FOREWORD INTRODUCTION

# *Chloromethane*

## *CAS:74-87-3*

# SIDS Initial Assessment Report

# For

# SIAM 15

(Boston, USA, October 2002)

| | |
|---|---|
| **1. Chemical Name:** | Chloromethane |
| **2. CAS Number:** | 74-87-3 |
| **3. Sponsor Country:** | United States<br>Oscar Hernandez,<br>U.S. Environmental Protection Agency<br>Director, Risk Assessment Division (7403M)<br>1200 Pennsylvania Ave., NW<br>Washington, DC 20460<br>Phone: 1 202-564-7641<br>e-mail: hernandez.oscar@epa.gov |
| **4. Shared Partnership with:** | ICCA |
| **5. Roles/Responsibilities of the Partners:** | |
| • Name of industry sponsor /consortium | ICCA contact:<br>Michael E. Thelen,<br>Chair, Methyl Chloride Industry Association (MCIA)<br>Dow Corning Corporation<br>2200 W. Salzburg Road, PO BOX 994<br>Mail #CO3101<br>Midland, MI USA 48686-0994<br>Tel: (989) 496-4168 Fax: (989) 496-5595<br>Email: mike.thelen@dowcorning.com |
| • Process used | |
| **6. Sponsorship History** | |
| • How was the chemical or category brought into the SIDS Programme? | Acute Daphnid testing has been performed to meet the needs of the SIDS program. Documents were prepared and reviewed by industry prior to submission to sponsor country. Sponsor country conducted reviews of submitted data and offered comments to industry. Industry prepared and resubmitted documents for consideration at SIAM 15. A toxicological review of chloromethane by the U.S. Environmental Protection Agency (EPA) is available through the EPA's Integrated Risk Information System (IRIS) at http://www.epa.gov/iris/index.html. |
| **7. Review Process Prior to the SIAM:** | |

**8. Quality check process:**

**9. Date of Submission:**

**10. Date of last Update:** 19 March 2003

**11. Comments:**

# SIDS INITIAL ASSESSMENT PROFILE

| | |
|---|---|
| **CAS No.** | 74-87-3 |
| **Chemical Name** | Chloromethane (Methyl chloride) |
| **Structural Formula** | $H_3C$-Cl |

## SUMMARY CONCLUSIONS OF THE SIAR

**Human Health**

Chloromethane is a gas, unless it is under pressure. Inhalation is the major route of exposure in the occupational setting. Most inhaled chloromethane is metabolized and rapidly excreted via urine and expired $CO_2$. Because of high volatility and rapid metabolism, chloromethane does not accumulate in the tissues. The blood clearance is rapid and biphasic. Chloromethane metabolism involves conjugation with reduced glutathione in the ultimate transformation to formate and $CO_2$.

Chloromethane exhibits low acute toxicity by the oral and inhalation routes. The rat oral LD50 is 800 mg/kg bw. Studies illustrate species, strain and sex differences in sensitivity following acute inhalation, such that male mice appear to be most susceptible (6-hour LC50 = 4500-4600 $mg/m^3$), followed by rats (4-hour LC50 = 5300-5400 $mg/m^3$), and then female mice (6-hour LC50 = 17,000-17,500 $mg/m^3$).

In a 90-day inhalation study with rats and mice exposed to 375, 750 and 1500 ppm (750, 1500 and 3000 $mg/m^3$) the NOAEL and LOAEL were 750 ppm (1500 $mg/m^3$) and 1500 ppm (3000 $mg/m^3$), respectively. The LOAEL is based on the observation of significant increases in SGPT activity (male mice) with histological hepatic changes, hepatic infarction (one male mouse and one female rat), increased liver weights, and lower body weights (male and female rats.) In a two-year, inhalation bioassay, rats and mice were exposed to 50, 225 and 1000 ppm (100, 450, 2000 $mg/m^3$) with interim sacrifices at 6, 12 and 19 months. The NOAEL and LOAEL for systemic effects in rats and mice were 225 ppm (450 $mg/m^3$) and 1000 ppm (2000 $mg/m^3$), respectively. In rats, at 1000 ppm (2000 $mg/m^3$), increased relative heart weights (males and females), relative kidney and liver weights (males), decreased absolute and relative testes weights and decreased absolute liver weights (females) were seen. Histopathology of testes showed bilateral and diffuse generation and atrophy of the seminiferous tubules at 6 months and their severity increased until the 18-month sacrifice. Mice were more affected than rats, severe effects were seen at 1000 ppm. Effects at 1000 ppm included: neurofunctional impairment (females); depressed growth, clinical signs suggestive of CNS disturbance, significantly elevated SGPT levels, and increased relative heart weights (males and females); increased relative liver weights (females); decreased absolute brain weights (males and females); and decreased absolute and relative testes weights. In addition, hepatocellular degeneration (males and females); renal tubule epithelial hyperplasia, and cerebellar lesions characterized by degeneration and atrophy of the cerebellar granular cells occurred at 1000 ppm and was treatment related (males). Splenic atrophy and lymphoid depletion were noted at 1000 ppm (males and females). In a 12-day inhalation study in rats (4000, 7000 or 10000 $mg/m^3$) and mice (1000, 2000 or 4000 $mg/m^3$), deaths occurred in both rats and mice at the highest concentration tested. Primary effects were CNS related with lesions also occurring in the liver, kidney and brain. Rats were evaluated for testicular degeneration in which a clear exposure-concentration related response was observed. Lesions did not affect all seminiferous tubules equally with the principle affects being a reduction in late-stage spermatids, separation of spermatocytes and early-stage spermatids, with sloughing of the cells into the lumen, formation or irregular, apparently membrane-bound vacuoles in the germinal epithelium and variable formation of the giant cells. In a 93-95 day multi-species inhalation study, CNS, liver, kidney and testes were evaluated in dogs, rats and mice. No specific target organ toxicity or unequivocal toxic manifestations of chloromethane were observed in rats, mice and dogs exposed to concentrations as high as 800 $mg/m^3$. The NOAEL for the study was determined to be 800 $mg/m^3$ (the highest dose tested). In an atypical repeated dose inhalation study, female mice were continuously exposed (22 hrs/day for 11 days) to 15, 50, 100, 150, 200 or 400 ppm (30, 100, 200, 300, 400 or 800 $mg/m^3$), the NOAEL was determined to be 100 $mg/m^3$ (50 ppm) and the LOAEL = 200 $mg/m^3$ (100 ppm) based on the presence of cerebellar lesions. In the same study, female mice were intermittently exposed (5.5 hrs/day for 11days) to 150, 400, 800, 1600 or 2400 ppm (300, 800, 1600, 3200 or 4800 $mg/m^3$) the NOAEL and LOAELs were 300 $mg/m^3$ (150 ppm) and 800 mg/m$^3$ (400 ppm), respectively.

The weight of evidence indicates that chloromethane, at high concentrations, is a direct-acting mutagen in bacteria and human cells in culture (*in vitro*) however, *in vivo* genotoxic effects were not seen due to cytotoxicity occuring at high doses. Existing information indicates that chloromethane exposure does not result in DNA alkylation.

In a 2-year bioassay, there were no statistically significant increases in tumors in rats exposed to 100, 450 or 2000 mg/m$^3$. A similar exposure in mice caused increased mortality at 2000 mg/m$^3$, and an increased incidence of kidney tumors in male mice only. Male mice exposed to 450 mg/m$^3$ had a slightly increased incidence of kidney tumors. Exposure of 100 mg/m$^3$ did not cause any increases in the tumor incidence in either sex of mice.

In a two-generation reproduction study in rats, repeated 6-hour exposures to 3000 mg/m$^3$ (1500 ppm) resulted in sterility (decreased spermatogenesis) that is consistent with the testicular degeneration and granulomas seen in the epididymis of male rats after seven weeks. Exposures to 950 mg/m$^3$ (475 ppm) also caused a decrease in fertility, but no effects were seen in rats exposed daily to 300 mg/m$^3$ (150 ppm) for two generations. Exposures of 300 mg/m$^3$ did not cause inflammation of the epididymis and did not effect reproduction in rats. The NOAEL was 300 mg/m$^3$ for both adults and offspring. Teratological studies have shown possible differences between species. In rats, severe maternal toxicity was seen at 3000 mg/m$^3$ (1500 ppm), but no teratological response was observed following repeated 6-hour daily exposures to 200, 1000, or 3000 mg/m$^3$ (100, 500 or 1500 ppm) during gestation. In two studies, an increased incidence of heart malformations in mice were reported at exposures that were not maternally toxic. In both studies, the NOAELs for maternal toxicity were 1000 mg/m$^3$ (500 ppm.) The NOAELs for developmental toxicity in these studies were 200 mg/m$^3$ (100 ppm) and 500 mg/m$^3$ (250 ppm).

In humans, the most common consequence of single or repeated exposures $\geq$ 400 mg/m$^3$ is functional changes in the CNS, which can involve unsteadiness, dizziness, etc. The liver, kidney, testes, epididymis and lungs can also be affected by these exposures, but most of these effects are secondary, as pronounced CNS changes occur in the presence of these effects being observed.

**Environment**

Chloromethane has a vapor pressure of 4800 hPa at 20$^o$C, a melting point of -97.7$^0$C, a boiling point of -24.22$^0$C (at 1013 hPa), a log Kow of 0.91 and a water solubility of 4800 to 5325 mg/l at 25$^0$C. Chloromethane's atmospheric residence time is estimated to be about 1 year. The major removal process for chloromethane is reaction with hydroxyl radicals with an estimated half-life of approximately one year. Natural environmental levels are about 700 parts per trillion in ambient air. The stratospheric steady-state ozone depletion potential (ODP) of methyl chloride has been determined to be 0.02 relative to CFC 11 (ODP=1). Hydrolysis of chloromethane in water is relatively slow (does not readily hydrolyze) with a half-life of about 1.1 years at pH 7 and 25$^o$C. Considering its solubility, volatility and resultant Henry's Law Constant, chloromethane is expected, under equilibrium conditions, to exist principally in the air and is not expected to be present in the aquatic or terrestrial compartments. Fugacity (Level III) modeling performed based upon release data to the respective compartments, indicates that about 99.8% of the total, steady state mass of chloromethane will reside in the air compartment and about 0.1% will reside in each of the soil and water compartments. However, when chloromethane is released only to the water compartment it is predicted to remain primarily in that compartment (80% water and 20% air). Chloromethane is not readily biodegradable but may be degraded by adapted bacteria and under anaerobic conditions. The calculated BCF ranges from 2.98 to 3.16.

Based on the chemical's volatility, results based on nominal concentrations may be considered an underestimation of the actual toxicity; however, this may be mitigated by the chemical's high water solubility and dependent upon test conditions. The LC50 from the 96-hr fish study using nominal concentrations is 270 mg/L. In daphnia, the 48-hr reported EC50 based on nominal concentrations is 200 mg/L. The algal toxicity thresholds of 550 and 1450 mg/L were 7 day tests using nominal concentrations. Due to the possibility that the algae may not have been in the exponential growth phase throughout the tests, the ECOSAR predicted 96-hour EC50 value of 231 mg/L is preferred. In addition, the predicted acute toxicity of chloromethane (ECOSAR; version 0.99g) is in good agreement with the experimental data as indicated above for green algae along with acute toxicity for fish (96-h LC50 = 396 mg/L) and daphnia (48-h LC50 = 394 mg/L.). In combination with the chemicals environmental fate characteristics, the chemical is considered to be a low concern for the environment.

**Exposure**

Chloromethane is used almost entirely as a chemical intermediate to make other chloromethanes, silicone intermediates, pesticides, quaternary amines and surfactants, and as a methylation reactant for various other processes. The various uses of chloromethane were estimated at the following percentages in 1987: 74% silicones, 7% agricultural chemicals, 6% methyl cellulose, 5% quaternary amines, 2% butyl rubber, 2% miscellaneous, 4%

exports. These estimates do not recognize captive use for other chloromethane production. Most chloromethane is released to the air from non-anthropogenic sources (forest fires and releases from the ocean). The natural levels of chloromethane are about 700 parts per trillion in ambient air. Monitoring near non-industrial anthropogenic sources have shown much higher levels. Chloromethane has been observed at low concentrations (< 222 ng/l) in water. The total global production from sources other than manufacture is estimated at about 4.5 x $10^9$ tonnes. The 1997 global manufactured production of chloromethane was estimated at 1.54 x $10^6$ tonnes. This estimate is based on the assumption that the U.S. produces 35-45% of the total global estimate and the 1997 U.S. production volume of 6.3 x $10^5$ tonnes. Under the US EPA Toxic Release Inventory, 109 U.S. facilities reported in 1998, that approximately 1.2 x $10^6$ kgs were released to air, representing approximately 90% of the total on-and of-site releases of chloromethane. People who smoke or use wood as a heat source are likely exposed to much higher than normal background concentrations of chloromethane. Higher exposures may also occur in or near industrial plants producing or using this chemical. Individuals engaged in chloromethane production may be exposed to concentrations greater than background; however, most U.S. industries have maintained their worker-exposure levels well below the ACGIH guideline of 50-ppm TWA, which was adopted by OSHA in 1989. Chloromethane is not used in any commercial product currently manufactured.

## RECOMMENDATION

The chemical is currently of low priority for further work.

## RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for human health. Based on data presented by the Sponsor country, exposure to humans and the environment is anticipated to be low, and therefore this chemical is currently a low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

## FULL SIDS SUMMARY

| CAS NO: 74-87-3 | | SPECIES | PROTOCOL | RESULTS |
|---|---|---|---|---|
| **PHYSICAL-CHEMICAL** | | | | |
| 2.1 | Melting Point | | Experimental | -97.7 °C |
| 2.2 | Boiling Point | | Experimental | -24.22 °C (at 1013 hPa) |
| 2.3 | Density | | Experimental | 1.74 (at 0oC, 1 atm, air=1) |
| 2.4 | Vapour Pressure | | Experimental | 4800 hPa at 20°C |
| 2.5 | Partition Coefficient (Log Pow) | | Experimental | 0.91 |
| 2.6 A. | Water Solubility | | Experimental | 4800 to 5325 mg/l at 25°C |
| B. | pH<br>pKa | | | |
| 2.12 | Oxidation: Reduction Potential | | | |
| **ENVIRONMENTAL FATE AND PATHWAY** | | | | |
| 3.1.1 | Photodegradation | | Experimental | In air T1/2 = 1 years |
| 3.1.2 | Stability in Water | | Experimental | T1/2 = 1.1 years |
| 3.2 | Monitoring Data | | Experimental | In air = 500-700 ppt<br>In surface water = not detected to 222 ppb<br>In soil/sediment = < 5 ppb |
| 3.3 | Transport and Distribution | | Calculated (Fugacity Level III type)<br><br>(local exposure) | In air: > 99%<br>In water: 0.4%<br>In soil: 0.4%<br><br>Overall residence time: 4 days |
| 3.5 | Biodegradation | | Experimental | Negligible |
| **ECOTOXICOLOGY** | | | | |
| 4.1 | Acute/Prolonged Toxicity to Fish | *Lepomis macrochirus* | Experimental | LC50 (96 hr) =550 mg/l |
| | | *Menidia beryllina* | | LC50 (96 hr) = 270 mg/l |
| | | *Micropterus salmoides* | | TL50(96 hr) = 1500 mg/l |
| | | ECOSAR | Predicted | LC50 (96 hr) = 396 mg/l |
| 4.2 | Acute Toxicity to Aquatic Invertebrates | *Daphnia magna* | Experimental | EC50(48 hr) = 200 mg/L (based on nominal concentrations) |
| | | ECOSAR | Predicted | LC50 (48 hr) = 394 mg/l |
| 4.3 | Toxicity to Aquatic Plants e.g. Algae | *Scenedemus quadricauda* | Experimental | Toxicity threshold conc.=1450 mg/l |
| | | *Microcystis aeruginosa* | | Toxicity threshold conc. = 550 mg/l |
| | | ECOSAR | Predicted | EC50 (96 hour) = 231 mg/l |
| 4.5.2 | Chronic Toxicity to Aquatic Invertebrates (Daphnia) | | | |
| 4.6.1 | Toxicity to Soil Dwelling Organisms | | | |
| 4.6.2 | Toxicity to Terrestrial Plants | | | |

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|---|---|---|---|---|
| (4.6.3) | Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds) | | | |
| **TOXICOLOGY** | | | | |
| 5.1.1 | Acute Oral Toxicity | Rat | Experimental | LD50 = 1800 mg/kg |
| 5.1.2 | Acute Inhalation Toxicity | Rat | Experimental | LC50 (4 hr) = 5300 - 5400 mg/$m^3$<br>LOEL=400 mg/$m^3$ (24hr/d; 2-3 days) |
| | | Mouse | | Sex not specified: LC50 (4-7 hr) = 4000-6300 mg/$m^3$<br>Male: LC50 (6 hr) = 4500-4600 mg/$m^3$<br>Female: LC50 (6hr) = 17,000-17,500 mg/$m^3$ |
| | | Cat | | NOEL= 1000 mg/$m^3$ (24 hr/d; 3days) |
| | | Dog | | NOEL = 400 mg/$m^3$ (24 hr/d; 3 days);<br>LOEL = 1000 mg/$m^3$ |
| 5.1.3 | Acute Dermal Toxicity | | | |
| 5.4 | Repeated Dose Toxicity | Rat/Mice | Inhalation | NOEL = 1500 mg/$m^3$ (13 week) |
| | | Rat | Inhalation | NOEL = 450 mg/$m^3$ (2 years) |
| | | Mice | Inhalation | NOEL = 450 mg/$m^3$ (2 years) |
| | | Rats and Mice | Inhalation | LOEL (rats) = 4000 mg/$m^3$ (12 days);<br>LOEL (mice) = 1000 mg/$m^3$ (12 days) |
| | | Mice | Inhalation | NOEL = 100 mg/$m^3$ (11 days) |
| | | Mice, Rats and Dogs, | Inhalation | NOEL (all) = 800 mg/$m^3$ (64-66 exposures in 93-95 days) |
| 5.5 | Genetic Toxicity In Vitro | | | |
| A. | Bacterial Test (Gene mutation) | Salmonella typhimurium: | | |
| | | TA98, TA100, TA1535, TA1537, and TA1538 | Dessicator test | Positive (with and without metabolic activation) at 50,000–400,000 mg/$m^3$ (25,000-200,000 ppm) |
| | | TA1535 | Gas exposure | Positive (with and without metabolic activation) at 10,000– 400,000 mg/$m^3$ (5000-207,000 ppm) |
| | | TA98, 100,1535 and 1537 | Gas exposure | Positive (with and without metabolic activation) in TA1535 and TA100 at 1%, 4% and 7% |
| | | TM677 | | Positive (without metabolic activation) at 100,000-600,000 mg/$m^3$ (50,000-300,000 ppm) |
| B. | Non-Bacterial In Vitro Test (Chromosomal aberrations) | Human lymphoblasts: | Experimental | |
| | | Sister chromatid exchange | | Positive (without metabolic activation) |
| | | Gene mutation | | Positive (without metabolic activation) |
| | | DNA strand breaks (alkaline elution) | | Negative (without metabolic activation) |
| | | Syrian Primary hamster embryo cells | | Positive (without metabolic activation) |
| | | Rat: UDS study in hepatocytes, spermatocytes, and tracheal epithelial cells | | Positive in hepatocytes and spermatocytes (without metabolic activation) |

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|---|---|---|---|---|
| 5.6 | Genetic Toxicity In Vivo | Rat (inhalation): UDS study in hepatocytes, spermatocytes, and tracheal epithelial cells | Inhalation | Negative in all 3 cell types at 6,000-7,000 mg/m$^3$ (3000-3500 ppm); Positive marginal increase in hepatocytes and negative in tracheal epithelial cells and spermatocytes at 15,000 ppm |
| | | Drosophilia | Sex-linked recessive lethal test | Positive at 400,000 mg/m$^3$ (200,000 ppm) |
| | | Rat | inhalation: Dominant lethal test | Positive. Apparent genetic effect is due to induction of inflammation in the epididymis since effect was negative when male rate treated with anti-inflammatory. |
| | | Mice | inhalation: alkaline elution | Positive for DNA protein cross links only in the kidney of male mice, not in kidney of female mice or hepatic tissue; likely due to formaldehyde production. |
| 5.8 | Toxicity to Reproduction | Rat. | 2-gen, Inhalation | NOEL = 300 mg/m$^3$ (General toxicity)<br>NOEL = 300 mg/m$^3$ (Repro. Tox. Parental)<br>NOEL = 300 mg/m$^3$ (Repro. Tox. F1 generation) |
| 5.9 | Developmental Toxicity/ Teratogenicity | Rat | Inhalation | NOEL = 1000 mg/m$^3$ (General toxicity)<br>NOEL = 3000 mg/m$^3$ (Pregnancy/litter)<br>NOEL = 3000 mg/m$^3$ (Foetal data) |
| | | Mice | Inhalation | NOEL = 1000 mg/m$^3$ (General toxicity)<br>NOEL = 1000 mg/m$^3$ (Pregnancy/litter)<br>NOEL = 500 mg/m$^3$ (Foetal data) |
| 5.11 | Experience with Human Exposure | | Experimental | Accidental Exposure Information<br>Voluntary Study Information<br>Epidemiology Information |

# SIDS Initial Assessment Report

## 1 IDENTITY

### 1.1 Identification of the Substance

CAS Number: 74-87-3
IUPAC Name: Chloromethane
Molecular Formula: $CH_3Cl$
Structural Formula: $H_3C$-Cl
Molecular Weight: 50.49

### 1.2 Purity/Impurities/Additives

Composition of chloromethane in the liquid phase is generally greater than 99.5% w/w. The most likely contaminants in chloromethane are water vapor (CAS # 7732-18-5) hydrogen chloride gas (CAS # 7647-01-0), dimethyl ether (CAS #115-10-6), methanol (CAS #67-56-1), acetone CAS #67-64-1), ethyl chloride (CAS #75-00-3), and vinyl chloride (CAS #75-01-04).

### 1.3 Physico-Chemical properties

**Table 1** Summary of physico-chemical properties

| Property | Value | Reference |
|---|---|---|
| Physical state | gas at room temperature | |
| Melting point | -97.7°C | (Torkelson and Rowe, 1981) |
| Boiling point<br>Relative density | -24.22°C<br>1.74 @ 0°C, 1 atm (air=1) | (Torkelson and Rowe, 1981)<br>(Ahlstrom and Steele, 1979) |
| Vapour pressure | 4800 hPa at 20°C | (Torkelson and Rowe, 1981) |
| Water solubility | 4800-5325 mg/l at 25°C | (Ahlstrom and Steele, 1979; Horvath, 1982) |
| Partition coefficient n-octanol/water (log value) | 0.91 $\log_{10}$ Kow at 25°C | (Hansch et al., 1975) |
| Henry's law constant | 8.82 x $10^{-3}$ atm-$m^3$/mol | (Gosset, J.M., 1987) |

# 2 GENERAL INFORMATION ON EXPOSURE

## 2.1 Production Volumes and Use Pattern

### Production

The 1997 global production of chloromethane was estimated at 1.54 x $10^6$ tonnes. This estimate is based on the assumption that the US produces 35-45% of the global total and the 1997 US production volume of 6.3 x $10^5$ tonnes. The 1997 Japan production volume was estimated to be 1.8 x $10^5$ tonnes (unpublished communication from the U.S. Methyl Chloride Industry Association).

