1,1-Trichloroethane			Carbon Tetrachloride		
Group	Initial No. of Animals	Number Alive at 78 Weeks	Number Alive at 110 Weeks[a]	Initial No. of Animals	Number Alive at 78 Weeks	Number Alive at 110 Weeks[a]
Male						
control	20	7	0	20	20	12
low dose	50	1	0	50	34	15
high dose	50	4	0	50	35	8
Female						
control	20	14	3	20	18	14
low dose	50	9	2	50	38	20
high dose	50	12	1	50	21	14

[a]Time in study at last weighing.

A variety of neoplasms (Table 3) were represented in 1,1,1-trichloroethane-treated and matched-control rats. However, each type of neoplasm has been encountered previously as a lesion in untreated rats. The neoplasms observed are not believed attributable to 1,1,1-trichloroethane exposure, since no relationship was established between the dosage 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 the carcinogenicity of 1,1,1-trichloroethane on the basis of this test, because of the abbreviated life spans of the rats. The NCI Clearing House on Environmental Carcinogens concluded that the carcinogenicity could not be determined from this study (NCI Clearing House 1977).

The Dow Chemical study (Quast et al. preprint 1978) treated groups of Sprague-Dawley rats by inhalation under conditions that were similiar to those experienced by workers (6 hours/day, 5 days/week, over one-half of a lifetime). Rats were treated 12 months and observed until death or until they reached the age of 31 months. The dose of 875 and 1750 ppm was 2.5 and 5 times the threshold limit value of 350 ppm. Composition of formulation of 1,1,1-trichloroethane is given in Table 4. Total tumor incidence in the treated animals was similar to that of controls (Table 5).

When tumors at each site by tumor type, both benign and malignant, were examined, there were eight differences between control and treated animals at the $P < 0.05$ level (Fisher Exact Probability Test). Seven of these were decreased tumor incidence; one was an increase in ovarian granulosa cell tumors in females at the 875 ppm dose. There were no ovarian tumors in 189 controls, three in 33 treated at 875 ppm ($P = 0.003$), and two in 82 treated at 1750 ppm ($P = 0.14$). Since ovarian granulosa cell tumors are rare and the P value was low for the animals treated at 875 ppm, it will be of interest to see whether this result is repeated in the NTP study.

TABLE 3. STATISTICAL ANALYSES OF THE INCIDENCE OF TUMORS AT SPECIFIC SITES IN MATCHED CONTROLS AND 1,1,1-TRICHLOROETHANE-TREATED RATS

Topography: Morphology	Males[a] Matched Control	Low Dose	High Dose	Females[a] Matched Control	Low Dose	High Dose
Total Animals: all tumors[b]	3/20	6/48	6/50	7/20	7/50	9/50
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor	72	28	50	58	64	56
Pituitary: Chromophobe						
Adenoma[b]	0/20	0/48	0/48	3/20	2/48	1/48
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor	--	--	--	--	--	--
Thyroid: Follicular-Cell						
Adenoma[b]	0/20	0/48	0/50	2/20	0/50	1/49
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor	--	--	--	--	--	--
Adrenal: Cortical						
Adenoma[b]	0/20	3/49	1/50	2/19	1/48	2/49
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor		28	106	85	99	106

[a]Low- and high-dose groups received 1,1,1-trichloroethane in corn oil by gavage 5 times per week in doses of 750 and 1,500 mg/kg body weight, respectively.

[b]Number of tumor-bearing animals/number of animals examined at site.

[c]Beneath the incidence of the matched controls is the probability level for the Armitage test for positive dose-related trend in proportions when it is below 0.10, otherwise N.S. = not significant. Beneath the dosed group incidence is the probability level for the Fisher exact (conditional) test for comparison of that dosed group with the matched control group when it is below 0.10, otherwise N.S. = not significant.

TABLE 4. COMPOSITION OF THE FORMULATION OF 1,1,1-TRICHLOROETHANE USED IN CHRONIC INHALATION STUDIES IN RATS (Quast et al. 1978)

Compounds[a]	Liquid volume %	Calculated weight %
1,1,1-Trichloroethane	94.71	95.88
Nitromethane	0.44	0.38
Butylene oxide	0.74	0.46
1,4-Dioxane	3.93	3.11

[a]Analysis of 1,1,1-trichloroethane Lot TA02013B by gas chromatography.