### Use

Chloromethane is used almost entirely as a chemical intermediate to make other chloromethanes, silicone intermediates, pesticides, quaternary amines and surfactants, and as a methylation reactant for various other processes. It is also used as a solvent for production of butyl rubber. It is estimated that well over 95% of production is consumed by the 30-40 major industries using it as a chemical intermediate. Virtually all of the uses for chloromethane are consumptive in that the chloromethane is reacted to form another product during use. Thus, chloromethane is consumed when used and is no longer available for release, disposal, or reuse (NTIS, 1990). The Chemical Marketing Reporter identified the different uses of chloromethane in 1987 at the following percentages: silicones at 74%, agricultural chemicals at 7%, methyl cellulose at 6%, quaternary amines at 5%, butyl rubber at 2%, miscellaneous at 2% and exports at 4% (Kavaler, A.R. 1987). Although this adds up to 100% and the estimates reflect a reasonable proportioning of these uses, it does not recognize captive use for other chloromethane production.

## 2.2 Environmental Exposure and Fate

### 2.2.1 Sources of Environmental Exposure

Since chloromethane is a gas, most industrial releases would be expected to be to the air. Any releases to surface water or surface soil would be expected to immediately evaporate. Releases of chloromethane to the environment are reported to the U.S. Environmental Protection Agency annually by producers and users. For the 109 facilities reporting in 1998, approximately 1.2 x $10^3$ tonnes were released to the air, represently about 90% of the total on-and of-site releases of chloromethane released during the calendar year 1998. This same report shows that all respondents released a total of 26 kgs to surface land, 1.47 x $10^2$ tonnes were injected underground, and 0.8 tonnes were discharged to surface water. In addition to the releases from industrial activity, there are large releases to the air from home wood burning, forest fires, and especially the oceans (about 4.5 x $10^9$ tonnes on a global basis, USEPA Toxic Release Inventory, 1998). Chloromethane was first measured in the atmosphere in 1975. Industrial activities add only a small (less than 1%) and probably insignificant amount of chloromethane to the ambient air levels relative to all of the non-industrial sources. The exact process by which chloromethane is produced in marine environments or in biomass burning is not known, but it is apparent chloromethane has been part of mankind's atmosphere throughout earth's development.

### 2.2.2 Photodegradation

The hydroxy radical atmospheric half-life is estimated to be approximately one year. The major removal process for chloromethane is probably the reaction with hydroxyl radicals

(Singh, et al., 1982; Khalil, 1979; Spence, et al., 1976). The exact pathway for decomposition in the troposphere is not known; however, the ultimate degradation products would be HCl, CO and $CO_2$ (Spence, et al., 1976; Singh, et al., 1982). The direct photolysis of chloromethane appears unimportant in the troposphere (Shold and Rebbert, 1978). Most of the HCl produced by tropospheric degradation of chloromethane will be removed via precipitation. HCl formed in the stratosphere probably plays some role in regulating stratospheric ozone, but the extent to which HCl is an active species; a temporary sink or permanent sink for chlorine is still being debated. A small amount of chloromethane may be removed with precipitation in the form of rain and/or snow, although this is not likely to be a significant atmospheric process. The stratospheric steady-state ozone depletion potential (ODP) of methyl chloride has been determined to be 0.02 relative to CFC 11 (ODP=1) (Solomon et al., 1992, WMO, 1994; Fabian et al., 1996). The Global Warming Potential of methyl chloride is similar to that of methane however the current industrial emission rates of methyl chloride are too low to contribute meaningfully to atmospheric greenhouse heating effects (Grossman et al., 1997). Greater than 99% of ambient air concentrations of methyl chloride originate from natural sources (US EPA Toxic Release Inventory (TRI), 1998), primarily from the ocean (Fabian, 1986; Rasmussen et al., 1982; Singh et al., 1979; Yung et al., 1975).

### 2.2.3 Stability in Water

#### 2.2.3.1 Hydrolysis

Hydrolysis of chloromethane in water is relatively slow with a half-life ranging from 62 days to about 1.1 years at pH 7 and 25°C (Mabey and Mill, 1978). Hydrolysis of chloromethane under mildly acidic and neutral conditions is essentially negligible. Under basic conditions at pH = 11, hydrolysis apparently takes place - albeit at a slow rate - yielding methanol as a transformation product. Based on hydrolysis characteristics alone, chloromethane would be expected to persist within normal pH regimes in the aquatic environment.

#### 2.2.3.2 Volatilizatio n from Water

Considering its solubility, volatility and resultant Henry's Law Constant, chloromethane is expected, under equilibrium conditions, to exist principally in the air. Equilibrium conditions in water will be attained faster if stirring or agitation (Dilling, 1975, 1977) expands the water/air interface area. Thus flowing or wind-agitated surface water will quickly lose nearly all of any chloromethane via evaporation to the air. Based on the EXAMS environmental model (USEPA 2001), the half-life for volatilization of chloromethane from a standard pond and lake was calculated to be 25 hours and 18 days, respectively (ATSDR, 1990). Similarly, the water volatilization model WVOLWIN® (USEPA 2000) estimates that chloromethane will have a half-life of 0.8 hours in a shallow, rapidly moving river with a strong surface wind and a half-life of 68 hours in a shallow lake with a weak surface wind.

Absorption of natural organic or inorganic materials in contact with water should not be a significant removal process due to volatility and relatively low octanol/water partition coefficient.

### 2.2.4 Terrestrial Fate

No reports were found on the environmental fate of chloromethane in soil. Since it has been reported to be detected in groundwater, it is apparent that it can travel with water through the soil to underground aquifers. Considering the physical properties of chloromethane, it should only be found at more than background levels in soil that has been protected from evaporative losses, or when it has been deliberately placed below soil surface levels and covered with a barrier of some type which could inhibit evaporation.

### 2.2.5 Transport between Environmental Compartments

Level I, II and III fugacity modeling of a type 1 chemical (i.e., chemical that partitions into all environmental media) were used for the assessment. Only Level III results are presented in the SIAR.

Level III simulations were first used to evaluate the effect of source of entry on the distribution and persistence of chloromethane. Chemical specific data required for the simulations are specified in the SIDS Dossier. The default emission rate of 1000 kg/h was used for each simulation. As was expected, emission of chloromethane directly to air resulted in > 99% of the total chemical mass residing in the air compartment, with advection in air the primary mechanism of removal. Degradation in air represented only a minor amount of the total chemical mass (< 1%) removed from the system. Intermedia exchange of chloromethane between the other compartments was insignificant. Similar results were obtained when the chloromethane emission was to the soil compartment. Because of the relatively high vapor pressure of chloromethane, only 3.6% of the total chemical mass remained in the soil compartment whereas 96% was found in the air compartment. Hence, the primary removal process from soil was volatilization and the primary removal process from the system was advection in air. Local persistence was about 4 days, regardless if the chloromethane emission is to the air or soil compartment. Similarly, reaction residence time was about 1.5 years.

In contrast to that observed for emission to the air and soil compartments, emission of chloromethane to the water compartment resulted in only about 20% the total chemical mass residing in the air, whereas about 80% remained in the water. Intermedia exchange of chloromethane with the other compartments (e.g., soil and sediment) was insignificant (< 1%). The dominant removal mechanism of chloromethane from the system was advection in air (69%), which was equal to the rate of volatilization from the water compartment. Significant amounts of the total chemical mass were also removed by advection and degradation in water (28% and 2.4%, respectively). Nonetheless, local persistence was about 15 days and reaction residence time about 1.4 years.

The above results indicate that the environmental compartments of concern, based on emission of chloromethane, are air and water. Insignificant amounts of chloromethane will be found in the soil or sediment compartments, regardless of source of entry to the environment. Since chloromethane is a gas, most industrial releases are expected to be directly to the air compartment. In the United States, it is estimated that about $1.20 \times 10^6$ kg of chloromethane is annually released to the environment (about 154 kg/h) from industrial activities. Of this amount, about 89% was released directly to air, 0.06% was released to water, and about 10% was added to soil or injected underground. These emission rates (137 kg/hr for air, 0.09 kg/hr for water, and 16.7 kg/hr for soil) were entered into the Level III simulation to obtain an overall assessment of the impact of industrial releases of chloromethane to the environment. Results of the simulation indicate that the total, steady state mass of chloromethane in the environment from industrial sources was about 15,300 kg. Greater than 99% of the total, steady state mass was found in the air compartment and about 0.4% was found in each of the soil and water compartments. Since chloromethane is expected to partition largely to the air, it is not expected to be present in the aquatic or terrestrial biota. The local persistence was about 4 days with advection in air accounting for >99% of the chloromethane removed from the system. Less than 1% was lost through degradation processes. Predicted concentrations in the environmental compartments, based on Level III fugacity modeling, were significantly less than reported concentrations in air (1000-1500 ng/m$^3$), water (<222 ng/L), and soil or sediment (<5,000 ng/kg).

### 2.2.6 Biodegradation

Like other chlorocarbons, chloromethane does undergo anaerobic biodegradation under some conditions, including industrial sewage treatment processes. There are a variety of indicators that biodegradation should occur, including liver detoxification (Kornbrust and Bus, 1983), bio-oxidation (Stirling and Dalton, 1979; Patel, et al., 1982), and enzyme catalyzed hydrolysis (Keuning, et al., 1985). Recent work also shows that a bacterium isolated from industrial sewage is very effective at degrading chloromethane with release of chloride ion. This bacterium uses the chloromethane as a source of carbon and energy for growth (Hartmans, et al., 1986). The extent, to which this degradation occurs in a real world, complete sewage system, or other media with potentially similar organisms, is not known. The SAR models available in the biodegradation probability program BIOWIN® (USEPA 2000) predict that chloromethane will biodegrade fast and have an ultimate biodegradation timeframe of weeks. Nonetheless, results from two studies using activated sludge (CSCL 1992) suggest that aerobic biodegradation does not occur, with <1% of the chloromethane being biodegraded after 28 days.

In conclusion, the substance is not considered readily biodegradable, but may be degraded by adapted bacteria and under anaerobic conditions.

### 2.2.7 Bioaccumulation

The log Kow for chloromethane is 0.91, indicating that chloromethane has a low potential for bioconcentration and will not accumulate to significant levels in aquatic organisms. The calculated bioconcentration factor for chloromethane, based on a log Kow of 0.91 ranges from 2.98 (NTIS 1990) to 3.16 (USEPA 2000).

### 2.2.8 Sewage Treatment

Most chloromethane that finds its way into a bio-oxidation wastewater treatment system is likely to volatilize directly to the air. Based on the fugacity model STPWIN® (USEPA 2000), 77% of the chloromethane that enters the model treatment facility is volatilized directly to the air and 22% released with the final effluent.

## 2.3 Human Exposure

### 2.3.1 Occupational Exposure

Monitoring information indicates that individuals engaged in chloromethane production or use are exposed to concentrations greater than the background concentrations that the general public are exposed to. The National Occupational Exposure Survey (NOES) reports 8853 employees are exposed to chloromethane. The typical occupational exposures seen in the plants of Dow Corning are less than 0.5 ppm as an 8-hour TWA; most exposures were at non-detectable levels (Heffel, 2000). Currently, personal monitoring indicates employee exposures at less than 1 ppm for an 8-hour TWA at a GE Silicones manufacturing plant (Browning, 2000). The potential for significant exposure in industrial operations is most likely related to leaks, accidental releases and maintenance efforts. Accidents or malfunctions in transportation and product transfer systems also offer a potential for significant exposure. All of these routes of potentially significant exposure would result in relatively short-term exposures, and prudent use of personal protection equipment should preclude potentially serious overexposures.

### 2.3.1.1 Occupational Exposure Limits

Several industrialized countries have adopted occupational exposure limit values (OELs); a summary is given in Table 2.

Table 2. Occupational Exposure Limit Values

| Country | TWA | | STEL | | Notation | Reference |
|---|---|---|---|---|---|---|
| | (ppm) | ($mg/m^3$) | (ppm) | ($mg/m^3$) | | |
| Austria | 50 | 105 | 100 | 210 | | Grenzwerteverordnu ng, 2001 |
| Belgium | 50 | 104 | 100 | 210 | Skin | Belgisch Staatsblad, 1999 |
| Denmark | 25 | 52 | - | - | - | Arbejdstilsynet, 2000 |
| France | 50 | 105 | 100 | 210 | - | INRS, 1999 |
| Germany | 50 | 100 | - | - | | TRGS 900 |
| Ireland | 50 | 105 | 100 | 210 | | IOELR 1994 |
| Italy | 100 | 303 | - | - | - | ACGIH |
| Japan | 50 | 100 | - | - | - | JSOH, 2000-2001 |
| Switzerland | 50 | 105 | 100 | 210 | - | Giftliste 1 |
| UK | 50 | 105 | 100 | 210 | - | EH40/2001 |
| USA | 50 | 105 | 100 | 210 | - | OSHA 29 CFR 1910.1000 |
| | 50 | - | 100 | - | - | ACGIH, 2002 |

TWA Time-weighted average concentration (8-h working period)

STEL Short-term exposure limit (15 min, unless specified otherwise)

### 2.3.1.2 Other Regulatory Standards

An IDLH (Immediately Dangerous to Life or Health) of 2000 ppm (4,131 $mg/m^3$) was established in the USA by NIOSH, 1997.

In addition, the American Conference of Govermental Industrial Hygienist (ACGIH) has classified the substance as an "A4" which is Not Classifiable as a Human Carcinogen. (ACGIH 2002)

The US EPA has performed an Integrated Risk Information System (IRIS) assessment on chloromethane. An inhalation Reference Concentration (RfC) was calculated to be 9E-2 $mg/m^3$. This is based upon the critical effect of cerebellar lesions from the Landry et al., 1983 and 1985 studies indicating a NOAEL: 50 ppm (103.2 $mg/m^3$) with the Human Equivalent Concentration (HEC) determined to be 94.6 $mg/m^3$. An uncertainty factor of 1000 and a modifying factor 1 was applied. Additional information may be obtained from http://www.epa.gov/iris/index.html.

### 2.3.2 Consumer Exposure

Chloromethane is not used in any commercial product currently manufactured, therefore, consumer exposure to chloromethane is highly unlikely.

#### 2.3.2.1 Indirect Human Exposure

Chloromethane is ubiquitous in the environment with an estimated 99% of the environmental burden due to natural sources. Therefore, every organism on the earth's surface, including mankind, is exposed to atmospheric levels in the range of 500-700 ppt (Rasmussen et al., 1980; Gschwend, et al., 1985; Pierroti et al., 1980). Some humans are exposed to much higher levels if they live near oceans or use wood for fuel in their homes. Although chloromethane has been observed at low levels in groundwater, it is unlikely that the general population will experience significant exposure from this source. Chloromethane is very volatile and will evaporate from surface waters and ground water. There is a small probability that some chloromethane will leach from disposal sites into groundwater, but such disposal practices have become uncommon and continue to decline. Considering these facts, the probability is very low that the general populace will be exposed to significant levels of chloromethane from any water source. Among the general population, people that smoke or use wood fires for heating and cooking could experience higher than normal exposures to chloromethane. Obviously, exposures depend on the frequency and duration, as well as ventilation, experienced by this population.

# 3 HUMAN HEALTH HAZARDS

## 3.1 Effects on Human Health

### 3.1.1 Toxicokinetics, Metabolism and Distribution

Inhalation is the only likely route of exposure of humans to chloromethane. Most inhaled chloromethane is metabolized and excreted; the metabolites being indistinguishable from other metabolites. As part of detoxification processes, glutathione readily combines with chloromethane and may be excreted in the urine. Additionally, some chloromethane may be metabolized and excreted as one-carbon fragments. Chloromethane is not stored in the body and does not bio-accumulate.

*Absorption:* Absorption of methyl chloride in humans is likely to occur almost exclusively through inhalation, although dermal absorption could constitute a minor route of exposure in certain scenarios. Ingestion of the compound seems highly improbable under normal circumstances, although it is moderately soluble in drinking water. Data on the absorption of methyl chloride are available only for the inhalation route of exposure. Nolan et al. (1985) determined an in vivo blood:air partition coefficient for humans in the range of 2.12 to 2.49 at 20.7 $mg/m^3$ (10 ppm). Gargas et al. (1989) found a similar value (2.47) for the rat using an in vitro technique. Under current modeling practices, it is a reasonable assumption that the partition coefficient for the mouse would be similar to that for the rat.

*Distribution*: A number of studies have directly or indirectly investigated methyl chloride's distribution to tissue in Fischer 344 rats and/or dogs (Bus et al., 1980; Kornbrust et al., 1982; Landry et al., 1983a; Xu et al., 1990). As in humans, rapid and biphasic blood clearance was found in both Fischer 344 rats and beagle dogs after exposures to 103 or 2065 $mg/m^3$ (50 or 1,000 ppm) for 6 hr (dogs) or 3 hr (rats) (Landry et al., 1983a). Rapid and slower phase half-times were 4 and 15 min, respectively, for rats and 8 and 40 min, respectively, for dogs.

*Metabolism*: As proposed by Kornbrust and Bus (1983), the metabolism of chloromethane involves conjugation with glutathione to yield S-methylglutathione, S-methylcysteine, and other sulfur-containing compounds. The compounds can be excreted in the urine, and S-methylglutathione may be further metabolized to methanethiol. Cytochrome P-450 dependent metabolism of methanethiol may yield formaldehyde and formic acid, whose carbon atoms enter the one-carbon pool for incorporation into macromolecules or formation of $CO_2$. Formaldehyde may also be a direct product of chloromethane via oxidative dechlorination.

The biochemical effects of chloromethane were investigated (Jager et al., 1988) in tissues of F-344 rats and $B_6C_3F_1$ mice (both sexes). Activities of glutathione-S-transferase (GST) were 2-3 times higher in livers of male $B_6C_3F_1$ mice, compared with those of female mice, and with rats of both sexes. In kidneys GST activities of (male) mice were about 7 times lower than those found in livers. The activity of formeldahyde dehydrogenase (FDH) was higher in livers of mice (both sexes) than in those of rats. No obvious sex difference was found in livers of rats and mice with respect to FDH. In kidneys, however, (minor) differences in FDH activities occurred between male and female $B_6C_3F_1$ mice (4.7 vs. 3.1 nmol/min per mg). Sex differences of FDH activity in kidneys were not observed in F-344 rats. The microsomal transformation (by cytochrome P-450) of chloromethane and S-methyl-L-cysteine to formaldehyde in tissues of $B_6C_3F_1$ mice occurred preferentially in the liver. More formaldehyde was produced in liver microsomes of male, compared to those of female mice. Kidney microsomes metabolized chloromethane to formaldehyde much less than liver microsomes.

After single exposure of mice of both sexes to 2065 mg/m$^3$ (1000 ppm) chloromethane no elevation in formaldehyde concentrations was observed in livers and kidneys ex vivo. The determination of DNA lesions, using the alkaline elution technique, revealed no DNA-protein crosslinks in kidneys of male $B_6C_3F_1$ mice after exposure to chloromethane (2065 mg/m$^3$ (1000 ppm), 6 h day-1, 4 days) and gave only minor evidence of single-strand breaks. Lipid peroxidation (production of thiobarbituric acid (TBA) reactive material), induced by single exposure to chloromethane (2065 mg/m$^3$ (1000 ppm), 6 h), was very pronounced in livers of male and female mice. Smaller increases in peroxidation were observed in the kidneys of exposed mice.

In humans (Warholm et al., 1994), interindividual variation in the *in vitro* conjugation of chloromethane with glutathione by erythrocyteglutathione transferase was investigated in healthy males and females from the southern and central parts of Sweden. It was found that 11.1 % of the individuals lacked this activity, whereas 46.2% had intermediate activity and 42.8% had high activity. This distribution of three phenotypes is compatible with the presence of one functional allele with a gene frequency of 0.659 and one defect allele with a gene frequency of 0.341. The proportion of non-conjugators in this Swedish material was considerably smaller than that previously found in Germany (Peter et al., 1989). The polymorphic distribution of another glutathione transferase, GST mu, was determined in the same individuals with a PCR method. No connection between the genotype for GST mu (GSTM1) and the glutathione conjugation with chloromethane in erythrocytes was found.

*Excretion*: Very little methyl chloride is excreted unchanged, and the bulk of that which is not used in various anabolic pathways or expired as CO2 appears to be excreted in the urine. The various reported or hypothesized urinary metabolites (Kornbrust and Bus, 1983) comprise several sulfur-containing compounds, all thought to be derived from the initial GSH conjugate (Smethylglutathione).

### 3.1.2 Acute Toxicity

Inhalation is the only significant route of exposure. Chloromethane is slightly toxic by inhalation in rats and mice. Some studies (White et al., 1982, von Oettingen et al., 1949) illustrate species, strain and sex differences in sensitivity, such that male mice appear to be most susceptible (6-hour $LC_{50}$ = 4500-4600 mg/m$^3$), followed by rats (4-hour $LC_{50}$ = 5300-5400 mg/m$^3$), and then female mice (6-hour $LC_{50}$ = 17,000-17,500 mg/m$^3$).

### 3.1.3 Irritation

Standard irritation testing is not applicable to chloromethane as it exists as a gas.

### 3.1.4 Sensitisation

Standard sensitization testing is not applicable to chloromethane as it exists as a gas.

### 3.1.5 Repeated Dose Toxicity

The systemic toxicity of repeated exposure to chloromethane has been extensively studied in laboratory animals (mice, rats, dogs) by the inhalation route.

Female mice (12/group) were exposed continuously to concentrations of 0,15, 50, 100, 150, 200 or 400 ppm (0, 30, 100, 200, 300, 400 or 800 mg/m$^3$). At 200 mg/m$^3$ (100 ppm) and higher (22 hours/day for 11 days) degenerative changes (slight in all 12 at 200 mg/m$^3$ (100 ppm) and moderate to severe in 100% of animals at higher levels) in granule cells of the cerebellum; higher exposure levels (300 mg/m$^3$ (150 ppm) and above) also led to a moribund condition and death.

There were no cerebellar lesions or mortality at 30 mg/m$^3$ (15 ppm) and 100 mg/m$^3$ (50 ppm). No histopathological evidence of damage in the spinal cord area or to peripheral nerves was reported at any exposure level. Decrements in neurofunctional testing (ability to stay on an accelerating rod after 4, 8, and 11 days of exposure) were observed at 300 mg/m$^3$ (150 ppm). Decreased glycogen content in 200 mg/m$^3$ to 400 mg/m3 mice was the principal significant change observed in the liver, although focal periportal hepatocellular degeneration and/or necrosis was noted in the 800 mg/m$^3$ (400 ppm) group. There was no histological evidence of kidney lesions. Duration-dependency of cerebellar lesions was observed upon serial necropsy of 300 mg/m$^3$ (150 ppm) animals (5/time period except on day 11 when 12/time period were sacrificed), with moderate degeneration and neurofunctional deficits on day 4 (not days 1 and 2) and a moribund condition by day 10.5. Based upon cerebellar damage, this study identifies a NOAEL and LOAEL of 100 mg/m$^3$ (50 ppm) and 200 mg/m$^3$ (100 ppm), respectively, for continuous exposure (22 hours/day). (Landry, TD; Quast, JF; Gushow, TS; et al. (1983) and (1985)

In the same study, mice were also exposed intermittently (5.5 hours/day) for 11 days to 0, 300 mg/m$^3$ (150 ppm), 800 mg/m$^3$ (400 ppm), 1600 mg/m$^3$ (800 ppm), 3,200 mg/m$^3$ (1,600 ppm), or 4,800 mg/m$^3$ (2,400 ppm). A concentration-related increase in the cerebellar incidence of granule-cell pyknosis and karyorrhexis (slight) was observed in the 800 mg/m$^3$ (400 ppm) and higher groups. Decreased hepatocyte size, without degeneration or necrosis, was variably seen in mice from the 800 mg/m$^3$ (400 ppm) through 4800 mg/m$^3$ (2,400 ppm) groups. Decreases in mean absolute and relative thymus weights were statistically significant and considered exposure-related (reflecting decreased body weights and stress) for the 4,800 mg/m$^3$ (2,400 ppm) and 3200 mg/m$^3$ (1,600 ppm) groups; the latter group evidenced a decrease in the size of the thymus. Evidence of kidney toxicity was found only in the 4,800 mg/m$^3$ (2,400 ppm) group and consisted of slight multifocal tubular degeneration and regeneration, and eosinophilic-staining tubular casts. Inanition was apparent in the 4800 mg/m$^3$ (2,400 ppm) group, as was thin, watery blood from the heart, a finding supported by low blood packed cell volume. The spleens of this group were considerably enlarged, suggestive of extramedullary hematopoiesis, which was microscopically confirmed. The in-life observation of red urine in the 4800 mg/m$^3$ (2,400 ppm) group was determined to result from hemoglobinuria consistent with intravascular hemolysis. These animals deteriorated (e.g., hind limb extensor rigidity) and were sacrificed moribund on days 8–9. For intermittent exposure (5.5 hours/day), the NOAEL and LOAEL are 300 mg/m$^3$ (150 ppm) and 800 mg/m$^3$ (400 ppm), respectively (Landry, TD; Quast, JF; Gushow, TS; et al. (1983) and (1985)).

Male and female Fischer 344 Rats and B6C3F1 mice were exposed 6 hours a day, 5 days/week for thirteen weeks to exposure concentrations of 750 mg/m$^3$ (375 ppm), 1500 mg/m$^3$ (750 ppm) and 3000 mg/m$^3$ (1500 ppm). Significant increases in SGPT activity were observed in male mice in the 3000 mg/m$^3$ (1500 ppm) dose group. These increases may be explained by the presence of histologic hepatic changes. One male mouse and one female rat at the 3000 mg/m$^3$ (1500 ppm) dose level each had evidence of hepatic infarction. All other changes in hematologic or hemochemical parameters were within the expected normal range and/or were changes for which a dose-response relationship could not be clearly established. Increased relative organ weights (liver) were observed in the 3000 mg/m$^3$ (1500 ppm) dose group. Both male and female rats of the 3000 mg/m$^3$ group (1500 ppm) had significantly lower body weights when compared to controls from week 3 through week 13 and males and females of the 1500 mg/m$^3$ (750 ppm) group from week 6 through week 12. The NOEL and LOEL for this thirteen week study were 1500 mg/m$^3$ (750 ppm) and 3000 mg/m$^3$ (1500 ppm), respectively (CIIT (1979)).

A 24 month inhalation was conducted in Fischer 344 rats. Male and females rats were exposed 6 hours/day, 5 days/week to exposure concentrations of 100 mg/m$^3$ (50 ppm), 450 mg/m$^3$ (225 ppm) or 2000 mg/m$^3$ (1000 ppm). Interim sacrifices were conducted at 6, 12 and 18 months. Rat survival was unaffected by exposure to any concentration. Ophthalmologic examinations revealed changes which were apparently due to a virus and which were also found in control animals, although at a lower incidence. Lenticular changes, which appeared in rats only at 18 months, may have been related to exposure. No neurofunctional impairments were observed that are attributable to chloromethane exposure. Clinical observations, clinical chemistry, hematology, and urinalysis were unaffected in rats exposed to all concentrations. Organ weights showed significant changes only in rats exposed to 2000 mg/m3. Increased relative heart weights were found in male rats exposed to 2000 $mg/m^3$ at 12, 18 and 24 months and in female rats at 12 and 18 months. Relative kidney weights were increased in male rats exposed to 2000 $mg/m^3$ at all sacrifice periods but female rats were unaffected. Male rats exposed to 2000 $mg/m^3$ had increased relative liver weights and female rats had decreased absolute weights. Testicular weights of male rats exposed to 2000 $mg/m^3$ were decreased when compared to the controls on both an absolute and relative basis. Relative lung weight was increased at all concentrations but only at the 6-month sacrifices. The testes were the only organ of the rats considered to have significant chloromethane induced lesions. Bilateral and diffuse degeneration and atrophy of the seminiferous tubules of the testes were first noted in males exposed to 2000 $mg/m^3$ for 6 months. The effect increased in degree and in number of animals affected until the 18-month sacrifice. By 24 months, the effects of normal ageing prevented interpretation. Testicular size was reduced at 2000 $mg/m^3$ but no changes in the testes were detectable at either 100 or 500 $mg/m^3$. Therefore, on the basis of these results, it appears reasonable to conclude that for systemic effects (not tumor formation) 450 $mg/m^3$ (225 ppm) is the NOEL and the LOEL is 2000 $mg/m^3$ (1000 ppm) in this 2-year (lifetime) study in rats. (Chemical Industry Institute of Toxicology (CIIT), 1981 and 1983).

B6C3F1 mice were exposed under the same conditions and concentrations as noted above. $B_6C_3F_1$ mice in general were much more severely affected than rats. The effects were very severe in the 2000 $mg/m^3$ (1000 ppm) groups, but were questionable in the 100 $mg/m^3$ (50 ppm) and 500 $mg/m^3$ (225 ppm) groups since they were not always related to exposure concentration, nor were they seen at all sacrifice periods. No changes were observed in mice during ophthalmic examination. Neurofunctional impairment (loss of clutch response), which was observed in the 2000 $mg/m^3$ (1000 ppm) groups at 18 and 21 months in males and 22 months in females, was statistically different than the controls. These observations, which were supported by histopathological observations in the 2000 $mg/m^3$ (1000 ppm) exposure groups, were not observed in the 100 $mg/m^3$ (50 ppm) or 500 $mg/m^3$ (225 ppm) groups. Growth of only the male mice exposed to 2000 $mg/m^3$ (1000 ppm) was depressed during the first 18 months. Clinical signs suggestive of disturbances of the central nervous system, such as tremors and paralysis, were observed. In male mice exposed to 2000 $mg/m^3$ (1000 ppm), significantly elevated serum glutamic-pyruvic-transaminase (SGPT) values occurred at 6, 12, and 18 months and at 6 months in 100 $mg/m^3$ (50 ppm) and 500 $mg/m^3$ (225-ppm) groups. In the 2000 $mg/m^3$ (1000 ppm) groups the increased values were associated with hepatocellular degeneration and necrosis. In female mice increases in SGPT found at 6 and 12 months in the 100 $mg/m^3$ (50 ppm), 500 $mg/m^3$ (225 ppm) and 2000 $mg/m^3$ (1000 ppm) groups did not correlate with any histopathology of the liver. Relative heart weights in the 2000 $mg/m^3$ (1000 ppm) exposure group were increased in female mice (12 and 18 months) and male mice (12, 18 and 24 months). Female mice exposed to 2000 $mg/m^3$ (1000 ppm) generally displayed increased relative liver weights. Decreased absolute brain weights were observed at all time periods in male and female mice exposed to 2000 $mg/m^3$ (1000 ppm) and absolute and relative testicular weights were decreased at 18 and 24 months. In the two lower exposure groups, the only significant change in organ weights was an increase in the relative weight of the hearts of female mice exposed to 500 $mg/m^3$ (225 ppm) for 24 months. Hepatocellular changes were observed at 6 months in male mice exposed to 2000 $mg/m^3$ (1000 ppm). These changes included centrilobular to midzonal hepatocellular vacuolization, karymegaly, cytomegaly, multinucleated hepatocytes, and degeneration. Females developed these changes to a lesser degree at 18 to 22 months. Renal tubuloepithelial hyperplasia and karymegaly were seen in male mice exposed to 2000 $mg/m^3$ (1000 ppm) for 12 months and progressed in severity throughout the study. Renal cortical cysts were predominately seen in mice in the 2000 $mg/m^3$ (1000 ppm) group, whereas microcysts were noted most frequently in the 100 $mg/m^3$ (50 ppm) group at 24 months. Both occurrences were different from controls but were not statistically significant. Cerebellar lesions first appeared in male and female mice at the 18-month sacrifice from the 2000 mg/m$^3$ (1000 ppm) group. The lesion, which was characterized by degeneration and atrophy of the cerebellar granular layer, did not appear in mice from any other exposure group or in the controls. Three of 7 males and 6 of 8 females from the 2000 mg/m$^3$ (1000 ppm) group were diagnosed as having the lesion at the 18-month sacrifice and 16 of 18 females terminated at 22 months had the lesion. Mice (2000 mg/m$^3$) that died spontaneously between 0 and 17 months (9 of 20 females, 15 of 24 males) and between 18 and 22 months (35 of 37 females, 45 of 47 males) had a similar lesion. This lesion is considered to be related to chloromethane exposure. At 18 months, axonal swelling and degeneration of minor severity were observed in the spinal nerves and cauda equina associated with the lumbar spinal cord. These effects were observed in all groups, including at a low incidence in the control group, and no dose-response relationship was established. Injury to the testes was only apparent at 2000 mg/m$^3$ (1000 ppm) and was described as degeneration of the seminiferous tubules; the atrophy was not accompanied by decreased organ weight. This lesion was considered biologically significant and a result of chloromethane exposure. Splenic alterations, ranging from lymphoid depletion to splenic atrophy, were present in male and female mice from the 2000 mg/m$^3$ (1000 ppm) group as early as 6 months and progressed throughout the study. Depletion was noted in only one control mouse during the study at the 6-month sacrifice. Splenic atrophy was noted in mice dying spontaneously between 0 and 17 months, but was not apparently increased over controls until the 18- to 24-month period. Both lesions are considered to be related to chloromethane exposure. The NOEL and LOEL for systemic effects (not tumor formation) for this study were 450 mg/m$^3$ (225 ppm) and 2000 mg/m$^3$ (1000 ppm), respectively (CIIT, 1983; Johnson, 1988).

Rats (Fischer 344) and mice (C3H, C57/BL/6 and B6C3F1) were exposed 6 hours a day up to 12 days to exposure concentrations of 4000, 7000 or 10,000 mg/m$^3$ (rat) or 1000, 2000 or 4000 mg/m$^3$ (mice). All male $B_6C_3F_1$ mice exposed 4000 mg/m$^3$ (2000 ppm) were dead or moribund by day 2, and all male and female mice in the remaining 4000 mg/m$^3$ (2000 ppm) groups were moribund by day 5. Prior to death many of these mice exhibited ataxia, and hematuria with the latter occurring mainly in females. Treatment associated lesions in mice included hepatocellular degeneration and necrosis, degeneration and necrosis of proximal convoluted tubules and/or basophilic tubules in the renal cortex, and focal areas of necrosis of the internal granular layer of the cerebellum. Brain lesions were most severe in female C57/BL/6 mice, while hepatocellular degeneration was most severe in male C57/BL/6 mice and $B_6C_3F_1$ strains. Approximately 50% of the male and female rats exposed to 10000 mg/m$^3$ (5000 ppm) were killed *in extremis* on day 5. The principal clinical signs, which were confined to the 10000 mg/m$^3$ (5000 ppm) and 7000 mg/m$^3$ (3500 ppm) groups, included severe diarrhea, incoordination of the forelimbs, and in a small number of animals, hind limb paralysis and convulsions. In rats, lesions were observed in the liver, kidney and brain, which resembled those seen in mice, but were generally less severe. Lesions observed in tissues examined only in rats included vacuolar degeneration of the zona fasciculata of the adrenal glands. Mice testes were not examined histologically but all groups of rats had testicular degeneration, with a clear exposure-concentration related response for the severity of the lesion. In affected testicles, the lesion did not involve all seminiferous tubules equally. The principal changes were reduced numbers of late-stage spermatids, with none in severely affected tubules, separation of spermatocytes and early-stage spermatids, with sloughing of these cells into the lumen, formation of irregular, apparently membrane-bound vacuoles in the germinal epithelium, and variable formation of multinucleate giant cells. Giant cells appeared to be formed by fusion of early-stage spermatids. In severely affected tubules only a thin layer of cells remained adjacent to the basement membrane. Based on the result of this study, the LOEL in rats and mice were 4000 mg/m$^3$ (2000 ppm) and 1000 mg/m$^3$ (500 ppm), respectively (Morgan et al., 1982).

A multi-species study was conducted with CD-1 mice, Sprague-Dawley rats and Beagle dogs. Animals were exposed 6 hours/day, 5 days/week for 93-95 days to exposure concentrations of 100, 300 or 800 mg/m$^3$ (mice/rat) or 800 mg/m$^3$ (dog). Male rats exposed to 800 mg/m$^3$ (400 ppm) chloromethane had decreased urinary specific gravity measurement when compared to controls. A decrease in urinary specific gravity was also seen in female rats exposed to 300 mg/m$^3$ (150 ppm), but not 800 mg/m$^3$ (400 ppm), chloromethane. The effects on specific gravity of the urine were not associated with any renal pathology, either gross or microscopic. Male rats and female mice of the 800 mg/m$^3$ exposure group had a slight but statistically significant increase in mean liver to body weight ratio. A similar increase in relative liver weight was suggested by the data from male mice exposed to 800 mg/m3 chloromethane as well as mice of both sexes exposed to 300 mg/m$^3$. However these findings were not supported by subsequent pathological evaluation or other clinical laboratory indicators of liver function. No specific target organ toxicity or unequivocal toxic manifestations of chloromethane were observed in rats, mice or dogs exposed to concentrations as high as 800 mg/m$^3$. The NOEL for the study was considered 800 mg/m$^3$ (McKenna et al., 1981b).

### 3.1.6 Mutagenicity

Characterization of the genotoxicity hazard for chloromethane is provided by both *in vitro* and *in vivo* mutation/chromosomal studies. When studied in rats, there has been no evidence of alkylation of DNA, even in a study designed to maximize analytical sensitivity (Kornbrust et al., 1982a; Peter et al., 1985). In unscheduled DNA synthesis (UDS) assays in rats, there was no genotoxic effect in hepatocytes, spermatocytes or tracheal epithelial cells at 6000-7000 mg/m$^3$ (3000-3500 ppm) (Working et al., 1986). There was also no effect in spermatocytes or tracheal epithelial cells in rats exposed to 30,000 mg/m$^3$ (15,000 ppm), with only a marginal increase in hepatocytes (Working et al., 1986). In certain *in vitro* and *in vivo* studies, exposures to gaseous chloromethane at concentrations of 50,000 to 400,000 mg/m$^3$ (25,000 to 200,000 ppm) appears to be a direct-acting mutagen for bacteria, *Drosophila* and some mammalian cells (Simmons et al., 1977 and 1978). The significance of certain *in vitro* test systems to mammalian systems is questionable since these systems are: 1) not designed to metabolize xenobiotics; 2) are deficient in glutathione (the normal constituent of mammalian cells which has been demonstrated to react very rapidly with chloromethane and start the detoxification procedure), and 3) very high exposure concentrations. Dominant lethal studies in rats have produced positive results (Rushbrook, 1982, SRI International, 1984 (as cited in HSDB, 1998), but subsequent investigations have shown this effect to be a result of cytotoxicity in the epididymis and vas deferens rather than a direct genetic effect. Specifically, the apparent genetic effect was determined to be the probable consequence of severe inflammation of the epididymis. Chloromethane exposure was associated with decreased weight of the testes, sperm granulomas in the epididymis, a significant decrease in testicular spermatid head counts, delay in spermiation, epithelial vacuolisation, luminal exfoliation of spermatogenic cells and multinucleated giant cells. Sperm isolated from the vas deferens showed significantly decreased numbers and an increased incidence of abnormal sperm head morphology at 1-week post-exposure. At 3-weeks post-exposure, a significant decrease in sperm motility and increased incidence of headless tails were observed. Most of these observations were reversed by 16 weeks post-exposure (Working et al., 1985b). In the dominant lethal studies, when females were bred to males concurrently treated with an anti-inflammatory agent that inhibited the inflammation caused by chloromethane, there was no characteristic increase in post-implantation embryonic death leading to the conclusion that choromethane-induced dominant lethal mutations, rather than being caused by direct interaction of the chemical with the germ cell DNA, were a consequence of its induction of inflammation in the epididymis (Chellman et al., 1986a). The recognition that chloromethane is cytotoxic rather than genotoxic to sperm cells is further substantiated by the results of the 2-generation reproductive toxicity discussed previously. Exposures that did not cause inflammation of the epididymis did not effect reproduction in rats and the ability to sire normal litters (no differences in litter size, sex ratio, pup viability, or pup growth) was regained in those affected animals when the inflammation of the epidiymis was resolved. Based on these observations, the need for further genotoxicity testing of chloromethane (chromosome aberration in spermatogonial cells, heritable translocation assay, alkaline elution assay or sister chromatic exchange assay in spermatogonial cells) is not a priority.

The weight of evidence indicates that chloromethane, at high concentrations, is a direct-acting mutagen in bacteria and human cells in culture (*in vitro*) however, *in vivo* genotoxic effects were not seen due to cytotoxicity occuring at high doses. Existing information indicates that chloromethane exposure does not result in DNA alkylation (i.e. no evidence of methylated products).

### 3.1.7 Carcinogenicity

The few studies that have examined methyl chloride's potential carcinogenicity in humans [Rafnsson and Gudmundsson, 1997 (trawler cohort study); Olsen et al., 1989 (Louisiana chemical worker study); Dow Corning Corporation, 1992] have failed to demonstrate any association. In animals, the only evidence of carcinogenicity comes from a single 2-year bioassay (CIIT, 1981), in which a statistically significant increased incidence of renal benign and malignant tumors occurred only in male $B6C3F_1$ mice at the high concentration 2000 mg/m$^3$ (1,000 ppm). Two renal adenomas occurred in 225-ppm males and should be considered related to exposure. Renal cortical tubuloepithelial hyperplasia and karyomegaly were also confined to 2000 mg/m$^3$ (1,000 ppm) male mice. Neoplasia was not found at lower concentrations or at any other site in the male $B6C3F_1$ mouse, nor at any site or concentration in female mice or F-344 rats of either sex. In the United States, chloromethane is classified as "Group D, Not classifiable as to its human carcinogenicity."

### 3.1.8 Toxicity for Reproduction

*Reproductive Toxicity*

A specific, secondary effect on the sperm of rats has been demonstrated to occur following repeated exposures to high concentrations of chloromethane. In a two-generation reproduction study (Hamm et al., 1985) in rats, male and female rats were exposed intermittently (10-week exposure period followed by 10-week recovery period) to 0, 300, 950 or 3000 mg/m$^3$ (0, 150, 475, or 1500 ppm) Exposures to 3000 mg/m$^3$ (1500 ppm) resulted in sterility (decreased spermatogenesis) that is consistent with the testicular degeneration and granulomas seen in the epididymis of male rats after seven weeks. Exposures to 950 mg/m$^3$ (475 ppm) also caused a decrease in fertility, but no effects were seen in rats exposed daily to 300 mg/m$^3$ (150 ppm) A LOAEL ($F_0$) of 950 mg/m$^3$ (475 ppm) was determined based on the reduced male fertility. A NOAEL ($F_0$) of 300 mg/m$^3$ (150 ppm) was determned. The effect of exosure on the $F_1$ generation is uncertain since no histopathology was performed; however, the only observation was a reduced percentage of offspring.

*Developmental Toxicity*

Teratological studies have shown possible differences between species. In rats (Wolkowski-Tyl et al., 1983b), severe maternal toxicity was seen at 3000 mg/m$^3$ (1500 ppm), but no teratological response was observed following repeated 6-hour daily exposures to 200, 1000, or 3000 mg/m$^3$ (100, 500 or 1500 ppm). In mice (Wolkowski-Tyl et al., 1983a - $B_6C_3F_1$ fetuses of C57BL/6 female mice crossed with $C_3H$ males), effects (increased incidence of heart malformations) on the heart were reported following repeated exposure at 1000 mg/m$^3$ (500 ppm) in an initial study and at 1000 and 1500 mg/m$^3$ (500 and 750 ppm) in a second study. In both studies, the NOAELs for maternal toxicity were 1000 mg/m$^3$ (500 ppm). The NOAEL for teratogenicity was 200 mg/m$^3$ (100 ppm) in the first study, and 500 mg/m$^3$ (250 ppm) in the second study.

### 3.1.9 Other

#### 3.1.9.1 Neurotoxicity

In mice (but not rats), repeated 6-hour exposure to 1000 ppm for two years produced very severe CNS changes and brain pathology. After two years of repeated exposure to 225 or 50 ppm, no changes were seen in the behavior and appearance or in the brain of either sex of either species.

In a study designed to measure decrements in motor performance in a susceptible strain of mice, no changes were seen after 11 repeated 5-1/2 hour daily exposures to 150 ppm or 11 repeated 22-hour daily exposures to 50 ppm. No pathology was observed in the brain at these exposure levels, but in this sensitive strain of mice, higher exposure concentrations (1000 to 1500 ppm) resulted in brain lesions and decrements in performance in neurofunctional tests (Landry et al., 1985).

Male cats and dogs were exposed 23-1/2 hours, three days in a row and subsequently examined for 2 weeks (cats) or 4 weeks (dogs). The no-effect-levels were 500 ppm for cats and 200 ppm for dogs. Higher concentrations caused neurological effects, including ataxia, paralysis and tremors (McKenna et al., 1981a).

No overt signs of toxicity were noted in any rats exposed to 0, 200, or 500 ppm of methyl chloride (Burek et al., 1981). From 24 through 40 hr of exposure, animals exposed to 1,000 or 2,000 ppm appeared progressively less alert, and by 48 hr the 1,000 ppm rats appeared lethargic, while the 2,000-ppm rats were lethargic, moribund, or dead. After 72 hr of exposure, the 1,000-ppm rats were either sick or moribund, though still alive, while all those in the 2,000-ppm group were dead. The primary cause of death in rats exposed to 1,000 or 2,000 ppm for 48 or 72 hr was kidney toxicity and subsequent renal failure. Kidneys were frequently dark and displayed varying degrees of renal tubular necrosis, degeneration, cytoplasmic heterogeneity, regeneration, and epithelial cell lipid accumulation. Evidence of renal toxicity in other exposure groups was not reported.

#### 3.1.9.2 Other Information

The mechanism of action of chloromethane-induced toxicity is not clear, however, metabolism of chloromethane may be critical. As noted above, the metabolism of chloromethane involves conjugation with glutathione to yield sulfur-containing compounds. Where gluthathione levels are depleted in target tissues, the alternative oxidative pathway involving P4502E1, which leads directly to the production of formaldehyde, appears to become more important. Critical studies indicate that species- and target organ-specific biotransformation of chloromethane may account for the sex- and species-specific toxicity of this chemical. Additionally, secondary inflammation has been shown to be responsible for toxicity in tissues following chloromethane exposure.

### 3.1.10 Human Experience

In man, the most common consequences of single or repeated exposures have been functional changes in the central nervous system. These have often been described as drunkenness similar to that resulting from consumption of excess alcohol, but are longer in persistence. A staggering gait, weakness, drowsiness, double vision, headache, apathy, anorexia, nausea, vomiting, abdominal pain, diarrhea, personality changes, spasms, loss of memory, paralysis, confusion, and unconsciousness have all been reported from high exposures. In general, the liver, kidney, testes, epididymis and lungs can be affected by high exposure to chloromethane, but human experience have shown they most often show injury only in the presence of pronounced CNS changes. Limiting exposure to prevent injury to the CNS should also protect against injury to other organs (SIDS Dossier, 2002).