TABLE 5. TUMOR INCIDENCE IN RATS TREATED WITH METHYL CHLOROFORM (Quast et al. 1978)

	Number of Animals		Total Neoplasms/Animal	
	male	female	male	female
control	189	189	1.06	2.97
875 ppm	91	92	0.85	2.67
1750 ppm	93	93	1.11	3.23

The Dow study suffers from two drawbacks: 1) the animals were treated for only 12 months rather than a lifetime but they were observed for another 12 months, and it is not evident that the maximum tolerated dose was used during the treatment period. There is no evidence that a range-finding study (subchronic) has been done before the start of experiment. The treated animals in the Dow study were no different in body weight, terminal organ weight, or mortality from untreated animals. The only sign of toxicity was an increased incidence of focal hepatocellular alterations in female rats at the highest dosage.

MICE

In the NCI bioassay (NCI 1977), B6C3F1 hybrids were used with 20 animals of each sex in the control group and 50 animals of each sex at each treatment dose. The time-weighted average dose was 2807 mg/kg and 5615 mg/kg. The mice were treated by gavage 5 days a week for 78 weeks and observed for another 12 weeks for a total of 90 weeks in the experiment.

In male mice, 10/20 (50%) of the matched-control group, 21/50 (42%) of the low-dose group, and 25/50 (50%) of the high-dose group died within a year of the start of the experiment. In female mice, 1/20 (5%) of the matched-control group, 9/50 (18%) of the low-dose group, and 20/50 (40%) of the high-dose group died within the first year of the study. The Tarone test for positive dose-related trend in the proportions surviving had a significance level of $P = 0.002$, although this differential mortality is not reflected in the survival at 78 weeks. Table 6 shows that a few mice receiving carbon tetrachloride survived until the planned termination of the test, and 25 to 40% of those treated with 1,1,1-trichloroethane reached the planned termination date. The

TABLE 6. COMPARISON OF SURVIVAL OF CONTROL GROUPS, 1,1,1-TRICHLOROETHANE-TREATED, AND CARBON TETRACHLORIDE-TREATED (POSITIVE CONTROL) MICE

	1,1,1-Trichloroethane			Carbon Tetrachloride		
Group	Initial No. of Animals	Number Alive at 78 Weeks	Number Alive at 90 Weeks	Initial No. of Animals	Number Alive at 78 Weeks	Number Alive at 90 Weeks
Male						
control	20	6	2	20	13	7
low dose	50	21	15	50	11	0
high dose	50	14	11	50	2	1
Female						
control	20	12	11	20	18	17
low dose	50	28	23	50	10	0
high dose	50	14	13	50	3	1

high early mortality in mice receiving 1,1,1-trichloroethane may have lowered the incidence of late-appearing tumors. The treated animals gained less than the controls.

A variety of neoplasms (Table 7) were represented in 1,1,1-trichloroethane-treated and matched-control mice. However, each type of neoplasm has been encountered previously as a lesion in untreated mice. In male mice there appeared to be an excess of tumors in the liver with one occurring among the controls and four among the treated, but the increase was not statistically significant. The neoplasms observed are not believed attributable to 1,1,1-trichloroethane exposure, since no relationship was established between the dosage groups, the species, sex, type of neoplasm, or the site of occurrence. 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 the mice.

TABLE 7. STATISTICAL ANALYSES OF THE INCIDENCE OF TUMORS AT SPECIFIC SITES IN MATCHED CONTROLS AND 1,1,1-TRICHLOROETHANE-TREATED MICE

Topography: Morphology	Males[a] Matched control	Males[a] Low Dose	Males[a] High Dose	Females[a] Matched Control	Females[a] Low Dose	Females[a] High Dose
Total Animal: All tumors[b]	2/15	2/47	6/49	4/18	2/48	3/50
P Values[c]	N.S.	N.S	N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor	80	89	50	80	54	26
Hematopoietic System:						
Malignant Lymphoma[b]	2/15	0/47	2/49	3/18	1/48	0/50
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor	80	--	64	80	90	--
Liver: Hepatocellular Adenoma or Carcinoma or Neoplastic Nodule[b]	0/15	0/47	4/49	0/18	0/48	0/50
P Values[c]	P = 0.035	N.S.	N.S.	N.S.	N.S.	N.S.
Weeks to first observed tumor	--	--	--	--	--	--

[a]Low- and high-dose groups received 1,1,1-trichloroethane in corn oil by gavage 5 times per week in time-weighted average doses of 2,807 and 5,615 mg/kg/ body weight, respectively.

[b]Number of tumor-bearing animals/number of animals examined at site.