An epidemiological study on occupationally exposed men (Holmes et al., 1986) summarized the causes of death in 852 workmen including carcinogenic deaths. There was no increase in deaths due to cancer in this study population, but the study has only limited statistical power.

With regards to neurotoxicity, human data consistently indicate a NOEL of 100- 200 mg/m$^3$ (50-100 ppm) for all effects from inhaled chloromethane. In humans, published studies from occupational exposure indicate no adverse effect when repeated, prolonged daily exposures were controlled to 200 mg/m$^3$ or less (100 ppm or less), but when they averaged more then 400 mg/m$^3$ (200 ppm), CNS effects occurred after long-term repeated exposure. When studied in the laboratory, repeated 7-1/2 hour exposures to 200 mg/m$^3$ (100 ppm) on 5 consecutive days caused no discernable impairment of human performance in tests of skill, memory and coordination - nor did two 7-1/2 hour exposures to 300 mg/m$^3$ (150 ppm). A three-hour exposure of humans to 440 mg/m$^3$ (220 ppm) had no effect on performance, nor did it enhance the effect of diazepam (Valium).

### 3.2 Initial Assessment for Human Health

Chloromethane is a colorless and nearly odorless gas. It is stored and shipped under pressure. It has long been recognized as highly flammable and has low acute toxicity by the oral and inhalation routes; however, procedures have been developed to handle it safely in industrial uses.

Commercially produced chloromethane is almost entirely consumed as a chemical intermediate, with the silicone industry the largest single consumer. It is also used to produce several pesticides and other products of various end uses. Chloromethane is not used in any commercial product currently manufactured.

Chloromethane is a natural product with an estimated 99% (about 4.5 x $10^9$ tonnes) of the atmospheric burden produced in oceans or by fires involving wood or other biomass. In the U.S. about 6.3 x $10^5$ tonnes is industrially produced at about seven locations, and nearly all of this is consumed as a chemical intermediate on-site or by 30-40 industrial chemical processors. Thus man's contribution to the atmosphere is probably well less than 1% of the atmospheric burden, with natural processes producing the remainder.

Human exposure is most likely to occur by inhalation. All humans are exposed by inhalation to natural levels of chloromethane of about 700 ppt in ambient air. Higher exposures may occur in or near industrial plants producing or using this chemical. People that smoke or use wood as a heat source (or are near such sources) are undoubtedly exposed to much higher than normal background concentrations of chloromethane.

Inhalation of chloromethane of sufficiently high levels can cause injury and death. The first observable consequence of over-exposure is impairment of the CNS, which can involve unsteadiness, dizziness, etc. The effects, which are similar in appearance to drunkenness, appear to be reversible, although a few cases of more permanent damage have been reported due to gross overexposure. Most U.S. industries have for several years maintained their worker-exposure levels well below the ACGIH guideline of 50 ppm (105 mg/m$^3$) TWA, which was adopted by OSHA in 1989.

Chloromethane is not likely to cause cancer, birth defects or other reproduction problems at normally encountered exposure levels or at reasonably anticipated higher exposure levels. This conclusion is based on an integration of the voluminous toxicity data developed over the past decades and human experiences for well over 80 years of industrial use.

In summary, extensive data are available regarding all anticipated toxicological effects and these data indicate that chloromethane is not likely to have a discernable health effect on any population, including the general public, under anticipated levels of exposure. Any exceptions to this conclusion would be related to an accidental release. Even in the latter case, any effects short of death from such one-time gross overexposure likely would be transient in nature and a full recovery expected.

# 4 HAZARDS TO THE ENVIRONMENT

## 4.1 Aquatic Effects

Since chloromethane is expected to partition largely to the air, it is not expected to present a significant hazard to aquatic biota. Input values for predicted results may be found in the dossier.

*Acute Toxicity Test Results*

Acute Toxicity in Fish

Measured results from 96-hour toxicity studies indicate chloromethane is of low toxicity to *Lepomis macrochirus* ($LC_{50}$ = 550 mg/l; $TL_{50}$ = 900 mg/l) Verschueren, 1983, Hamlin et al. (1971); *Micropterus salmoides* ($TL_{50}$ = 1500 mg/l), and *Menidia beryllina* ($LC_{50}$ = 270 mg/l) Verschueren, 1983, Hamlin et al. (1971). Older studies should be evaluated with caution because optimum test conditions were not used and that reported results may underestimate toxicity of the test substance. Based on weight of evidence the toxicity of methyl chloride to fish is considered to be 270 mg/l which is the most conservative value. The predicted acute toxicitiy of chloromethane (ECOSAR; version 0.99g) is in good agreement with the measured acute toxicitiy for fish (predicted 96-h $LC_{50}$ = 396).

Acute Toxicity in Aquatic Invertebrates

Results from a definitive study indicate that the acute toxicity ($EC_{50}$) of chloromethane to *Daphnia magna* exposed in a closed system (no head-space) under static-renewal conditions was 200 mg/l, based on nominal concentrations (Springborn Smithers Laboratories, Study Number 13776.6101, 2002). The predicted 48-h $LC_{50}$ of chloromethane (394 mg/L ECOSAR; version 0.99g) is greater than the measured 48-h $LC_{50}$ for daphnia(200 mg/L) .

Acute Toxicity in Algae

Toxicity threshold concentrations ranging from 550 to 1450 mg/l have been reported for selected algae, *Microcystis aeruginosa* and *Scenedemus quadricauda,* (Verschueren, 1983). Due to the possibility that the algae may not have been in the exponential growth phase throughout the tests, the ECOSAR predicted 96-hour $EC_{50}$ value of 231 mg/L is preferred.

*Chronic Toxicity Test Results*

No information is available.

*Toxicity to Microorganisms*

Methyl Chloride was tested against 3 bacteria groups: aeorobic heterotrophs, Nitrosomonas, and methanogens. The EC50 (24h) and EC50 (48h) in Methanogene Bakterien was approximately 39 mg/l (Blum and Speece, 1991b) and 50 mg/l (Blum and Speece, 1991a) respectively.

## 4.2 Terrestrial Effects

No information is available.

## 4.3 Other Environmental Effects

No information is available.

## 4.4 Initial Assessment for the Environment

Fugacity modeling indicates that > 99% of the total, steady state mass will reside in the air compartment and about 0.4% will reside in each of the soil and water compartments. The local persistence is about 4 days with advection in air accounting for > 99% of the chloromethane removed from the system. Less than 1% is lost through degradation processes. Predicted concentrations in the environmental compartments, based on Level III fugacity modeling, are significantly less than reported concentrations in air, water, and soil or sediment. Since chloromethane is expected to partition largely to the air, it is not expected to present a significant hazard to aquatic or terrestrial biota. Chloromethane is not readily biodegradable but may be degraded by adapted bacteria and under anaerobic conditions. The calculated BCF ranges from 2.98 to 3.16.

The $LC_{50}$ from the 96-hr fish study using nominal concentrations is 270 mg/L. In daphnia, the 48-hr reported $EC_{50}$ based on nominal concentrations is 200 mg/L. The algal toxicity thresholds of 550 and 1450 mg/L were 7 day tests using nominal concentrations. Due to the possibility that the algae may not have been in the exponential growth phase throughout the tests, the ECOSAR predicted 96-hour $EC_{50}$ value of 231 mg/L is preferred. In addition, the predicted acute toxicity of chloromethane (ECOSAR; version 0.99g) is in good agreement with the experimental data as indicated above for green algae along with acute toxicity for fish (96-h $LC_{50}$ = 396 mg/L) and daphnia (48-h $LC_{50}$ = 394 mg/L.). In combination with the chemicals environmental fate characteristics, the chemical is considered to be a low concern for the environment.

# 5 RECOMMENDATIONS

The chemical possesses properties indicating a hazard for human health. Based on data presented by the Sponsor country, exposure to humans and the environment is anticipated to be low, and therefore this chemical is currently a low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

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# *SIDS DOSSIER*
# *CHLOROMETHANE*
# *CAS No. 74 - 87- 3*

Sponsor Country: United States

DATE: January 2002

CONTENTS

# 1. GENERAL INFORMATION

## 1.01 SUBSTANCE INFORMATION

**A. CAS Number** 74- 87- 3

**B. Name** *(IUPAC name)* Chloromethane

**C. Name** *(OECD name)* Chloromethane

**D. CAS Descriptor** Methane, chloro

**E. EINECS-Number** 200-817-4

**F. Molecular Formula** $CH_3Cl$

**G. Structural Formula** $H_3C$-Cl

**H. Substance Group**

**I. Substance Remark** None

**J. Molecular Weight** 50.49

## 1.02 OECD INFORMATION

**A. Sponsor Country:** United States

**B. Lead Organisation:**

Name of Lead Organisation: Methyl Chloride Industry Association
Contact person: Michael E. Thelen, Chair
Address:
Company: Dow Corning Corporation
Street: 2200 W. Salzburg Road, PO BOX 994
Mail #CO3101
Postal code: 48686-0994
Town: Midland, MI
Country: USA
Tel:(989) 496-4168; Fax: (989) 496-5595;
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**C. Name of responder**

Name: Michael E. Thelen; Manager, U.S. Regulatory Affairs
Address:
Company: Dow Corning Corporation
Street: 2200 W. Salzburg Road, PO BOX 994
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Postal code: 48686-0994
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**Sponsor Companies**

**Europe**

Ineos Chlor Ltd
LII Europe GmbH
Wacker Chemie

**Japan**

Asahi Glass Co.,Ltd.
Dow Corning Toray Silicone Co.,Ltd.
GE Toshiba Silicones Co.,Ltd.
Nihon Tokusyu Kagaku Kogyo K.K.
Shin-Etsu Chemical Co.,Ltd.
Tokuyama Corporation

**United States**

Dow Chemical Company
Dow Corning Corporation
GE Silicones
ExxonMobil Corporation
Vulcan Chemicals Corporation

## 1.1 GENERAL SUBSTANCE INFORMATION

**A. Type of Substance** organic

**B. Physical State** *(at 20°C and 1.013 hPa)* gaseous

**C. Purity** > 99.5% w/w (liquid phase)

## 1.2 SYNONYMS Methyl chloride

## 1.3 IMPURITIES

CAS No: CAS# 7732-18-5; CAS# 7647-01-0; CAS# 115-10-6; CAS# 67-56-1; CAS# 67-64-1; 75-00-3; 75-01-04
EINECS No:
Name: Water; Hydrogen chloride gas; Dimethyl ether; Methanol; Acetone, Ethyl chloride, Vinyl chloride
Value:
Remarks: USEPA Chemical Hazard Information Profile (1978) (As cited in HSDB, 1998); Ahlstrom & Steele, 1979

## 1.4 ADDITIVES

## 1.5 QUANTITY

Remarks: United States production (5 producers: Dow Corning Corporation (Carrollton, KY; Midland, MI), Dow Chemical Company (Freeport, TX; Plaquemine, LA), GE Silicones, General Electric Company (Waterford, NY) and Vulcan Materials Company (Wichita, KS; Geisman, LA)) of 6.9 x $10^5$ ton (based on 35-45% of the total global production of 1.7 x $10^6$ ton in 1997)
Reference:

Remarks: Japan production (6 producers: Toray Dow-Corning Silicone Co., Ltd., Toshiba Silicone Co., Ltd., Shin-Etsu Chemical Co., Ltd., Asahi Glass Co., Ltd., Tokuyama Corp. and Nihon Tokushu Chemical Industries Co., Ltd.) of 200,000 tons;

Reference:

Remarks: European production (9 producers: Dow Chemical Company (Germany), Dow Corning Corporation (United Kingdom), Elf Aquitane (France), Solvay (France and Italy), Rhodia (France), ICI (United Kingdom), Novartis (Switzerland), Ausimont (Italy) and Wacker Chemie (Germany));
Information on quantity not available.

Reference:

## 1.6 LABELLING AND CLASSIFICATION

## 1.7 USE PATTERN

### A. General Use Pattern

| Type of Use: | | Category: | |
|---|---|---|---|
| (a) | main industrial use | Silicones | 74% |
| | | Agricultural chemicals | 7% |
| | | Methyl cellulose | 6% |
| | | Quaternary amines | 5% |
| | | Butyl rubber | 2% |
| | | Miscellaneous | 2% |
| | | Exports | 4% |

Reference: Kavaler, A.R. 1987 (As cited in HSDB, 1998).

### B. Uses in Consumer Products None

## 1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

Exposure limit value
Type: Threshold Limit Value (TLV) (US): TWA
Value: 103 mg/m$^3$ (50 ppm)

Short term exposure limit value
Value: 207 mg/m$^3$ (100 ppm) (skin)
Length of exposure period:15 minutes
Reference: Threshold Limit Values (TLVs) for Chemical Substances and Physical Agents and Biological Exposure Indices (BEIs). American Conference of Governmental Industrial Hygienists (ACGIH), 1995-1996.

Exposure limit value
Type: OSHA PEL (US) - 8-hour TWA
Value: 105 mg/m$^3$ (50 ppm)

Short term exposure limit value
Value: 210 mg/m$^3$ (100 ppm)
Length of exposure period: 15 minutes
Remarks: Ceiling Limit

Value: <300 ppm

Length of exposure period: Maximum of 5 minutes
Frequency: Every 3 hours
Remarks: Peak Limit; Cumulative exposure for the entire 8-hour work shift must not exceed a weighted average of 100 ppm
Reference: 29 CFR 1910.1000

## 1.9 SOURCES OF EXPOSURE

Source: Media of Release: Production and processing
Estimated Global Production (1997) 1.7 x $10^6$ Ton

Remarks: U.S. manufacturers of chloromethane (MeCl) include Dow Corning Corporation (Carrollton, KY; Midland, MI), Dow Chemical Company (Freeport, TX; Plaquemine, LA), GE Silicones, General Electric Company (Waterford, NY) and Vulcan Materials Company (Wichita, KS; Geisman, LA). Japanese manufacturers include Toray Dow-Corning Silicone Co., Ltd., Toshiba Silicone Co., Ltd., Shin-Etsu Chemical Co., Ltd., Asahi Glass Co., Ltd., Tokuyama Corp. and Nihon Tokushu Chemical Industries Co., Ltd. European producers include Dow Chemical Company (Germany), Dow Corning Corporation (United Kingdom), Elf Aquitane (France), Solvay (France and Italy), Rhodia (France), ICI (United Kingdom), Novartis (Switzerland), Ausimont (Italy) and Wacker Chemie (Germany).

It is difficult to estimate the total production levels for chloromethane on a global basis because many of the producers consume their output internally as a feedstock principally for the production of silicones, although other chemicals including higher chlorinated methanes are also produced.

The estimated 1997 global production of 1.7 x $10^6$ ton reported above is based on the assumption that the US produces 35-45% of the global total and the 1997 US production volume of 6.9 x $10^5$ ton.

References: Unpublished communication with: U.S. Methyl Chloride Industry Association, Japan Association for Hygiene of Chlorinated Solvents and European Chlorinated Solvent Association; Confidential survey of US 1997 production conducted by the Methyl Chloride Industry Association in 1999; Edwards et al., 1982b; SRI, 1996.

Remarks: Because of the chemical/physical properties of, chloromethane must necessarily be produced in a closed system.

Remarks: "Chloromethane is produced industrially by either reaction of methanol and hydrogen chloride (HCl) or by chlorination of methane (Ahlstrom and Steele, 1979; Key et al., 1980; Edwards et al., 1982a). While the reaction of methanol with HCl is the most common method, the process chosen depends, in part, on the HCl balance at the site (the methane route produces HCl; the methanol route uses it) (Ahlstrom and Steele, 1979; Edwards et al., 1982a)."

"The methanol-HCl process involves combining vapor-phase methanol and HCl at 180-200°C, followed by passage over a catalyst where the reaction occurs (Ahlstrom and Steele, 1979). Catalysts include alumina gel, gamma alumina, and cuprous or zinc chloride on pumice or activated carbon. The exit gases from the reactor are quenched with water to remove unreacted HCl and methanol. The quench water is stripped of the dissolved methanol and chloromethane and the remaining dilute HCl solution is used in-house or treated and discharged (Ahlstrom and Steele, 1979).

The chloromethane is then dried by treatment with concentrated sulfuric acid, then compressed, cooled, and stored."

"In the methane chlorination process, a molar excess of methane is mixed with chlorine, and the mixture is then fed to a reactor which is operated at 400$^{o}$C and 200 kPa pressure (Ahlstrom and Steele, 1979; Key et al., 1980). The exit gases can then be scrubbed with chilled chloromethanes (mono- to tetrachloromethane) to remove most of the reaction chloromethanes from unreacted methane and HCl. The by-product HCl is removed by water wash, stripped of any chloromethanes, and either used in-house or sold; the unreacted methane is recycled through the process. The condensed chloromethanes are then scrubbed with dilute NaOH to remove any HCl, dried, compressed, cooled, and then fractionally distilled to separate the four chloromethanes. While there are some variations to this process, including the use of catalysts, the above description is a general overview of the basic steps in the process."

Reference: As cited in ATSDR, 1990.

Remarks: Since chloromethane is a gas, most industrial releases would be expected to be to the air environment. Any releases to surface water or to the surface of the soil would be expected to immediately evaporate to the air unless deliberately placed in the earth at some significant depth below the surface.

In the U.S., releases of chloromethane to the environment are reported to the US EPA annually by producers and processors as required by 40 CFR part 370 -- Emergency and Hazardous Chemical Inventory and Community Right-To-Know Reporting Requirements (TRI). The 1998 TRI results available on the Internet indicate that a total of 109 locations (100 from original industries and 9 from new industries) reported:

| | |
|---|---|
| Total air release | 2,641,306 lbs. |
| Total water release | 1,742 lbs. |
| Total land release | 57 lbs. |
| Total underground injection | 323,201 lbs. |
| Transfers off-site to disposal | 959 lbs. |
| TOTAL ENVIRONMENTAL RELEASE | 2,967,265 lbs. (1.4x10$^{3}$ TON) |

Assuming that the US processes 35-45% of the global production, that releases in Japan and the EU are similar to the US and assuming a 25% data uncertainty factor, the estimated total Global Environmental Anthropogenic Release during manufacture and processing is 6-8 x 10$^{6}$ lbs. (3-4 x 10$^{3}$ TON).

Reference: USEPA Toxic Release Inventory (TRI), 1998.

Source: Produced naturally (see various media below)

Remarks: In addition to direct manufacture, chloromethane is also produced naturally and from a number of human activities. The amount of chloromethane produced naturally far exceeds the amount manufactured at least by a factor of 1,000.

"The total production of chloromethane from sources other than manufacture account for approximately (3.2-8.2) x10$^{12}$ g/year (7-18 billion pounds). Greater than 99% of ambient air concentrations of chloromethane appear to come from releases from natural sources rather than releases from manufacturing or use."

Reference: USEPA Toxic Release Inventory (TRI), 1998.

Source: Media of release: Air and water - Ocean production
Quantities per media: (3-5)x10$^{12}$ g/year (6.6-11 billion pounds/year)

Remarks: "Most chloromethane produced on earth comes from the ocean."

Reference: Fabian, 1986; Rasmussen et al., 1982a; Singh et al., 1979; Yung et al., 1975 (As cited in ATSDR, 1990).

Source: Media of release: Air - Biomass burning
Quantities per media: $(0.2\text{-}0.4)\times10^{12}$ g/year (0.44-0.88 billion pounds/year)
Remark: Includes both natural and resulting from human activity, e.g., forest fires, wood burning, cigarette smoking, volcanoes, burning plastic, coal burning
Reference: Chopra and Sherman, 1972; Crutzen et al., 1979; Edgerton et al., 1984, 1987; Fabian 1986; Kadaba et al., 1978; Khalil et al., 1983; Khalil et al., 1985; Kleindienst et al., 1986; Palmer 1976; Rasmussen et al., 1980; Tassios and Packham, 1985. (As cited in ATSDR, 1990).
Remark: Studies in England during the 1976 drought, when brush fires were common, showed ground levels as high as 30,000 ppt recorded over a period of 3 days.
Reference: Lovelock, 1978.

Source: Media of release: Air and water - Microbial activity
Quantities per media: Insufficient information to quantify releases.
Reference: Fabian 1986; Harper and Hamilton 1988; Harper 1985; Harper et al., 1988 (As cited in ATSDR, 1990).

Source: Media of release: Air - Trees
Quantities per media:
Remarks: "Some controversy exists concerning wood burning as a source of chloromethane (DeGroot 1989)."
Reference: Isidorov et al., 1985. (As cited in ATSDR, 1990).

Source: Other Exposures
Remarks: Cigarette smoke has been shown to contain chloromethane. In the earlier work there was some indication that chlorinated pesticides may have been involved to furnish the chlorine for chloromethane production (Hansch, 1975; Chopra, et al., 1970). However, subsequent work has shown that the amount of chloromethane found in cigarette smoke is independent of the pesticide content (Chopra and Sherman, 1972). Since chlorine is present in most biomass, any significant contribution from the pesticide seems unlikely. It is most likely that combustion of all organic matter with chloride present will lead to chloromethane, especially under lower temperature, smouldering conditions.
Reference: Noted above.

## 1.10 ADDITIONAL REMARKS

### A. Options for disposal

Remarks: "A potential candidate for rotary kiln incineration at a temperature range of 820 to 1,600°C and residence times of seconds for liquids and gases, and hours for solids. A potential candidate for fluidized bed incineration at a temperature range of 450 to 980°C and residence times of seconds for liquids and gases, and longer for solids."
Reference: USEPA; Engineering Handbook for Hazardous Waste Incineration (1981) (As cited in HSDB, 1998).

### B. Other remarks

Remarks: Since chloromethane is a chemical intermediate with most unreacted material recycled, there probably has been very little disposal of methyl chloride, per se, in recent years. A small amount of unrecoverable methyl chloride may be present in many of the waste streams from various processes. Much of this material in nonaqueous media is incinerated to recover fuel value and byproduct HCl. Smaller users may have had waste streams with unrecoverable levels of chloromethane that have been disposed of by deep well injection, hazardous landfills or incineration.
Aqueous wastes with low levels of chloromethane are generally treated in on-site water treatment plants or sent to publicly owned treatment works. Both of these

methods operate under permits for discharge to ambient surface water. Very little direct discharge (without treatment) of wastewater-containing chloromethane is permitted into surface waters.
Plastic foams that were produced with chloromethane are unlikely to contain significant residual chloromethane at disposal time since this chemical diffuses quite rapidly from the foam products and is emitted to the ambient atmosphere at low levels over a relatively short time after production.

"No information was located in the literature concerning the disposal of chloromethane. Since most chloromethane is used consumptively, little remains to be disposed of. Nonetheless, some chloromethane is present in waste, since it has been detected in hazardous waste landfills. These concentrations may result from the landfilling of still bottoms or other residues from the manufacture and use of chloromethane. Its presence in municipal waste landfills may suggest that consumer products containing chloromethane were landfilled (e.g., propellants for aerosol cans). In a study of the products of initial combustion using mixtures of chloromethane under simulated incinerator conditions, chloromethane was destroyed under oxygen-rich conditions (Taylor and Dellinger 1988). Under oxygen starved conditions, however, chloromethane can combine with other components of the mixture to form, among other compounds, chlorinated ethanes, hexachlorobenzene and octachlorostyrene."

Reference: ATSDR, 1990.

## 2. PHYSICAL-CHEMICAL DATA

### 2.1 MELTING POINT

Value: -97.7 °C
Method: other
GLP: unknown
Remark: handbook data
Reference: Torkelson and Rowe, 1981

Value: -97 °C
Method: other
GLP: unknown
Reference: The Aldrich Catalogue, 1998-1999

Value: -124 °C
Method: Estimated using MPBPWIN (ver. 1.40)
GLP: no
Remarks: The estimation is based on molecular structure (SMILES: ClC). The model was used as received from EPA.
Reference: U. S. EPA 2000

### 2.2 BOILING POINT

Value: -24.22°C
Pressure: at 1013 hPa
Method: other
GLP: unknown
Remark: handbook data
Reference: Torkelson and Rowe, 1981

Value: -23.73°C
Method: other
GLP: unknown
Remark: handbook data
Reference: Encyclopedia of Chemical Substances, 1979

Value: -24°C
Method: other
GLP: unknown
Remark: handbook data
Reference: ICB internal databases

Value: 10.9 °C
Method: Estimated using MPBPWIN (ver. 1.40)
GLP: no
Remarks: The estimation is based on molecular structure (SMILES: ClC). The model was used as received from EPA.
Reference: U. S. EPA 2000

### 2.3 DENSITY (relative density)

Type: Density (liquid)
Value: 0.920 $kg/m^3$
Temperature: 20°C
Method: other
GLP: unknown

Remark: handbook data
Reference: Ahlstrom and Steele, 1979.

Type: Density (liquid)
Value: 0.915 $gm/m^3$
Temperature: not reported
Method: other
GLP: unknown
Reference: The Aldrich Catalogue, 1998-1999

Type: Density (gas)
Value: 1.74 (air = 1)
Temperature: 0°C (1 atm)
Method: other

GLP: unknown
Remark: handbook data
Reference: Ahlstrom and Steele, 1979.

## 2.4 VAPOUR PRESSURE

Value: 4800 hPa
Temperature: 20 °C
Method: other
GLP: unknown
Remark: handbook data
Reference: Torkelson and Rowe, 1981

Value: $1.01 \times 10^5$ Pa
Temperature: -24.2 °C
Method: other
GLP: unknown
Reference: BUA, 1986

Value: $2.03 \times 10^5$ Pa
Temperature: -6.2 °C
Method: other
GLP: unknown
Reference: BUA, 1986

Value: $3.04 \times 10^5$ Pa
Temperature: 5.5 °C
Method: other
GLP: unknown
Reference: BUA, 1986

Value: $4.05 \times 10^5$ Pa
Temperature: 14.5 °C
Method: other
GLP: unknown
Reference: BUA, 1986

Value: $5.01 \times 10^5$ Pa
Temperature: 20 °C
Method: other
GLP: unknown

| | |
|---|---|
| Reference: | BUA, 1986 |
| | |
| Value: | $5.75 \times 10^5$ Pa |
| Temperature: | 25 °C |
| Method: | other |
| GLP: | unknown |
| Reference: | BUA, 1986 |
| | |
| Value: | 76.7 kPa |
| Temperature: | -30°C |
| Method: | other |
| GLP: | unknown |
| Remark: | handbook data |
| Reference: | Encyclopedia of Chemical Substances, 1979 |
| | |
| Value: | 118.8 kPa |
| Temperature: | -20°C |
| Method: | other |
| GLP: | unknown |
| Remark: | handbook data |
| Reference: | Encyclopedia of Chemical Substances, 1979 |
| | |
| Value: | 177.2 kPa |
| Temperature: | -10°C |
| Method: | other |
| GLP: | unknown |
| Remark: | handbook data |
| Reference: | Encyclopedia of Chemical Substances, 1979 |
| | |
| Value: | 255.7 kPa |
| Temperature: | 0°C |
| Method: | other |
| GLP: | unknown |
| Remark: | handbook data |
| Reference: | Encyclopedia of Chemical Substances, 1979 |
| | |
| Value: | 358.2 kPa |
| Temperature: | 10°C |
| Method: | other |
| GLP: | unknown |
| Remark: | handbook data |
| Reference: | Encyclopedia of Chemical Substances, 1979 |
| | |
| Value: | 489.3 kPa |
| Temperature: | 20°C |
| Method: | other |
| GLP: | unknown |
| Remark: | handbook data |
| Reference: | Encyclopedia of Chemical Substances, 1979 |
| | |
| Value: | 652.5 kPa |
| Temperature: | 30°C |
| Method: | other |
| GLP: | unknown |
| Remark: | handbook data |
| Reference: | Encyclopedia of Chemical Substances, 1979 |

| | |
|---|---|
| Value: | 5.45 x $10^5$ Pa |
| Temperature: | 25°C |
| Method: | Estimated using MPBPWIN (ver. 1.40) |
| GLP: | no |
| Remarks: | The estimation is based on molecular structure (SMILES: ClC). The model was used as received from EPA. |
| Reference: | U. S. EPA 2000 |

## 2.5 PARTITION COEFFICIENT (log10$P_{ow}$)

| | |
|---|---|
| Log $P_{ow}$: | 0.91 |
| Temperature: | 25°C |
| Method: | Instrumentation: The partition coefficient was determined in an octanol-water system. A Varian Model 2740 chromatograph with a Vidar (6300) digital integrator was employed. The column (6 ft) was packed with Se-30 (5) on 80-100 mesh ChromosorbW AW-DMCS. A U-tube of 4.5 in., one-third packed with 60-80 mesh firebrick and two-thirds packed with 8-20 mesh ascarite, 0.2-0.5 silica gel, or 8-12 mesh $CaCl_2$, was placed in the oven before the column. This trap removed the water. To be consistent, the trap was used for analysis of both octanol and water phases. The temperatures employed were in the 60-90° range. The chloromethane studies used research grade material of > 99% purity. |
| Partitioning: | The gas was allowed to bubble through octanol and water placed in a vacutainer (100 x 16 mm) with a rubber serum stopper. The gas was introduced via a needle and withdrawn via a syringe. In the process of withdrawing a sample, the system was kept at atmospheric pressure by a second needle connected to a reservoir of gas at atmospheric pressure. Five analyses were conducted. |
| GLP: | unknown |
| Reference: | Hansch et al., 1975. |

| | |
|---|---|
| Log $K_{ow}$: | 1.1 (estimated) |
| Temperature: | 25°C |
| Media: | octanol/water |
| Method: | Estimation using KOWWIN (ver. 1.66) |
| Remarks: | The estimation is based on molecular structure (SMILES: ClC) using fragment constants. The model was used as received from EPA. |
| Reference: | U. S. EPA 2000 |

## 2.6 WATER SOLUBILITY

### A. Solubility

| | |
|---|---|
| Value: | 4800 mg/l; 5325 mg/l |
| Temperature: | 25 °C |
| Description: | Slightly soluble |
| Method: | other |
| GLP: | unknown |
| Remark: | handbook data |
| Reference: | Ahlstrom and Steele, 1979; Horvath, 1982. |

| | |
|---|---|
| Value: | 2772 mg/l; |
| Temperature: | 20 °C |
| Method: | other |
| GLP: | unknown |
| Remark: | handbook data |
| Reference: | The Merck Index, 1989 |

| | |
|---|---|
| Value: | $2.312 \times 10^4$ mg/L (estimated) |
| Temperature: | 25°C |
| Method: | Estimation using WSKOW (ver. 1.40) |
| Remarks: | The model WSKOW was used as received from EPA. The estimation was based on molecular structure and the following input data:<br>SMILES: ClC<br>log Kow: 0.91<br>melting point: -97.7°C |
| Reference: | U. S. EPA 2000 |

**B. pH Value, pKa Value**

**2.7 FLASH POINT** *(liquids)*

| | |
|---|---|
| Value: | <0 °C |
| Type of test: | Open cup |
| Method: | other |
| GLP: | unknown |
| Remark: | handbook data |
| Reference: | Ahlstrom and Steele, 1979 |

**2.8 AUTO FLAMMABILITY (solid/gases)**

| | |
|---|---|
| Value: | 634°C |
| Method: | other |
| GLP: | unknown |
| Remark: | handbook data |
| Reference: | Torkelson and Rowe, 1981 |

**2.9 FLAMMABILITY**

| | |
|---|---|
| Results: | Extremely flammable |
| Method: | other |
| GLP: | unknown |
| Remarks: | Flammability Limits 10.7 - 17.4 vol. %. |
| Remark: | handbook data |
| Reference: | Ahlstrom and Steele, 1979; U.S. DOT, 1996; (As cited in HSDB, 1998). |

**2.10 EXPLOSIVE PROPERTIES**

| | |
|---|---|
| Results: | Explosive under influence of a flame |
| Method: | other |
| GLP: | unknown |
| Remarks: | Lower limit 8.1%, Upper 17% |
| Reference: | SAX Danger Props Indus Mater. 6th Ed. 1984, p. 730 (HSDB, 1998). |
| Remarks: | Explosion Hazard: Moderate, when exposed to heat or flame. |
| Reference: | SAX, 1984 (as cited in HSDB, 1998). |
| Remarks: | "When chloromethane contacts magnesium an explosion occurs. Sodium and other alkali metals react explosively with chloromethane. chloromethane in contact with sodium-potassium alloy is impact-sensitive." |
| Remark: | Handbook data |
| Reference: | NFPA, 1986 (as cited in HSDB, 1998). |

**2.11 OXIDISING PROPERTIES**

**2.12 OXIDATION: REDUCTION POTENTIAL**

## 2.13 ADDITIONAL REMARKS

### A. Partition co-efficient between soil/sediment and water ($K_d$)

Results: Log $K_{oc}$
Remarks: 0.7 (estimated)
Reference: PCGEMS (equ 4-10) As cited in ATSDR, 1990.

Type: Log $K_{oc}$
Media: soil
Method: Estimation using PCKOCWIN (ver. 1.66)
Results: 1.2 (estimated).
Remarks: The estimation is based on molecular structure (SMILES ClC) using the default parameters of the model.
Reference: U. S. EPA 2000

### B. Other remarks

Results: Henry's Law constant
Remarks: 8.82 x $10^{-3}$ atm-$m^3$/mol
Reference: Gossett, J.M., 1987

Type: Henry's Law constant
Results: 8.20 x $10^{-3}$ atm-$m^3$/mol (estimated)
Method: Estimation using HENRYWIN (ver. 1.90)
Remarks: The model HENRYWIN was used as received from EPA. The estimation was based on molecular structure using the bond contribution method
Reference: U. S. EPA 2000

Type: Henry's Law constant
Results: 8.88 x $10^{-3}$ atm-$m^3$/mol (estimated)
Method: Estimation using HENRYWIN (ver. 1.90)
Remarks: The model HENRYWIN was used as received from EPA. The estimation was based on molecular structure using the group contribution method
Reference: U. S. EPA 2000

Results: Surface Tension
Remarks: 16.2 dynes/cm @ 20 °C
Reference: Chris. Hazard. Chem. 1984-5

Results: Viscosity
Remarks: 0.1834 cP @ 20 °C
Reference: Weast Handbook Chem. & Phys., 1986-87

Results: Hydroxyl radical rate constant
Remarks: 4.36 x $10^{-14}$ cu-m/molc sec @ 25 °C
Reference: Atkinson, R., 1989

# 3. ENVIRONMENTAL FATE AND PATHWAYS

## 3.1 STABILITY

### 3.1.1 PHOTODEGRADATION

Type: Air
Indirect Photolysis:
Type of sensitizer: OH
Concentration of sensitizer: 500000
Rate constant (radical): 0.0000000000000436 $cm^3$/molecule*sec
Degradation: approximately 50% after 360 days
Method: calculated (used data of Howard and Evenson (1976) [discharge flow-laser magnetic resonance], Perry et al. (1976) [flash photolysis-resonance fluorescence], Paraskevopoulos et al. (1981) [flash photolysis-resonance adsorption] and Jeong and Kaufman (1982) [discharge flow-resonance fluorescence])
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: At temperature 298°K
Reference: Atkinson, 1985 (As cited in ATSDR, 1990).

Type: Air
Indirect Photolysis:
Type of sensitizer: OH
Rate constant (radical): 0.000000000000043 $cm^3$/molecule*sec
Method: calculated (used data of Howard and Evenson (1976) [discharge flow-laser magnetic resonance], Perry et al. (1976) [flash photolysis-resonance fluorescence], and Jeong and Kaufman (1982) [discharge flow-resonance fluorescence])
GLP: unknow n
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: Over the temperature range 247-483°K
Reference: NASA, 1981 (As cited in ATSDR, 1990).

Type: Air
Indirect Photolysis:
Type of sensitizer: OH
Concentration of sensitizer: 1500000 molecule/$cm^3$
Rate constant (radical): 0.0000000000000547 $cm^3$/molecule*sec
Degradation: approximately 50% after 195 days
Method: calculated (APOWIN, version 1.55), Syracuse Research
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Reference: Kloepffer and Daniel, 1990.

Type: Air
Indirect Photolysis:
Type of sensitizer: OH
Concentration of sensitizer: $1.56 \times 10^6$ molecule/$cm^3$ (12-hr day)
Rate constant (radical): $0.517 \times 10^{-12}$ $cm^3$/molecule*sec (estimated)
Degradation: approximately 50% after 207 days
Method: calculated using APOWIN (ver. 1.90)
Remarks: The model APOWIN was used as received from EPA. The estimation was based on molecular structure using fragment constants.
Reference: U. S. EPA 2000$$$

Type: Air
Indirect Photolysis:
Type of sensitizer: OH
Rate constant (radical): 0.00000000000034 $cm^3$/molecule*sec
Method: calculated
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: Value for 0°C; at 25°C the rate constant is 0.48 x $10^{-13}$
Reference: Hampson, 1980.

Type: Air
Indirect Photolysis:
Type of sensitizer: OH
Rate constant (radical): 0.00000000000048 $cm^3$/molecule*sec
Method: calculated (Arrhenius equation)
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: 25°C
Reference: Crutzen et al., 1978.

Type: Air
Indirect Photolysis:
Type of sensitizer: OH
Rate constant (radical): 0.0000000000296 $cm^3$/molecule*sec
Degradation: approximately 50% after 1.9 year
Method: other
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: At -8°C
Reference: Singh et al., 1979.

Type: Air
Indirect Photolysis:
Type of sensitizer: OH
Concentration of sensitizer: 1000000 molecule/$cm^3$
Method: Three field studies were conducted in Los Angeles, California; Phoenix, Arizona; and Oakland, California, to better characterize the atmospheric abundance, fate and human exposure of selected organic chemicals that may be potentially hazardous. During field data collection, *in situ* analysis using an instrumented mobile laboratory was performed for a total of 33 organics. The concentrations, variability's and average daily dosages from exposure to the organics were determined. The diurnal behaviour and the atmospheric fate of both primary and secondary pollutants were studied. Residence times for a typical polluted atmosphere were estimated. The rate constant with hydroxyl radical (HO) in units of $cm^3$ $molec^{-1}s^{-1}$ was 0.05 $10^{12}$ x $k_{HO}$. The chemical residence time of $CHCl_3$ measured in this study based on a daily average (24 h) HO abundance of $10^6$ mol/$cm^3$ in the boundary layer of a polluted atmosphere was determined to be 231 days. The percent loss in one day (or 12 sunlit hours) was estimated to be 0.4%. The daily loss rate would be significantly reduced in colder winter months.
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Result: Residence time: 231 days; 4% loss/day
Reference: Singh et al., 1981.

Type: Air
Indirect Photolysis:

Type of sensitizer: OH
Concentration of sensitizer: 2000000 molecule/$cm^3$
Degradation: ca 50% after 124 days
Method: The National Science Foundation-supported Global Atmospheric Measurements on Tropospheric Aerosols and Gases program (GAMETAG) conducted a field sampling program. Based on the results of their observations, approximate photochemical lifetimes based on oxidation by OH at a level of 2 x $10e^6$ molecules/$cm^3$ were determined.
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Reference: Davis et al., 1982.

Type: Air
Method: Photooxidation was carried out in a cylindrical glass reaction cell 9.1 m long and 0.31 m in diameter. The cell was surrounded by 96 ultraviolet fluorescent lamps capable of photo-dissociating molecular chlorine with a half-life of about 4 minutes. Reactants and products were analysed by long path infrared absorption using a Fourier transform spectrometer. The reactions were conducted in one atmosphere of dry air. The oxidation of each halocarbon was initiated by the photolysis of molecular chlorine. Hydrogen chloride produced in the initial oxidation step does not participate in subsequent reactions and shows only in an unobtrusive way in the infrared spectrum.
Result: Degradation in presence of Cl radicals and air.
30% degradation: products: formyl chloride: 5 ppm,
H202: 0.5 ppm, CO: 1 ppm, HCl: 7 ppm
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: Glass chamber, fluor lamps dry air, 20-ppm test compound, 5 ppm C12 irradiated to produce Cl radicals, irradiated 5 minutes.
Reference: Spence et al., 1976.

Type: Air
Indirect Photolysis:
Type of sensitizer: OH
Concentration of sensitizer: 500000 molecule/$cm^3$
Degradation: approximately 50% after 15 month
Method: other
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Reference: Gusten et al., 1984.

Type: Air
Indirect Photolysis:
Type of sensitizer: O atomic
Rate constant (radical): 0.00000000000017 $cm^3$/molecule*sec
Method: The rate constant is based on the results of discharge-flow mass-spectrometry experiments. This rate is valid over the temperature range 350-1000 K and should not be exptapolated to higher temperatures.
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: 25°C; reactant; atomic oxygen
Reference: Herron and Huie, 1973.

Type: Air
Indirect Photolysis:
Type of sensitizer: OH atomic

Rate constant (radical): 0.000000000000015 $cm^3$/molecule*sec
Method: see remarks
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: Reactant: O; Test compound: 0.243 x $10^9$ mole/$cm^3$, 0 produced by microwave discharge, diluted with he, flow system, 2.95 torr, 25°C, O concentration in large excess. Test substance: CO, HCl, H, $H_2O$, $COCl_2$
Reference: Barassin and Combourieu, 1974.

Remarks: Chloromethane has an atmospheric residence time, estimated to be about 1-2 years based on calculations comparing hydroxyl radical reactivity to that of methyl chloroform (Khalil, 1979). Other sources have estimated the residence time as somewhat shorter, but it appears that 1-2 years is still a reasonable estimate. Another way to express the atmospheric removal time is the daily removal rate expressed as 0.4% per day of the amount released to the atmosphere (Singh, et al., 1982). The precise atmospheric residence time probably is not too important, for any of the reported values would indicate chloromethane has little or no involvement in tropospheric ozone generation, and the magnitude of natural emissions precludes anthropogenic sources from playing any significant additional role in potential stratospheric ozone depletion.
Remarks: Once in the ambient air, whatever the "precise" residence time may be, chloromethane's fate follows three pathways. A small amount may be removed with precipitation in the form of rain and/or snow (Pearson and McConnel, 1975). This is not likely to be a significant atmospheric process.
Remarks: The major removal process for chloromethane is probably the reaction with hydroxyl radicals (Singh, et al., 1982; Khalil, 1979; Spence, et al., 1976). The exact pathway for decomposition in the troposphere is not known; however, the ultimate chlorine production would be HCl, with CO and $CO_2$ the fate of carbon (Spence, et al., 1976; Singh, et al., 1982). The direct photolysis of chloromethane appears unimportant in the troposphere, although laboratory studies of pure chloromethane have shown that at very short wavelengths (below 200 nm) a variety of products can form (Shold and Rebbert, 1978). In a real-world atmosphere, these sequences of reaction are unlikely.
Remarks: Most of the HCl produced by tropospheric degradation of methyl chloride will be removed via precipitation. HCl formed in the stratosphere probably plays some role in regulating stratospheric ozone, but the extent to which HCl is an active species, temporary sink or permanent sink for chlorine is still being debated.
Reference: Noted above.

### 3.1.2 STABILITY IN WATER

Type: Abiotic (hydrolysis)
Half-life: .≈ 2 years at pH 7.0 at 20°C
Method: calculated using the thermodynamic constants. Rate data and derived parameters for the hydrolysis of methyl chloride in water were determined. The methyl chloride was of reagent grade and was purified by distillation to give physical constants in agreement with the literature; it was then passed through alumina for adsorption. The purified sample was protected from light and refrigerated during the kinetic study. The distilled water was passed through an ion exchange column and sufficient backing electrolyte of the common anion added to give a concentration 0.001-0.003 M. The solution

| | |
|---|---|
| | was evacuated and the halide introduced under vacuum. The rate was determined by the conductance method. Temperature determination was by a platinum thermometer and temperature-controlled Mueller bridge. Temperature control was usually +/- 0.001-0.002°C. The approximation log $(1/R_2 - 1/R_1) = k_1t + c$ was justified by the low concentrations used, and the small range of concentration involved (0.002 – 0.005 M). |
| GLP: | unknown |
| Test substance: | As prescribed, sections 1.1 to 1.4 |
| Remarks: | Methanol and HCl are the only products; Hydrolysis rate first-order: $0.76 \times 10^{-6}$ at 50°C. |
| Reference: | Heppolette and Robertson, 1966. |

| | |
|---|---|
| Type: | Abiotic (hydrolysis) |
| Half-life: | 1.1 years at pH 7.0 at 25°C |
| Method: | other |
| GLP: | unknown |
| Test substance: | As prescribed, sections 1.1 to 1.4 |
| Remarks: | Hydrolysis rate first order: $0.237 \times 10^{-7}$; Rate is independent of pH below 10. |
| Remark: | Handbook data |
| Reference: | Mabey and Mill, 1978. |

| | |
|---|---|
| Type: | Abiotic (hydrolysis) |
| Half-life: | = 2.5 at pH 7.0 at 20°C |
| Degradation: | 50% at 0°C after 88 year |
| Method: | The rate for this reaction was calculated by extrapolation of the very accurate data of Moelwyn-Hughes (1938). The data were extended over the 40-120°C range and equations for the T dependence were determined. |
| GLP: | unknown |
| Test substance: | As prescribed, sections 1.1 to 1.4 |
| Remarks: | Hydrolysis rate first order: $0.89 \times 10^{-8}$ at 20°C, $0.25 \times 10^{-9}$ at 0°C, $0.16 \times 10^{-8}$ at 10°C. |
| Reference: | Zafiriou, 1975. |

| | |
|---|---|
| Type: | Abiotic (hydrolysis) |
| Half-life: | = 120 days at pH 3.0 at 25.0°C; 62 days at pH 7.0 at 25.5°C; and 31 days at pH 11.0 at 25.0°C |
| Method: | In general conformance with USEPA TSCA Test standard 796.3500 |
| GLP: | Yes |
| Test substance: | As prescribed, sections 1.1 to 1.4 |
| Remarks: | Hydrolysis rate constant = $2.3 \times 10^{-4}$/hr at pH 3.0 and 25.0°C; $4.6 \times 10^{-4}$ at pH 7.0 and 25.5°C; and $9.1 \times 10^{-4}$ at pH 11.0 and 25.0°C. The measured rate constants indicate that hydrolysis of chloromethane under mildly acidic and neutral conditions is essentially negligible. Under basic conditions at pH = 11, hydrolysis apparently takes place - albeit at a slow rate - yielding methanol as a transformation product. Based on hydrolysis characteristics alone, chloromethane would be expected to persist within normal pH regimes in the aquatic environment. |
| Reference: | Ann Arbor Technical Services, Inc., 1989. |

| | |
|---|---|
| Type: | Abiotic (hydrolysis) |
| Degradation: | = 50% at 10°C after 14 year |
| Method: | The rate for this reaction was calculated by extrapolation of the very accurate data of Moelwyn-Hughes (1938). The data were extended over the 40-120°C range and equations for the T dependence were determined. |
| GLP: | unknown |
| Test substance: | As prescribed, sections 1.1 to 1.4 |

Remarks: Hydrolysis rate first order: $0.89 \times 10^{-8}$ at 20°C, $0.25 \times 10^{-9}$ at 0°C, $0.16 \times 10^{-8}$ at 10°C.
Reference: Zafiriou, 1975.