[c]Beneath the matched controls incidence is the probability level for the Armitage test for positive dose-related trend in proportions when it is below 0.10, otherwise N.S. = not significant.
Beneath the dosed group incidence is the probability level for the Fisher exact test for comparison of that dosed group with the control group when it is below 0.10, otherwise N.S. = not significant.

CARCINOGENICITY OF 1,4-DIOXANE

Methyl chloroform contains a small amount of stabilizing substances. The concentration of specific stabilizers that had been identified in various commercial methyl chloroform products is shown below (Aviado 1977 and Detrex 1976, cited by Mazaleski 1979).

	Volume %
Nitromethane	0.4 - 1.8
Butylene oxide	0.4 - 0.8
Dioxane	2.5 - 3.5
Dioxolane	1.0 - 1.4
Methyl ethyl ketone	1.0 - 1.4
Toluene	1.0 - 1.4
2-Butyl alcohol	0.2 - 0.3
Isobutyl alcohol	1.0 - 1.4

Not all of these stabilizers are in every product, but the maximum total inhibitor package (combinations of stabilizers) appears to be between 7 and 8% by volume (Aviado 1977, cited by Mazaleski 1979).

Since dioxane is a contaminant in methyl chloroform (about 3%) the carcinogenicity of dioxane has been studied extensively. The results of these studies are summarized Table 8.

It should be noted that dioxane causes liver and nasal tumors in more than one strain of rats and hepatocellular carcinomas in mice. Liver tumors have been induced by dioxane in both male and female rats as well as in mice. These animal results, coupled with a reported finding of nasal carcinomas in furniture workers exposed to dioxane (NCI 1978, p. 108), suggest that dioxane is a potential human carcinogen. A detailed evaluation of the carcinogenicity of 1,4-dioxane is currently being prepared by the CAG.

VII. UNIT RISK ESTIMATE

No data exist which can be used to estimate quantitatively the potential human carcinogenicity of methyl chloroform.

TABLE 8. SUMMARY OF ANIMAL CARCINOGENICITY STUDIES FOR DIOXANE

Species	Strain	Route, Frequency of Administration	Sex	Control	Dose	Tumor type	Reference
Rats	Wistar	In drinking water for 63 weeks	M	Untreated	300 mg/day average	Hepatocellular carcinoma, renal transitional cell carcinoma, myeloid leukemia and lymphosarcoma	Argus et al. 1965
Rats	Sprague-Dawley derived Charles River CD	In drinking water for 13 months	M	Untreated	0.75, 1.0, 1.40, and 1.8%	Hepatocellular carcinoma (dose-response) 4/30, 9/30, 16, 30, 23/30	Argus et al. 1973
Guinea Pigs		In drinking water for 23 months	M	Untreated	588-635 g in 23 mo.	Gall bladder carcinoma, hepatoma, renal adenoma	Hoch-Ligeti and Argus 1970
Rats	Sprague-Dawley derived Charles River CD	In drinking water for 13 months	M	Untreated	0.75, 1.0, 1.40, and 1.80%	Squamous cell carcinoma (nasal cavity), heptacellular carcinoma and fibroma	Hoch-Ligeti et al. 1970
Mice	Swiss Webster	Applied to shaved skin of back 3 times/week for 60 weeks	M F	Acetone Acetone	Unspecified Unspecified	Carcinoma, subcutaneous tumor	King et al. 1973
Rats	Sherman	In drinking water for 2 years	M & F	Untreated	0.01, 0.1 and 1%	Hepatic tumors P = 00022 (all types) Hepatocellular carcinoma P = 00033 Nasal carcinoma P = 054 (these tumors are at the 1% level)	Kociba et al. 1974

(continued on following page)

TABLE 8. (continued)

Species	Strain	Route, Frequency of Administration	Sex	Control	Dose	Tumor type	Reference
Rats	Wistar	Inhalation 7 hrs daily 5 day/week	M & F	Filtered air	111 ppm	No hepatic or nasal carcinoma Reticulum cell sarcoma M 18/150 vs. 37/206 ($P < 0.08$) F 18/139 vs. 30/207 Found many other types of tumor but not significant	Torkelson et al. 1974
Rats	Osborne-Mendel	In drinking water for 110 weeks	M & F	Untreated	0.5 and 1.0%	Hepatocellular adenoma ($P = 0.001$) and squamous cell carcinoma of the nasal turbinataes ($P = 0.008$) (both sexes)	NCI Bioassay 1978
Mice	B6C3F1	In drinking water for 90 weeks	M & F	Untreated	0.5 and 1.0%	Hepatocellular carcinoma ($P = 0.001$) (both sexes)	

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