Remarks: Chloromethane has been observed at low levels in water. Considering its solubility, volatility and resultant Henry's Law Constant, chloromethane would be expected, under equilibrium conditions, to be principally in the air. Equilibrium conditions will be attained faster if the water/air interface area is expanded by stirring or agitation (Dilling, 1975, 1977). Thus flowing or wind-agitated surface water will quickly lose nearly all of any chloromethane via evaporation to the air.
Remarks: Absorption of natural organic or inorganic materials in contact with water should not be a significant removal process due to volatility and relatively low octanol/water partition coefficient.
Remarks: Hydrolysis of chloromethane in water is relatively slow with a half-life of about 1.1 years reported at pH 7 and 25°C (Mabey and Mill, 1978). Data were not found to confirm the expected dependency of this rate on temperature, pH, and other dissolved constituents that would vary under real-world conditions.
Remarks: Biodegradation of chloromethane has not been studied extensively based on information found in the literature available at this time. Most chloromethane that finds its way into a bio-oxidation wastewater treatment system is likely to be volatilized to the air. It is likely that, like other chlorocarbons, chloromethane does undergo anaerobic biodegradation under some conditions, including industrial sewage treatment processes. There are a variety of indicators that biodegradation should occur, including liver detoxification (Kornbrust and Bus, 1983), bio-oxidation (Stirling and Dalton, 1979; Patel, et al., 1982), and enzyme catalyzed hydrolysis (Keuning, et al., 1985).
Remarks: Recent work also shows that a bacterium isolated from industrial sewage is very effective at degrading chloromethane with release of chloride ion. This bacterium uses the chloromethane as a source of carbon and energy for growth (Hartmans, et al., 1986). The extent to which this degradation occurs in a real world, complete sewage system, or other media with potentially similar organisms, is not known.
Remarks: Degradation of chloromethane in groundwater, by any process, has not been studied based on the literature available. Since there is not likely to be much chloromethane in such water--and most would be lost to the air during withdrawal, treatment, distribution, and use patterns--a lack of such data probably is not important.
Reference: Noted above.

### 3.1.3 STABILITY IN SOIL

Remarks: No reports were found on the environmental fate of chloromethane in soil. Since it has been reported to be detected in groundwater, it is apparent that it can travel with water through the soil to underground aquifers. Considering the physical properties of chloromethane, it should only be found at more than background levels in soil that has been protected from evaporative losses, or when it has been deliberately placed below soil surface levels and covered with a barrier of some type that could inhibit evaporation.

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## 3.2 MONITORING DATA (ENVIRONMENTAL)

Type of Measurement: Background
Media: Air
Results: Urban/Suburban (mean ppt):

| | |
|---|---|
| Los Angeles, CA (4/9-21/79) | 3001 |
| Phoenix, AZ (4/23/79-5/6/79) | 2391 |
| Oakland, CA (6/28/79-7/10/79) | 1006 |

Reference: Singh et al., 1981. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Air
Results: Urban/Suburban (mean ppt):

| | |
|---|---|
| Houston, TX (5/15-24/80) | 955 |
| St. Louis, MO (5/30/80-6/8/80) | 732 |
| Denver, CO (6/16-26/80) | 763 |
| Riverside, CA (7/2-12/80) | 703 |
| Staten Island, NY (3/27/80-4/5/80) | 701 |
| Pittsburgh, PA (4/8-16/80) | 665 |
| Chicago, IL (4/21-30/80) | 856 |

Reference: Singh et al., 1982. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Air
Results: Urban/Suburban: range 570-5700 ppt; median 1000 ppt
Remarks: US (389 samples, 12 sites)
Reference: Brodzinsky and Singh, 1982. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Air
Results: Urban/Suburban: mean 3000 ppt; max 7000 ppt
Remarks: Delft, the Netherlands (densely populated area of the country)
Reference: Guicherit and Schulting, 1985. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Air
Results: Urban/Suburban: peak chloromethane concentrations in December and May of 680 and 700 ppt, respectively.
Remarks: A suburban site in Hillsboro, OR; these levels have been attributed to wood burning and backyard burning
Reference: Edgerton et al., 1984. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Air
Results: Urban/Suburban (mean ppt):
Los Angeles, CA (4/29/76-5/4/76): 834 ppt
Stanford Hills, CA (11/24-30/75): 1022 ppt (*)
Remarks: (*) Marine air may influence levels.
Reference: Singh et al., 1977a. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Air
Results: Rural/Remote (mean ppt):
Pullman, WA (12/74-2/75): 530 ppt
Remarks: Samples were taken in downtown Pullman, Washington State University campus, 1.2, 1.8, 2.4, 3.0, and 3.6 km in altitude.
Reference: Grimsrud and Rasmussen, 1975. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Air

Results: Rural/Remote (range ppt):
Alaska (5/24-30/75): 505-970 ppt
Remarks: Samples were taken at altitudes up to 14.5 km. Results read from a graphical presentation of the data.
Reference: Robinson et al., 1977. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Air
Results: Rural/Remote (mean ppt):
Point Barrow, AK (5/7 & 13/82): 647 ppt
Remarks: Samples were taken at altitudes up to 4.3 km.
Reference: Rasmussen and Khalil, 1983. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Air
Results: Rural/Remote (mean ppt):
Pacific Northwest (3/11/76): 569 ppt
Remarks: Samples were taken at altitudes up to 14.5 km. Results read from a graphical presentation of the data.
Reference: Cronn et al., 1977. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Air
Results: Rural/Remote (mean ppt):
Point Arina, CA (12/8/79-2/18/81): 754 ppt
Remarks: 4-6 samples were taken in a 24-hour period on each of 17 sampling days.
Reference: Singh et al., 1981b. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Air
Results: Rural/Remote (mean ppt):
Point Reyes, CA (12/2-12/75): 1260 ppt (*)
Yosemite, CA (5/12-17/75): 713 ppt
Palm Springs, CA (5/24-27/76): 1058 ppt
Remarks: (*) Marine air may influence levels.
Reference: Singh et al., 1977. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Air
Results: Rural/Remote median = 1300 ppt; range = 590-1300 ppt
Remarks: US (191 samples at four sites)
Reference: Brodzinsky and Singh, 1982. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Air
Results: Rural/Remote
Remarks: The concentration of chloromethane decreases with altitude, declining to 50 ppt at 29 km.
Reference: Fabian and Goemer, 1984. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Air
Results: Rural/Remote: Mean = 700 ppt
Remarks: The island of Terschelling, the Netherlands (least populated area of the country)
Reference: Guicherit and Schulting, 1985. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Air
Results: Rural/Remote: Range = 630-730 ppb
Remarks: From the coast to the forest in Guyana
Reference: Gregory et al., 1986. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Air
Results: Rural/Remote range = 564-687 ppt
Remarks: Eight background locations, 1980, time series over seasons; concentration highest in spring and lowest in fall and highest in tropics, however, there is no significant difference between hemispheres.
Reference: Khalil and Rasmussen, 1981. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Indoor Air
Results: 6950 ppt
Remarks: Chloromethane concentrations are elevated due to biomass combustion. In rural Nepal, where stoves are used for cooking and heating, chloromethane levels in one house were 6950 ppt.
Reference: Davidson et al., 1986. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Air
Results: Median Concentration (ppt) for different air masses:
Remote - 713 ppt - 5 data points
Rural - 923 ppt - 2 data points
Suburban - 641 ppt - 599 data points
Urban - 810 ppt - 100 data points
Remarks: A volatile organic carbon (VOC) database contained 706 data points (300 cities from 42 states.
Reference: Shah and Singh, 1988. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Air
Results: Median Concentration (500-700 ppt)
Remarks: Air in all parts of the United States, indeed the entire world, contains at least 500-700 ppt chloromethane as a natural background level (Rasmussen et al., 1980; Gschwend, et al., 1985; Pierroti et al., 1980). Monitoring near natural non-industrial anthropogenic sources have shown much higher levels, even in the thousands of ppt range (Lovelock, 1975; Hoyt and Rasmussen, 1985; Khalil et al., 1983). Homes fires for cooking and heating, while very common in China and Nepal, have also been shown to contribute to chloromethane levels, in the thousands of ppt range (Davidson et al., 1986; Rasmussen et al, 1982b; Khalil and Rasmussen, 1984).
Reference: Shah and Singh, 1988. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Surface Water (mean ppb):
Results: Delaware River and Raritan Canal: Not detected
Remarks:
Reference: Granstrom et al., 1984. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Surface Water (mean ppb):
Results: Lake Ontario (7/82-5/83): < 1 ppb

Remarks: Ten locations on Lake Ontario.
Reference: Otson, 1987. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Surface Water (range ppb):
Results: Lake Ontario: Detected
Remarks:
Reference: Great Lakes Water Quality Board, 1983. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Surface Water (range ppb):
Results: Surface waters in New Jersey: <0.1-222 ppb
Remarks: 605 samples. 4% occurrence
Reference: Page, 1981. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Surface Water (median ppb):
Results: 895 stations in USEPA STORET database: median < 10 ppb
Remarks: 1.4% occurrence
Reference: Staples, 1985. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Surface Water (mean ppb):
Results: Mean < 5 ppb
Remarks: Raw water from 30 Canadian potable water treatment facilities
Reference: Otson, et al., 1982. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Surface Water (mean ppb):
Results: Detected
Remarks: Detected in the Niagara River and the open water of Lake Ontario
Reference: Great Lakes Water Quality Board, 1982. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Groundwater (range ppb):
Results: New Jersey: <0-1.6
Remarks: 408 wells; 0.3% occurrence.
Reference: Page, 1981 and Greenberg et al., 1982. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Groundwater:
Results: Identified, not quantified in drinking water in New Orleans, Cincinnati, Miami, Philadelphia, and Ottumwa, IA of the 10 cities surveyed.
Reference: Abrams, 1975 (as cited in HSDB, 1998)

Type of Measurement: At contaminated site
Media: Groundwater (range ppb):
Results: Minnesota: Detected
Remarks: Groundwater under municipal solid waste landfills; 13 samples; 69% occurrence.
Reference: Sabel and Clark, 1984. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Groundwater (range ppb):
Results: Minnesota: Detected
Remarks: 7 samples; 29% occurrence
Reference: Sabel and Clark, 1984. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Groundwater (mean ppb):
Results: Massachusetts: Detected
Reference: Burmaster, 1982. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Drinking water (range ppb):
Results:

| | |
|---|---|
| Miami, FL | Detected |
| Seattle, WA | Detected |
| Ottumwa, IA | Detected |
| Philadelphia, PA | Detected |
| Cincinnati, OH | Detected |

Reference: Coleman et al., 1976. (as cited in ATSDR, 1990)

Type of Measurement: Background
Media: Seawater (ppt):
Results: Pacific Ocean: 26.8 ppt at surface; 3.3 ppt at 300 m depth
Reference: Singh, et al., 1979. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Seawater (ppt):
Results: Eastern Pacific (latitude 29 deg N to - 29 deg S): 6.3-42 ppt, mean of 11.5 ppt, 200-300% supersaturation
Remarks: These results confirm the findings of Singh et al., 1977 and Lovelock, 1975.
Reference: Singh, et al., 1983. (as cited in HSDB, 1998)

Type of Measurement: Background
Media: Seawater (ppt):
Results: Point Reyes, CA (near shore): 1200 ppt
Remarks:
Reference: Singh, et al., 1977. (as cited in HSDB, 1998)

Type of Measurement: At contaminated site
Media: Landfill leachate (range ppb):
Results: Minnesota. Detected
Remarks: Municipal solid waste leachate; 6 samples; 66 % occurrence
Reference: Sabel and Clark, 1984. (as cited in ATSDR, 1990)

Type of Measurement: At contaminated site
Media: Landfill leachate (range and mean ppb):
Results: Wisconsin: 170 ppb
Remarks: Municipal solid waste leachate; 5 samples; 20 % occurrence
Reference: Sabel and Clark, 1984. (as cited in ATSDR, 1990)

Type of Measurement: At contaminated site
Media: Landfill leachates (range and mean ppb):
Results: Love Canal, NY: 180 ppb
Kin-Buc Landfill, NJ: 3.1 ppb
Remarks: Industrial landfill
Reference: Shuckrow et al., 1982. (as cited in ATSDR, 1990)

Type of Measurement: At contaminated site
Media: Landfill leachate (range and mean ppb):

| | |
|---|---|
| Results: | Hazardous Waste Sites: range: 5.4-500 ppb<br>mean: 115 ppb |
| Reference: | CLPSBD, 1987. (as cited in ATSDR, 1990) |

| | |
|---|---|
| Type of Measurement: | At contaminated site |
| Media: | Landfill leachate (range ppb): |
| Results: | 11 National Priority Lists Sites: Detected |
| Reference: | NPLTDB, 1989. (as cited in ATSDR, 1990) |

| | |
|---|---|
| Type of Measurement: | At contaminated site |
| Media: | Landfill leachate |
| Results: | Median < 10 ppb |
| Remarks: | 1298 stations in the USEPA STORET database; 3.5% positive |
| Reference: | Staples et al., 1985. (as cited in HSDB, 1998) |

| | |
|---|---|
| Type of Measurement: | At contaminated site |
| Media: | Landfill leachate |
| Results: | Not specified |
| Remarks: | Chloromethane has also been detected in the leachate of hazardous waste landfills. |
| Reference: | Brown and Donnelly, 1988; Kosson et al., 1985; and Venkataramani et al., 1984. (as cited in ATSDR, 1990) |

| | |
|---|---|
| Type of Measurement: | Background |
| Media: | Urban Runoff |
| Results: | 15 United States cities: Not detected |
| Remarks: | |
| Reference: | Cole et al., 1984. (as cited in ATSDR, 1990) |

| | |
|---|---|
| Type of Measurement: | Other |
| Media: | Effluents |
| Results: | Petroleum refinery effluents (range ppb):<br>Biotreatment effluents <100 - >100 ppb<br>Final effluent < 10 ppb |
| Remarks: | 17 samples |
| Reference: | Snider and Manning, 1982. (as cited in ATSDR, 1990) |

| | |
|---|---|
| Type of Measurement: | Other |
| Media: | Effluents |
| Results: | Chloromethane detected in the following industrial categories (frequency of occurrence, median concentration in ppb):<br>Nonferrous metals: 1, 21.6 ppb<br>Paint and ink: 2, 4128.7 ppb<br>Printing and publishing: 1, 6.0 ppb<br>Organics and plastics: 1, 156.7 ppb<br>Pharmaceuticals: 1, 2558.3 ppb<br>Organic chemicals: 3, 49.0 ppb |
| Remarks: | In a comprehensive survey of wastewater from 4000 industrial and publicly owned treatment works (POTWs) sponsored by the Effluent Guidelines Division of the U.S. EPA |
| Reference: | Shackelford et al., 1983. (as cited in HSDB, 1998) |

| | |
|---|---|
| Type of Measurement: | Other |
| Media: | Effluents |
| Results: | Pharmaceutical manufacturing: mean 2000 ppb<br>Organic chemical manufacturing/plastics: mean 0.1 ppb<br>Timber products processing: mean 140 ppb |

| | |
|---|---|
| | Raw wastewater from metal finishing: mean 610 ppb |
| Remarks: | Chloromethane detected in treated wastewater from these industries |
| Reference: | USEPA, 1981. (as cited in HSDB, 1998) |

| | |
|---|---|
| Type of Measurement: | Other |
| Media: | Effluents |
| Results: | Median < 10 ppb |
| Remarks: | 1298 stations in the USEPA STORET database; 3.5% positive |
| Reference: | Staples et al., 1985. (as cited in HSDB, 1998) |

| | |
|---|---|
| Type of Measurement: | Other |
| Media: | Soil/Sediment |
| Results: | Median < 5 ppb |
| Remarks: | 345 stations in USEPA STORET database; 0.3 % positive |
| Reference: | Staples et al., 1985. (as cited in HSDB, 1998) |

| | |
|---|---|
| Type of Measurement: | At contaminated site |
| Media: | Soil |
| Results: | Soil at hazardous waste sites (mean ppb): 5 - 500 ppb |
| Remarks: | Detected in soil of 357 hazardous waste sites. |
| Reference: | Contract Laboratory Program Statistical DataBase (CLPSDB), 1987. (as cited in ATSDR, 1990) |
| Remarks: | "No additional information on chloromethane in the soil was found except references to fungi production." |
| Reference: | Harper, 1985; Cowan, 1973; Turner et al., 1975. |

## 3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

### 3.3.1 TRANSPORT

| | |
|---|---|
| Type: | Volatility |
| Media: | water-air |
| Method: | other |
| Results: | Evaporation from water: t1/2 = 2.4 hours |
| Remarks: | Calculated with wind of 3 m/sec, current of 1 m/sec, 1 m depth. |
| Remark: | Handbook data |
| Reference: | Lyman et al., 1982. |

| | |
|---|---|
| Type: | Volatility |
| Media: | water-air |
| Method: | A hollow fiber-mass spectrometric procedure was used to determine the evaporation rate. Experimental conditions included 200 rpm stirring of the solution with a shallow-pitch propeller stirrer, at approximately 25ºC, still air (< 0.2 mph air currents), an average solution depth of 6.5 cm, and a 250-ml beaker as the vessel. Two to five compounds were run simultaneously in the same solution. The initial concentration of each compound was 1.0 ppm (weight basis). Evaporation rate curves over time were generated. The ion-peak height was correlated with concentration by extrapolation of the decay portion of the curves to zero time. This extrapolated concentration at zero time was taken as 1.0 ppm. Successive half-lives were determined from the decay portion of the curves and reported. |
| Results: | Evaporation from water: t1/2 = 0.46 hours |
| Remarks: | 1 ppm test compound, stirred at 200 rpm, 6.5 cm depth, analysed by MS, using hollow-fiber probe. |
| Reference: | Dilling, 1977. |

Type: Volatility
Media: air
Method:
Remarks: "Most chloromethane discharged to the environment will be released to air where it will be subjected to transport and diffusion into the stratosphere (Singh et al., 1979, 1982, 1983). The relatively uniform concentration of chloromethane in the northern and southern hemispheres indicated its widespread distribution and the importance of transport processes in its distribution."
Reference: As cited in ATSDR, 1990.

Type: Volatility
Media: water-air
Method: Based on the EXAMS environmental model that predicts the behaviour of a chemical in surface waters
Results: "Using the code test data developed by the Athens Environmental Research Laboratory of the EPA for a pond, the half-life for volatilization was calculated to be 25 hours. For a lake, the half-life was calculated to be 18 days."
Reference: As cited in ATSDR, 1990.

Type: Volatility
Media: water-air
Method: U.S. EPA Model, 2000
Results: The water volatilization model WVOLWIN® (USEPA 2000) estimates that chloromethane will have a half-life of 0.8 hours in a shallow, rapidly moving river with a strong surface wind and a half-life of 68 hours in a shallow lake with a weak surface wind. The half-life is based on the following input values to the model;
Solubility: 5325 mg/l
Vapor Pressure: 4313 mm Hg @ 25°C
Henry's Law Constant: 0.00882 atm-m$^3$/mole

| | River | Lake |
|---|---|---|
| Water depth (m) | 1 | 1 |
| Wind Velocity (m/s) | 5 | 0.5 |
| Current Velocity (m/s) | 1 | 0.05 |

All other parameters used model defaults.

Remarks: Based on the WVOLWIN environmental model that predicts the behaviour of a chemical in surface waters
Reference: U.S. EPA

Type: Volatility
Media: Soil
Remarks: "In soil, the dominant transport mechanism for chloromethane that is present near the surface probably will be volatilization (based on its Henry's law constant, water solubility, and vapor pressure), but no experimental information was located in the literature to confirm this. The actual volatilization rate for a chemical in soil is influenced by a number of factors including surface roughness, soil type, rainfall, leaching, depth of incorporation, temperature, and ground cover (Jury et al., 1987). Since chloromethane is not expected to sorb to soils, any chloromethane present in lower layers of the soil will be expected to leach to lower horizons as well as

| | |
|---|---|
| | diffuse to the surface and volatilize. The presence of chloromethane in groundwater confirms the importance of leaching as a transport route (Greenberg et al., 1982; Jury et al., 1987; Page, 1981)." |
| Reference: | As cited in ATSDR, 1990. |

### 3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

The transport and distribution of chloromethane between environmental compartments (air, water, soil, sediment, suspended sediment, fish, and aerosols) was evaluated using the EQC model (ver. 1.0), which is described elsewhere (Mackay et al. 1996). Level I, II, and III fugacity modeling of a type 1 chemical (i.e., chemicals that partitions into all environmental media) were used for the assessment. Default values for compartment dimensions and properties were used for all simulations that were conducted at a data temperature of 25°C.

**Level I Simulation**

A Level I simulation evaluates the equilibrium distribution of a fixed quantity of chemical in a closed environment, with no degradation reactions, no advective processes, and no intermedia transport process (e.g., no wet deposition or sedimentation). Output from the simulation provides a general indication of the likely media into which a chemical will tend to partition and the relative concentrations in each medium.

Chemical specific data required for the Level I simulation were molecular weight (50.46 g/mol), water solubility (5,325 mg/L; Horvath 1982), vapor pressure (573,286 Pa; Daubert and Danner 1985), log $K_{OW}$ (0.91; Hansch and Leo 1985), and melting point (-97.7°C; Riddick et al. 1986). The data values used for the simulation are the values recommended by the Syracuse Research Corporation (SRC) and were obtained from the SRC Environmental Fate Data Base.

Results from the Level I simulation indicate the chloromethane will partition almost exclusively into the air compartment. The following are a breakdown by compartment:

| | |
|---|---|
| Air | > 99% |
| water | ≤ 0.09% |
| soil, sediments, suspended sediments, and fish. | ≤ 0.001% |

**Level II Simulation**

A Level II simulation evaluates the equilibrium distribution of a chemical that is continuously discharged to the environment at a constant rate, and achieves a steady-state condition at which the input and output rates are equal. Degradation reactions and advective processes are treated as the mechanism of loss or output. Intermedia transport processes are not quantified (e.g., no wet deposition or sedimentation). Similar to a Level I simulation, output from a Level II simulation provides an indication of the likely media into which a chemical will tend to partition and the relative concentrations in each medium. In addition, the Level II simulation also provides an indication of environmental persistence and the loss processes that are likely to be most important.

Chemical specific data required for the Level II simulation include the Level I data (molecular weight, water solubility, vapor pressure, and melting) and the reaction half-lives in air, water, soil, and sediment. The most significant degradation mechanism for chloromethane in the air compartment appears to be reaction with hydroxyl radicals (Atkinson 1994). The reported rate constant for OH radical degradation ranges from $1.50\times10^{-14}$ to $5.47\times10^{-14}$ $cm^3 \cdot molecule^{-1} \cdot sec^{-1}$ (Davis et al 1982; Singh et al 1981; Kloepffer and Daniel 1990; Hampson 1980; Crutzen et al 1978; Atkinson 1985; NASA 1981; Gusten et al 1984; Singh et al 1979; Barassin and Combourieu 1974). Assuming an average concentration of OH radicals to be $5.00\times10^{5}$ $molecule \cdot cm^{-3}$ (Atkinson 1994), the reaction half-life for chloromethane in the air compartment ranges from 7,038 to 25,667 hours. The reported reaction half-life for chloromethane in water ranges from 1,488 to 21,629 hours (Zafiriou 1975; Heppolette and Robertson 1966; Mabey and Mill 1978; AATS 1989). Reaction half-lives for chloromethane in soil and sediment are not known.

Based on output from the Level I simulation, it was assumed that air was the primary environmental compartment in which chloromethane would be found. Therefore, Level II simulations were used to evaluate the effect of reaction half-life in air on the local and global persistence of chloromethane. For the purpose of these simulations, reaction half-lives in water, sediment, and soil were assumed to be negligible ($1.00\times10^{11}$ hours). Results from the simulations indicate that a change in reaction half-life in air from 7,038 to 25,667 hours (0.8 to 2.9 years) had essentially no effect on local distribution or persistence (overall residence time of about 4 days). In both simulations, >99% of the total chloromethane mass resided in the air compartment. Similarly, ≥99% of the chloromethane was removed from the local region by advection. In contrast, the change in reaction half-life in air significantly increased global persistence (i.e., reaction residence time) of chloromethane from about 1 year to 4 years. Given these results, the reaction half-life in air was assumed to be 9,293 hours (1.06 years), which represents the arithmetic mean of the reported rate constants for OH radical degradation. This value is very similar to the half-life of 1.01 years reported by Atkinson (1985) and 1.02 years reported by NASA (1981).

The next step of the Level II evaluation was to determine the effect of reaction half-life in water on the local and global persistence of chloromethane. For the purpose of these simulations, the reaction half-live in air was set at 9,293 hours, as previously discussed. Reaction half-lives in sediment and soil were again assumed to be negligible ($1.00\times10^{11}$ hours). Results from the simulations indicated that a change in reaction half-life in water from 1,488 to 21,629 hours (0.2 to 2.5 years) had no effect on local distribution (>99% of total mass found in the air compartment), local persistence (overall residence time of about 4 days), or global persistence (reaction residence time of about 1.5 years) of chloromethane. In both simulations, >99% of the total chloromethane mass resided in the air compartment. Similarly, ≥99% of the chloromethane was removed from the local region by advection in air. Less than 0.01% of the total mass of chloromethane was removed by advection or degradation in the water compartment. Given these results, the reaction half-life in water was assumed to be 8,122 hours (0.9 years), which was determined by Mabey and Mill (1978) and is the value recommended by the Syracuse Research Corporation.

The last step of the Level II evaluation was to determine the effect of reaction half-lives in soil and sediment on local and global persistence. As previously indicated, the reaction half-lives for chloromethane in these two environmental compartments are not known and were assumed to be negligible. For the purpose of these simulations, reaction half-live in air and water were set at 9,293 hours and 8,122 hours, respectively, as previously discussed. Results from the simulations indicate that a change in reaction half-life in soil and water from $1.00\times10^{11}$ hours ($1.14\times10^{7}$ years) to 1 hour had no effect on local distribution (>99% of total mass in the air compartment), local persistence (overall residence time of about 4 days), or global persistence (reaction residence time of about 1.5 years) of chloromethane. These results confirm that the original assumption, that reaction rates in soil and sediment were negligible, was appropriate.

For the purpose of the final Level II simulation, reaction half-lives in air and water were set at 9,293 hours and 8,122 hours respectively, and reaction half-lives in soil and sediment were assumed to be negligible ($1.00\times10^{11}$ hours). Results from the final Level II simulation showed the same distribution characteristics as the Level I simulation, with >99% of the total chemical mass being found in the air compartment. The results also demonstrated that advection in air was the primary mechanism of removal for chloromethane in the local environment. Total advection and degradation in the other three compartments (water, sediment, and soil) accounted for >0.7% the chloromethane removed from the system. Output from the model indicated that chloromethane would have a local persistence of about 4 days and a global persistence of 1.5 years.

**Level III Simulation**

A Level III simulation is similar to a Level II simulation in that a) the chemical is continuously discharged to the environment at a constant rate, b) achieves a steady-state condition at which the input and output rates are equal, and c) the mechanism of loss is determined by degradation reactions and advective processes. However, unlike a Level II simulation, equilibrium between environmental compartments is not assumed and intercompartmental transport processes are quantified (e.g., wet deposition, sedimentation, resuspension, soil runoff, aerosols, etc. are taken into account). Output from a Level III simulation provides a more realistic description of a chemical's fate, including the important degradation and advective losses and the intermedia transport processes. In addition, the simulation gives an indication on how source of entry of a chemical to the environment (e.g., to air, to water, and/or to soil) effects distribution and persistence.

Level III simulations were first used to evaluate the effect of source of entry on the distribution and persistence of chloromethane. Chemical specific data required for the simulations were the same as that previously described for the Level II simulation. The default emission rate of 1000 kg/h was used for each simulation. As expected on the basis of the Level II simulation, emission of chloromethane directly to air resulted in >99% of the total chemical mass residing in the air compartment, with advection in air representing the primary mechanism of removal. Degradation in air represented only a minor amount of the total chemical mass (< 1%) removed from the system. Intermedia exchange of chloromethane between the other compartments was insignificant. Similar results were obtained when the chloromethane emission was to the soil compartment. Because of the relatively high vapor pressure of chloromethane, only 3.6% of the total chemical mass remained in the soil compartment whereas 96% was found in the air compartment. Hence, the primary removal process from soil was volatilization and the primary removal process from the system was advection in air. Local persistence was about 4 days, regardless if the chloromethane emission was to the air or soil compartment.

In contrast to that observed for emission to the air and soil compartments, emission of chloromethane to the water compartment resulted in only about 20% the total chemical mass residing in the air, whereas about 80% remained in the water. Intermedia exchange of chloromethane with the other compartments (e.g., soil and sediment) was insignificant. The dominant removal mechanism of chloromethane from the system was advection in air, which was equal to the rate of volatilization from the water compartment. However, advection and degradation in water also removed significant amounts (28% and 2.4%, respectively) of the total chemical mass. Nonetheless, local persistence was about 15 days.

The above results indicate that the environmental compartments of concern, based on emission of chloromethane, are air and water. Insignificant amounts of chloromethane are expected to be found in the soil or sediment compartments, regardless of source of entry to the environment. Since chloromethane is a gas, most industrial releases are expected to be directly to the air compartment. In the United States, it is estimated that about $1.346 \times 10^6$ kg ($2.97 \times 10^6$ pounds) of chloromethane are annually released to the environment (about 240 kg/h) from industrial activities (Section 1.9). Of this amount, about 89% is released directly to air, 0.06% is released to water, and about 11% is added to soil or injected underground. These emission rates (137 kg/hr for air, 0.09 kg/hr for water, and 16.7 kg/hr for soil) were entered into the Level III simulation to obtain an overall assessment of the impact of industrial releases of chloromethane to the environment. Results of the simulation suggest that the total, steady state mass of chloromethane in the environment from industrial sources is about $1.53 \times 10^4$ kg. Greater than 99% of the total, steady state mass is expected to reside in the air compartment and about 0.4% in each of the soil and water compartments. The local persistence is expected to be about 4 days with advection in air accounting for >99% of the chloromethane removed from the local system. Less than 1% is expected to be lost through degradation processes. Predicted concentrations in the environmental compartments, based on industrial rates of emissions and Level III fugacity modeling, are significantly less than reported concentrations in Section 3.2;

| | |
|---|---|
| Air | 1000-1500 ng/m$^3$ |
| Water | <222 ng/L |
| Soil or Sediment | <5,000 ng/kg |

Indicating that industrial sources are insignificant with respect to natural sources.

### 3.3.3 ADDITIONAL REMARKS

Type: Global Warming Potential

Remarks: The global warming potential of the test substance is similar to that of methane. However, the current industrial emission rates of the test substance are too low to contribute meaningly to atmospheric greenhouse heating effects.

Reference: Grossman et al. 1997.

Type: Ozone Depletion Potential
Remarks: The stratospheric steady-state ozone depletion potential (ODP) of the test substance has been determined to be 0.02 relative to CFC 11 (ODP=1.0)
References: Solomaon et al. 1992; WMO 1994; Fabian et al. 1996.

Type: Source
Remarks: Greater than 99% of ambient air concentrations of the test substance originate from natural sources, primarily from the ocean.
References: USEPA Toxic Release Inventory 1998; Fabian et al. 1986; Rasmussen et al. 1982; Singh et al. 1979; Yung et al. 1975.

## 3.4 MODE OF DEGRADATION IN ACTUAL USE

Remarks: "The dominant tropospheric removal mechanism for chloromethane is generally regarded to be hydrogen abstraction by hydroxyl radical (Dilling et al., 1982; Fabian and Goemer, 1986; Gusten et al., 1984; Lovelock, 1975; Rasmussen et al., 1980; Robbins, 1976; Singh et al., 1979)."
Reference: As cited in ATSDR, 1990.

Remarks: "In water, chloromethane can degrade either by hydrolysis or biodegradation. Although few data are available on the biodegradation of chloromethane in water, neither hydrolysis nor biodegradation in surface water appears to be rapid when compared with volatilization."
Reference: As cited in ATSDR, 1990.

Remarks: "No information concerning soil transformation and degradation was located in the literature. In lower soil horizons, hydrolysis may be a significant process since no other removal mechanism has been identified."
Reference: As cited in ATSDR, 1990.

## 3.5 BIODEGRADATION

Type: aerobic
Inoculum: activated sludge
Concentration of the chemical: 3.79 mg/l related to test substance
Degradation: = 1 % after 28 day
Results: under test condition no biodegradation observed
Method: Other: Closed bottle test
GLP: unknown
Test substance: As prescribed, sections 1.1-1.4
Reference: CSCL, 1992.

Type: aerobic
Inoculum: activated sludge
Concentration of the chemical: 19.2 mg/l related to test substance
Degradation: = 0 % after 28 day
Results: under test condition no biodegradation observed
Method: Other: Kagaku Bousaisisin
GLP: unknown
Test substance: As prescribed, sections 1.1-1.4
Reference: CSCL, 1992.

Type: aerobic
GLP: unknown
Test substance: As prescribed in 1.1-1.4

| | |
|---|---|
| Remarks: | Degradation; rate is not increased by addition of formaldehyde as external source of carbon. Whole cell suspension with and without 4 mmol/l formaldehyde as a source of carbon; Species: *Methylcoccus capsulatus.* |
| Reference: | Stirling and Dalton, 1979. |

| | |
|---|---|
| Type: | aerobic |
| Media: | water |
| Method: | U.S. EPA Model, 2000 |
| Results: | The SAR models available in the biodegradation probability program BIOWIN® (USEPA 2000) predict that chloromethane will biodegrade fast and have an ultimate biodegradation timeframe of weeks. The estimation is based on molecular structure using the fragment constants. |
| Remarks: | Based on the BIOWIN® environmental model that predicts the behaviour of a chemical in surface waters. |
| Reference: | U.S. EPA 2000 |

### 3.6 $BOD_5$, COD OR RATIO $BOD_5$/COD

### 3.7 BIOACCUMULATION

| | |
|---|---|
| Type: | Log BCF |
| Results: | 0.46 (estimated) |
| Reference: | PCGEMS (equ 5-5) as cited in ATSDR, 1990. |

| | |
|---|---|
| Type: | Log BCF |
| Media: | water/fish |
| Method: | Estimation using BCFWIN (ver. 2.14) |
| Results: | 0.50 (estimated). |
| Remarks: | The estimation is based on molecular structure (SMILES: ClC) and a Log $K_{ow}$ of 0.91. The model was used as received from EPA. |
| Reference: | U. S. EPA 2000 |

### 3.8 ADDITIONAL REMARKS

#### A. SEWAGE TREATMENT

| | |
|---|---|
| Type: | aerobic |
| Media: | water |
| Method: | U.S. EPA Model, 2000 |
| Results: | Based on the fugacity model STPWIN® (USEPA 2000), 77% of the chloromethane that enters the model treatment facility is volatilized directly to the air and 22% released with the final effluent. The above values were estimated based on the following input values entered in the model;<br>Solubility: 5325 mg/l<br>Vapor Pressure: 4313 mm Hg @25°C<br>Henry's Law Constant: 0.00882 atm-$m^3$/mole<br>Log $P_{ow}$: 0.91<br>Temp: 25°C<br>All other parameters used the model defaults. |
| Remarks: | Based on the STPWIN® environmental model that predicts the behaviour of a chemical in surface waters. |
| Reference: | U.S. EPA 2000 |

#### B. OTHER

# 4. ECOTOXICITY

## 4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type of test: SAR calculation
Species: freshwater fish
Exposure period: 96 hour (acute toxicity)
Results: 96-h $LC_{50}$ = 396 mg/l
Method: calculated using ECOSAR (ver. 0.99g)
GLP: no
Test substance: As prescribed, sections 1.1-1.4
Remarks: The model ECOSAR was used as received from EPA. The estimation was based on molecular structure and the following input data:
SMILES: ClC
log Kow: 0.91
melting point: -97.7°C
water solubility: 5325 mg/L
Reference: U. S. EPA 2000

Type of test: SAR calculation
Species: saltwater fish
Exposure period: 96 hour (acute toxicity)
Results: 96-h $LC_{50}$ = 54 mg/l
Method: calculated using ECOSAR (ver. 0.99g)
GLP: no
Test substance: As prescribed, sections 1.1-1.4
Remarks: The model ECOSAR was used as received from EPA. The estimation was based on molecular structure and the following input data:
SMILES: ClC
log Kow: 0.91
melting point: -97.7°C
water solubility: 5325 mg/L
Reference: U. S. EPA 2000$$$

Type of test: static
Species: *Lepomis macrochirus*
Exposure period: 96 hour
Results: $LC_{50\ (96h)}$ = 550 mg/l
Method: other
GLP: unknown
Test substance: As prescribed, sections 1.1-1.4
Remarks: Bioassay in fresh water at 23°C, mild aeration applied after 24 hr.
Remarks: Handbook data. Results of study should be evaluated with caution because optimum test conditions (i.e., measured concentrations, closed system, flow-through conditions) were not met and the reported results may underestimate the toxicity of the test substance. Nonetheless, reported results are comparable to the 96-h $LC_{50}$ of 396 mg/l predicted by ECOSAR.
Reference: Verschueren, 1983 (As cited in HSDB, 1998).

Type of test: static
Species: *Menidia beryllina*
Exposure period: 96 hour
Results: $LC_{50\ (96h)}$ = 270 mg/l
Method: other
GLP: unknown
Test substance: As prescribed, sections 1.1-1.4
Remarks: Bioassay in synthetic seawater at 23°C, mild aeration applied after 24 hr.

Remarks: Handbook data. Results of study should be evaluated with caution because optimum test conditions (i.e., measured concentrations, closed system, flow-through conditions) were not met and the reported results may underestimate the toxicity of the test substance. Nonetheless, reported results are comparable to the 96-h $LC_{50}$ of 396 mg/l predicted by ECOSAR.

Reference: Verschueren, 1983 (As cited in HSDB, 1998).

Type of test: static
Species: *Lepomis macrochirus*
Exposure period: 96 hour
Results: (median tolerance limit) $TL_{50}$ (96h) = 900 mg/l
Method: Tests were conducted in reconstituted deionized water at five concentration levels with 10 fish per exposure. After a 24-h acclimation period, the test systems were exposed by bubbling the gaseous test materials through air stones in the reconstituted water. Gas chromatography was used to measure concentrations of the test materials in water samples collected at 1, 6, 24, 48, 72, and 96 hours after bubbling. Dissolved oxygen and pH were also determined throughout the studies.
GLP: unknown
Test substance: As prescribed, sections 1.1-1.4
Remarks: The following numbers of survivors for the five concentrations tested were reported as follows at 1-6, 24, 48, 72 and 96 hours:
At 330-ppm: 10, 10, 10, 10, 10
At 1019-ppm: 10, 6, 4, 3, 3
At 1242-ppm: 10, 2, 2, 1, 1
At 1884-ppm: 10, 0, 0, 0, 0
At 2284-ppm: 10, 0, 0, 0, 0
The percent survival was 100%, 30%, 10%, 0%, and 0% at 330-, 1019-, 1242-, 1884- and 2284-ppm, respectively.
Remarks: Results of study should be evaluated with caution because optimum test conditions (i.e., closed system, flow-through conditions) were not met and the reported results may underestimate the toxicity of the test substance. Reported results are considerably greater than the 96-h $LC_{50}$ of 396 mg/l predicted by ECOSAR.
Reference: Hamlin et al. (1971)

Type of test: static
Species: *Micropterus salmoides*
Exposure period: 96 hour
Results: (median tolerance limit) $TL_{50}$ (96h) = 1500 mg/l
Method: Tests were conducted in reconstituted deionized water at five concentration levels with 10 fish per exposure. After a 24-h acclimation period, the test systems were exposed by bubbling the gaseous test materials through air stones in the reconstituted water. Gas chromatography was used to measure concentrations of the test materials in water samples collected at 1, 6, 24, 48, 72, and 96 hours after bubbling. Dissolved oxygen and pH were also determined throughout the studies.
GLP: unknown
Test substance: As prescribed, sections 1.1-1.4
Remarks: The following numbers of survivors for the five concentrations tested were reported as follows at 1-6, 24, 48, 72 and 96 hours:
At 890-ppm: 10, 10, 10, 10, 9
At 1090-ppm: 10, 10, 10, 10, 10
At 1158-ppm: 10, 10, 10, 10, 9
At 1591-ppm: 10, 10, 10, 8, 4
At 2075-ppm: 10, 4, 0, 0, 0

The percent survival was 90%, 100%, 90%, 40%, and 0% at 890-, 1090-, 1158-, 1591-, and 2075-ppm, respectively.

Remarks: Results of study should be evaluated with caution because optimum test conditions (i.e., closed system, flow-through conditions) were not met and the reported results may underestimate the toxicity of the test substance. Reported results are considerably greater than the 96-h $LC_{50}$ of 396 mg/l predicted by ECOSAR.

Reference: Hamlin et al. (1971)

## 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

### A. DAPHNIA -

Type of test: static **[ ]**; semi-static **[x]**; flow-through **[ ]**; other *(e.g. field test)* **[ ]**; open-system **[ ]**; closed-system **[x]**

Species: *Daphnia magna*

Exposure period: 48 hours

Results: $EC_{50}$ (24h) = 360 mg/l
$EC_{50}$ (48h) = 200 mg/l
$EC_{xx}$ (..h) = . . . . . . . . mg/l
NOEC = 53 mg/l

Analytical monitoring: Yes **[ ]** No **[ x ]** ? **[ ]**

Method: OCED Guideline No. 202

GLP: Yes **[x ]** No **[ ]** ? **[ ]**

Test substance: chloromethane gas, lot No. 09512HI, CAS No. 74-87-3, received from Aldrich Chemical Company on 21 August 2001 with specified purity of >99.5%.

Remarks: Definitive testing was conducted to determine the 48-hour $EC_{50}$ based on nominal concentrations in a closed (no head-space) system under static-renewal conditions. Concentrations tested included 63, 130, 250, 500, 1000 and 2000 mg/L (nominal). Nominal concentrations were used because an acceptable analytical method could not be validated. The efforts of Springborn Smithers Laboratories to develop and validate an analytical method to accurately quantify levels of chloromethane in exposure solutions proved difficult and were ultimately unsuccessful. Several conditions that contributed to the lack of success were the relatively high concentrations of chloromethane in the exposure solutions (50 to 2000 mg/L) and the relatively large amount of sample handling required to prepare samples for analysis.

Reference: Springborn Smithers Laboratories, Study Number 13776.6101, 2002

Type of test: SAR calculation

Species: *Daphnia magna*

Exposure period: 48 hour (acute toxicity)

Results: 48-h $LC_{50}$ = 394 mg/l

Method: calculated using ECOSAR (ver. 0.99g)

GLP: no

Test substance: As prescribed, sections 1.1-1.4

Remarks: The model ECOSAR was used as received from EPA. The estimation was based on molecular structure and the following input data:
SMILES: ClC
log Kow: 0.91
melting point: -97.7°C
water solubility: 5325 mg/L

Reference: U. S. EPA 2000

### B. OTHER

Type of test: SAR calculation

Species: *Mysidopsis bahia* (Mysid shrimp)

| | |
|---|---|
| Exposure period: | 96 hour (acute toxicity) |
| Results: | 96-h $LC_{50}$ = 249 mg/l |
| Method: | calculated using ECOSAR (ver. 0.99g) |
| GLP: | no |
| Test substance: | As prescribed, sections 1.1-1.4 |
| Remarks: | The model ECOSAR was used as received from EPA. The estimation was based on molecular structure and the following input data:<br>SMILES: ClC<br>log Kow: 0.91<br>melting point: -97.7°C<br>water solubility: 5325 mg/L |
| Reference: | U. S. EPA 2000 |

**B. OTHER AQUATIC ORGANISMS**

**4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae**

| | |
|---|---|
| Species: | *Scenedemus quadricauda* |
| Endpoint: | Growth rate |
| Exposure period: | 7 day |
| Results: | SG = 1450 mg/l |
| Analytical monitoring: | no |
| Method: | other: Cell multiplication inhibition test |
| GLP: | unknown |
| Test substance: | As prescribed, sections 1.1-1.4 |
| Remarks: | Toxicity threshold concentration = 1450 mg/l |
| Remarks: | Handbook data. Results of study should be evaluated with caution because optimum test conditions were not met and algae may not have been in exponential growth phase through out the test period. Reported results are considerably greater than the 96-h $EC_{50}$ of 231 mg/l predicted by ECOSAR. |
| Reference: | Verschueren, 1983 (As cited in HSDB, 1998). |

| | |
|---|---|
| Species: | *Microcystis aeruginosa* |
| Endpoint: | Growth rate |
| Exposure: | 7 day |
| Results: | SG = 550 mg/l |
| Analytical monitoring: | no |
| Method: | other: Cell multiplication inhibition test |
| GLP: | unknown |
| Test substance: | As prescribed, sections 1.1-1.4 |
| Remarks: | Toxicity threshold concentration = 550 mg/l |
| Remarks: | Handbook data. Results of study should be evaluated with caution because optimum test conditions were not met and algae may not have been in exponential growth phase through out the test period. Reported results are considerably greater than the 96-h $EC_{50}$ of 231 mg/l predicted by ECOSAR. |
| Reference: | Verschueren, 1983 (As cited in HSDB, 1998). |

| | |
|---|---|
| Type of test: | SAR calculation |
| Species: | freshwater green algae |
| Exposure period: | 96 hour (acute toxicity) |
| Results: | 96-h $EC_{50}$ = 231 mg/l |
| Method: | calculated using ECOSAR (ver. 0.99g) |
| GLP: | no |
| Test substance: | As prescribed, sections 1.1-1.4 |
| Remarks: | The model ECOSAR was used as received from EPA. The estimation was based on molecular structure and the following input data:<br>SMILES: ClC<br>log Kow: 0.91 |

melting point: -97.7°C
water solubility: 5325 mg/L

Reference: U. S. EPA 2000

## 4.4 TOXICITY TO BACTERIA

Type: Aquatic
Species: *Entosiphon sulcatum*
Exposure Period: 72 hour
Results: SG > 8000 mg/l
Analytical monitoring: no
Method: other: Cell multiplication inhibition test
GLP: unknown
Test substance: As prescribed, sections 1.1-1.4
Remarks: Toxicity threshold concentration = 8000 mg/l
Remarks: Handbook data
Reference: Verschueren, 1983 (As cited in HSDB, 1998).

Type: Aquatic
Species: *Pseudomonas putida*
Exposure Period: 24 hour
Results: SG = 500 mg/l
Analytical monitoring: no
Method: other: Cell multiplication inhibition test
GLP: unknown
Test substance: As prescribed, sections 1.1-1.4
Remarks: Toxicity threshold concentration = 500 mg/l
Remarks: Handbook data
Reference: Verschueren, 1983 (As cited in HSDB, 1998).

Type: Aquatic
Species: Methanogene Bakterien
Exposure Period: 48 hour
Results: $IC_{50}$ (48 h) = 50 mg/l
Method: other: Owen, W.F., Wat. Res. 13:485, 1979.
GLP: unknown
Test substance: As prescribed, sections 1.1-1.4
Reference: Blum and Speece, 1991a.

Type: Aquatic
Species: Methanogene Bakterien
Exposure Period: 1 day
Results: $EC_{50}$ (24 h) = approximately 39 mg/l
Method: other
GLP: unknown
Test substance: As prescribed, sections 1.1-1.4
Reference: Blum and Speece, 1991b.

Type: Aquatic
Species: Nitrobacter
Exposure Period: 1 day (25°C, pH 9.1)
Results: $IC_{50}$ (24 h) = 2010 mg/l (Inhibition of $NO_2$-N production)
Method: A *Nitrobacter*-enriched culture was established in a batch-fed 20L reactor with 10L of actively nitrifying activated sludge as seed. The daily feed included NaNO2 and KNO2 as the substrate, NH4HCO3 and NaHCO3 as both carbon source and buffer, with 20 other chemicals as the inorganic element supply. NH4 served as a nitrogen source for cell synthesis.

After the *Nitrobacter* concentration in the reactor had reached an equilibrium level (approximately 250 mg/L VSS), the toxicity bioassays began.

A serum bottle technique was used in the bioassay study. The technique was designed to be as similar as possible to those used for bacteria under study by Blum and Speece (1991) so that the results would be comparable. The 24-hr assay time was used. The initial $NO_2$-N concentration was determined by identifying the substrate concentration, which was not inhibitory but was not so low as to be a limiting factor during a 24-hr period of bio-oxidation. The initial substrate concentration was increased twice during the data gathering, from 500 to 700 mg/L, then to 1000 mg/L, because the final substrate concentration in the control bottles became too low.

A 50-ml sample volume, which consisted of the enriched *Nitrobacter* culture(46 ml), substrate (4 ml) , and the toxic chemical (in ul range), was placed in a 150-ml serum bottle. The bottle was sealed with a rubber stopper. The oxygen supply for bio-oxidation was 30 ml of pure $O_2$ injected into the bottle by a syringe. The bottles were then placed on a shaker to provide adequate oxygen transfer.

After the 24-hr assay time, the sample was centrifuged to remove the microorganisms. The $NO_2$-N concentration in the supernatant was determined by a colorimetric method, using NitriVer 2 powder pillows by Hach Company, in which nitrite reacted to form a pink azo dye. The intensity of the color was directly proportional to the concentration of nitrite in the sample. A total of 36 bottles was used for each experiment. Usually, four bottles were controls, in which no toxic chemical was added. For each chemical, four to five samples covering a range of toxicant concentrations were tested in each experiment. The $IC_{50}$ value of each chemical was obtained by interpolation of a plot of percent inhibition versus concentration. The values for three to four replicate experiments were averaged. The observed $IC_{50}$ value of 3224 ml/L for methyl chloride was then corrected for volatilization. The $IC_{50}$ value corrected for volatilization was determined to be 2010 mg/L.

GLP: unknown
Test substance: As prescribed, sections 1.1-1.4
Reference: Tang et al., 1992.

## 4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

### 4.5.1 CHRONIC TOXICITY TO FISH

### 4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES (e.g., DAPHNIA REPRODUCTION)

## 4.6 TOXICITY TO TERRESTRIAL ORGANISMS

### 4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

### 4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Species: Tomatoes (*Lycopersicum esculentum* Miller); bush bean (*Phaseolus vulgaris* L.), nasturtium (*Tropaeolum majus* L.), sugar beet (*Beta vulgaris* L.), soya bean (*Glycine maxima* (L.) Merill) and wheat (*Triticum aestivum* L.)
Endpoint: Visible symptoms, Photosynthesis and Transpiration

Exposure period: 3-hour exposure in gas phase
Results: Visible symptoms: 5-10 $g/m^3$
Photosynthesis: > 5 $g/m^3$
Transpiration: > 5 $g/m^3$
Method: other
GLP: unknown
Test substance: As prescribed, sections 1.1-1.4
Reference: Christ, 1996

### 4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

### 4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

### 4.8 BIOTRANSFORMATION AND KINETICS

Type: Animal
Results: Absorption: Since chloromethane is a gas, unless it is under pressure, inhalation is the only significant route of toxic exposure. Following intravenous injection into the bloodstream and injection into the peritoneal cavity, only a small amount is excreted in the breath. However, as occurs following inhalation exposure, a large portion is quickly conjugated and excreted or subsequently metabolized. According to an old report, 80% disappeared from the blood almost immediately following IV injection and an additional 10% in the first hour. Pulmonary excretion of unchanged chloromethane accounted for only 5% of the total.
References: Sperling et al., 1950.

Type: Animal
Results: Absorption: Soucek (1962) reported 70% of subcutaneously injected chloromethane was “metabolically changed” in 20-30 minutes. Twenty-seven percent was exhaled unchanged by rats in 120-135 minutes.
References: Soucek, 1962 (through translation of abstract).

Type: Animal
Results: Absorption: When studied in rats and dogs, steady-state was quickly reached when the animals inhaled 50 or 1000 ppm, and the steady-state concentrations in the blood were proportional to the inhaled concentrations (Landry et al., 1983). The first measurements were made in rats and dogs after fifty minutes of exposure and by that time blood concentrations were already as high as achieved at the end of six hours. Blood was analyzed periodically following six hours of exposure and "rapid, biphasic, non dose-dependent decline in blood concentrations" was found. For rats the alpha-phase half time was about 4 minutes and the beta-phase half time about 15 minutes following both 50 and 1000-ppm exposures. In two dogs exposed to 50 ppm, alpha-phase half times of 8.1 and 6.4 minutes were determined while at 1000-ppm alpha-phase half-times of 10.4 and 8.3 minutes were determined. Two dogs exposed to 50 ppm had beta-phase half times of 35.4 and 51 minutes, while at 1000-ppm beta-phase half times were 40 and 27 minutes. Equilibrium blood concentrations were similar in rats and dogs.
References: Landry et al., 1983.

Type: Other
Remark: Distribution: Little data exist regarding the concentration of chloromethane *per se* in the organs of animals or humans. While it is probably safe to assume the bloodstream carries it to all organs and a short-lived equilibrium is reached in each, the high volatility and rapid metabolism of

chloromethane precluded storage in the tissues for more than brief periods of time. However, metabolic products may be found in proportion to the rate of metabolism in each organ due to incorporation of the one-carbon fragments which occurs by normal anabolic processes.

Type: Animal

Results: Metabolism: A Russian report (Polonskaya, 1974) available only as an abstract, describes the effects of cysteine on chloromethane metabolism. Male rats were administered 300 or 750 mg/kg of cysteine and 30 minutes later received 190 mg/kg of chloromethane. The route of treatment is not specified in the abstract. Controls received no cysteine. After 1, 4, 24 or 72 hours, glutamic-alaninetransaminase (ALT) and glutamic-asparagine-transaminase (AST) were measured in blood serum, liver, kidneys and brains. The author concluded that acute chloromethane poisoning altered ALT and AST activity and that administration of cysteine prior to chloromethane prevented disruption of AST and ALT activity. A similar report by Nozdrachev (1974) described effects of chloromethane on glycolytic enzymes and the prophylactic effect of cysteine in male rats. The author concluded that chloromethane increased aldolase activity and decreased phosphoglucomutase activity. Cysteine apparently reduced the effect on aldolase but not on phosphoglucomutase activity. While of interest, these two papers do not appear as useful as later studies discussed subsequently.

References: Polonskaya, 1974 (abstract only); Nozdrachev, 1974.

Type: Animal

Results: Metabolism: Kornbrust et al. (1982a) exposed rats by inhalation to $^{14}C$-labeled chloromethane in order to assess incorporation into macromolecules. Rats were given 6-hour exposures to either 500 or 1500 ppm of the gas. Radioactivity, which accumulated in lipid, RNA, DNA, and protein isolated from lung, liver, kidney, testes, brain, muscle, and intestine, was associated with acid- insoluble material. Most of the activity was in labeled protein and lipid, although the concentration of $^{14}C$ was found to be over 10-fold higher in nucleic acids when compared on a molar basis of nucleotide to amino acid residue. Radioactivity in purine bases was not due to methylation. This is consistent with rapid metabolism to formate discussed subsequently.

Kornbrust et al. showed further that pretreatment of the rats with cycloheximide reduced the amount of radioactivity associated with tissue protein by 42-58% indicating that most of the incorporation was due to normal protein synthesis. Pretreatment with methotrexate, which inhibits folate-dependent formate metabolism, inhibited the incorporation of $^{14}CH_3Cl$ into lipid, acid-insoluble material, RNA, and DNA by 47, 64, 65 and 93%, respectively, and pretreatment with methanol inhibited $^{14}CH_3Cl$ uptake by acid-insoluble material by 66%. These investigators concluded that these findings were consistent with incorporation due to the radioactivity entering the one-carbon pool. However, since ethanol, 4-methylpyrazole and 3-amino-1,2,4-triazole failed to inhibit $^{14}CH_3Cl$ incorporation, the chloromethane did not appear to be metabolized to methanol *per se*. Methanol itself inhibited $CO_2$ evolution indicating metabolism via single-carbon pathways is of major quantitative significance, and supports the conclusion that direct alkylation is negligible.

References: Kornbrust et al., 1982a and b.

Type: Animal

Results: Metabolism: Similar results were obtained by Peter et al. (1985) who extended the work of Kornbrust et al. by using $^{14}CH_3Cl$ of high radioactivity and by using Fischer 344 rats and $B_6C_3F_1$ mice of both sexes. Based on body weight, mice were found to metabolize $^{14}C$-labeled chloromethane 2.5 to 3.5 times more rapidly than rats. It was shown that although there was considerable incorporation of $^{14}C$ activity in DNA and RNA, it was not due to methylation but was due rather to incorporation of one-carbon metabolic fragments. Because tumors of the kidneys of male mice were the only tumors increased in the 1981 lifetime studies in rats and mice, a search was made for radioactivity in possible DNA alkylation products. Despite maximizing sensitivity by pooling samples, activity was found only in the natural purines (adenine and guanine) with no indication of the methylation products (7-N-methylguanine or $0^6$-methylguanine). Non-alkylating incorporation of radioactivity was particularly high in the DNA of mouse kidney, "suggesting a high turnover to $C_1$ bodies (formaldehyde, formate) in this tissue." In rats, which did not develop kidney tumors, more radioactivity was found in hepatic DNA than in renal DNA.

References: Peter et al., 1985.

Type: Animal

Results: "The biochemical effects of chloromethane were investigated in tissues of F-344 rats and $B_6C_3F_1$ mice (both sexes). Activities of GST were 2-3 times higher in livers of male $B_6C_3F_1$ mice, compared with those of female mice, and with rats of both sexes. In kidneys GST activities of (male) mice were about 7 times lower than those found in livers. The activity of FDH was higher in livers of mice (both sexes) than in those of rats. No obvious sex difference was found in livers of rats and mice with respect to FDH. In kidneys, however, (minor) differences in FDH activities occurred between male and female $B_6C_3F_1$ mice (4.7 vs. 3.1 nmol/min per mg). Sex differences of FDH activity in kidneys were not observed in F-344 rats. The microsomal transformation (by cytochrome P-450) of chloromethane and S-methyl-L-cysteine to formaldehyde in tissues of $B_6C_3F_1$ mice occurred preferentially in the liver. More formaldehyde was produced in liver microsomes of male, compared to those of female mice. Kidney microsomes metabolized chloromethane to formaldehyde much less than liver microsomes. After single exposure of mice of both sexes to 1000-ppm chloromethane no elevation in formaldehyde concentrations was observed in livers and kidneys *ex vivo*. The determination of DNA lesions, using the alkaline elution technique, revealed no DNA-protein crosslinks in kidneys of male $B_6C_3F_1$ mice after exposure to chloromethane (1000 ppm, 6 h day-1, 4 days) and gave only minor evidence of single-strand breaks. Lipid peroxidation (production of TBA reactive material), induced by single exposure to chloromethane (1000 ppm, 6 h), was very pronounced in livers of male and female mice. Smaller increases in peroxidation were observed in the kidneys of exposed mice. The theory that renal tumors observed in male mice after chronic exposure of the test animals to high (1000 ppm) concentrations of chloromethane, are evoked by intermediates and in situ produced formaldehyde is proven unlikely by our results."

References: Jäger et al., 1988.

Type: Animal

Results: Metabolism: Kornbrust and Bus (1983) proposed the following scheme for metabolism which seems consistent with known metabolic products, incorporation of radioactivity, and the mode of toxic action of chloromethane.

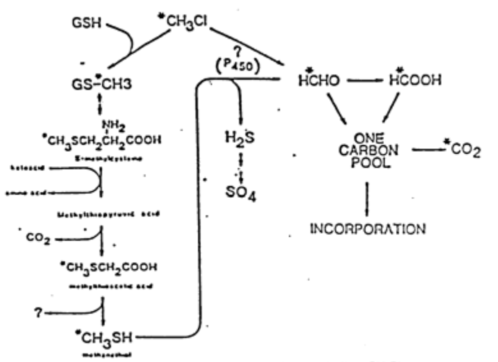

Fig. 4-1 Scheme proposed for metabolism $CH_3Cl$ by Kornbrust and Bus, 1983.

The following is from their discussion of the figure:

"The metabolic scheme depicted accounts for the present as well as previous findings on the metabolism of chloromethane. The reaction of $CH_3Cl$ with glutathione was previously demonstrated both *in vitro* (Redford-Ellis and Gowenlock, 1971a,b) and *in vivo* (Dodd et al., 1982). The reaction appears to be primarily enzyme catalyzed, probably by GSH-transferase, as has been demonstrated for methyl iodide (Johnson, 1966). The product of this reaction, methylglutathione, may be metabolized by transpeptidases to S-methylcysteine, which has been detected in the urine of rats (Landry et al., 1983) and humans (van Doorn et al., 1980) exposed to $CH_3Cl$."

References: Kornbrust and Bus, 1983.

Type: Animal

Results: Metabolism: Landry et al. (1983) showed S-methyl cysteine was not a sensitive indicator of chloromethane exposure in Beagle dogs but that this metabolite did occur in rats. Another species difference has been observed in the stability of chloromethane in blood of rats and humans. Landry et al. found that when using headspace analysis for volatile $CH_3Cl$, rat blood samples were stable for several hours, whereas human blood had to be immediately heat treated at 100°C for one minute to prevent loss apparently due to enzymatic reactions.

References: Landry et al., 1983.

Type: Animal

Results: Metabolism: The major pathway for chloromethane metabolism involves conjugation with reduced glutathione (Dodd et al., 1982; Kornbrust and Bus, 1983) with ultimate transformation to formate and $CO_2$. This conjugation step may lead to the toxic action of chloromethane. According to Working and Bus 1980, chloromethane is a potent glutathione-depleting agent in all target tissues (Dodd et al., 1982; Chapin et al., 1984). Under the conditions of reduced glutathione, 5HPETE (5-hydroperoxeicosotetraenoic acid), the immediate precursor of four major leukotrienes, accumulates in the tissue. Upon cessation of exposure, chloromethane is rapidly eliminated and glutathione concentrations in tissue rapidly return to normal (Dodd et al., 1982). When this occurs, 5-HPETE is rapidly converted to glutathione-derived leukotrienes ($LTC_4$, $LTD_4$, and $LTE_4$). These three leukotrienes are potent vasoconstrictors resulting in increased capillary permeability and tissue edema.

Hence, this burst of synthesis of vasoactive leukotrienes may result in edematous and anoxic episodes in the tissues with resultant tissue damage.

This postulated mode of toxic action is strongly supported by studies with Burroughs-Welcome test compound, BW755C, which has been shown to have antidotal and prophylactic effects when used in conjunction with chloromethane. BW755C functions as a strong anti-inflammatory agent by inhibiting the synthesis of prostaglandins and leukotrienes. Figure 4-2, taken from Working and Bus, illustrates the postulated mechanism.

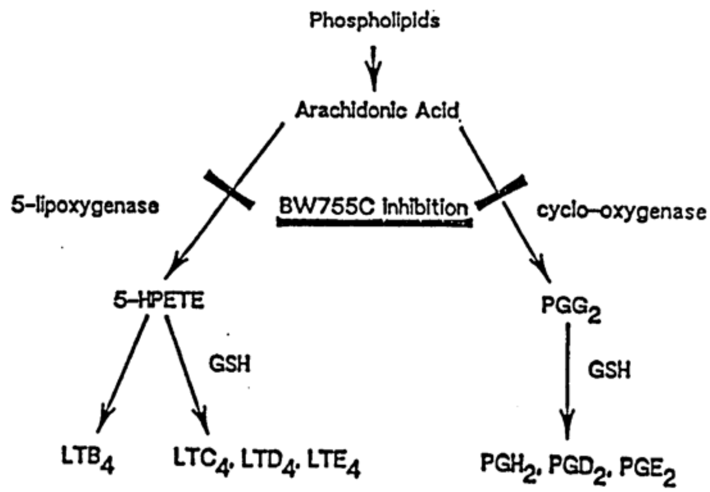


**Fig. 4-2. Biosynthetic pathways for leukotrienes (LT) and prostaglandins (PG). BW755C has dual action and inhibits the lipoxygenase enzyme of the LT pathway and the cyclo-oxygenase enzyme of the PG pathway, where indicated by the solid bar. (Working and Bus, 1986)**

Boroughs-Welcome Compound, BW755C, inhibits 5-lipoxygenase and cyclo-oxygenase activity preventing production of 5-HPETE and $PGG_2$ from arachidonic acid. Thus when BW755C is administered with chloromethane, 5-HPETE and $PGG_2$ do not accumulate and are not available to react with glutathione to form leukotrienes $LTC_4$, $LTD_4$, and $LTE_4$ or prostaglandins $PGH_2$, $PGD_2$, or $PGE_2$.

It has been shown that the toxic action of chloromethane on sperm and the subsequent dominant lethal effect, as well as the effect on the liver, kidneys, and brain, is the likely result of an inflammatory response. All of these actions are also markedly reduced by BW755C.

References: Working and Bus, 1986.

Type: Animal

Results: Metabolism: The effect of chloramine on formic-acid metabolism was studied in mice. The impetus for the study was a patient who developed metabolic acidosis and permanent blindness as a result of simultaneous exposure to chloromethane and chloramine. Examination of the case suggested that chloromethane toxicity could be potentiated by chloramine and that the increased toxicity would be related to an effect on formic-acid metabolism. The potentiating mechanism was investigated by exposing mice to chloromethane followed by ammonia chloramine, and then the level of formate in urine samples was measured with an enzyme coupling method to detect disturbance of formate metabolism. Mice dosed with 0.05 mL 1.0 mM chloramine after chloromethane exposure excreted a significantly larger amount of urinary formate than mice treated with only chloromethane. There was no difference in urinary formate levels between mice treated with only 0.05 mL 1.0 mM chloramine and those given only the vehicle (0.1 M phosphate buffer pH 6.0) for chloramine. The underlying biochemical mechanism of deterioration of formate metabolism was found to be the inhibition of the enzyme, N10-formyl tetrahydrofolate (N10-f-THF) dehydrogenase by 0.56-3.35 uM chloramine in the *in vitro* experiment using the purified enzyme. Positive control mice, given orally 0.1 mL 10% methanol in 0.1 M phosphate buffer (pH 6.0) excreted the same amount of urinary formate as those receiving 0.05 mL 1.0 mM chloramine after methanol administration. This was ascribed to the inhibitory effect of chloramine on formaldehyde dehydrogenase and depletion of substrate for further metabolism. The inhibition of the enzyme by chloramine (2.7-100.8 uM) was confirmed by *in vitro* experiments, using the purified enzyme, formaldehyde dehydrogenase (FDH). Therefore, the authors concluded that the toxicity of chloromethane plus ammonium chloramine is due to an inhibitory effect on FDH activity

Reference: Minami et al., 1993. (As cited in Toxline, 1998).

## 4.9 ADDITIONAL REMARKS

# 5. TOXICITY

## 5.1 ACUTE TOXICITY

### 5.1.1 ACUTE ORAL TOXICITY

| | |
|---|---|
| Type: | $LD_{50}$ |
| Species/strain: | rat |
| Value: | 1800 mg/kg b.w. |
| Method: | other |
| GLP: | unknown |
| Test substance: | As prescribed, sections 1.1 to 1.4 |
| Reference: | Prehled Prumyslove Toxikol Org Latky, 1986 (as cited in RTECS, 1998). |

### 5.1.2 ACUTE INHALATION TOXICITY

| | |
|---|---|
| Type: | $LC_{50}$ |
| Species/strain: | Rat |
| Exposure time: | 4 hour |
| Value: | 5300 mg/m$^3$ |
| Method: | other |
| GLP: | unknown |
| Test substance: | As prescribed, sections 1.1 to 1.4 |
| Reference: | Toxic Param Ind Tox Chem Under Single Exposure, 1982 (as cited in RTECS, 1998). |

| | |
|---|---|
| Type: | $LC_{50}$ |
| Species/strain: | Mouse |
| Exposure time: | 7 hour |
| Value: | 6300 mg/m$^3$ |
| Method: | other |
| GLP: | unknown |
| Test substance: | As prescribed, sections 1.1 to 1.4 |
| Reference: | von Oettingen et al., 1950 (as cited in IARC Monographs, 1986). |

| | |
|---|---|
| Type: | $LC_{50}$ |
| Species/strain: | Mouse |
| Exposure time: | 6 hour |
| Value: | 2200 ppm (4400 mg/m$^3$) |
| Method: | Male $B_6C_3F_1$ mice were exposed to varying concentrations of chloromethane for 6 hours to determine the $LC_{50}$ value for acute inhalation. |
| GLP: | unknown |
| Test substance: | As prescribed, sections 1.1 to 1.4 |
| Reference: | Chellman et al, 1986b |

| | |
|---|---|
| Type: | $LC_{50}$ |
| Species/strain: | Rat |
| Exposure time: | 30 minute |
| Value: | 152 ml/liter (73,600 ppm) (147,200 mg/m$^3$) |
| Method: | other |
| GLP: | Unknown |
| Test substance: | As prescribed, sections 1.1 to 1.4 |
| Remarks: | According to the available abstract, Bakhishev (1973) found 50% survival following 30-minute exposure of rats to 152 mg/liter (73,600 ppm) but the levels seem unreasonably high. |

Reference: Bakhishev, 1973.

Type: $LC_{50}$
Species/strain: Mice and Rat/strains not specified
Exposure time: 4 hours
Value: 2700 ppm (5400 mg/m$^3$) for rats; 3000 ppm (6000 mg/m$^3$) for mice
Method: other
GLP: Unknown
Test substance: As prescribed, sections 1.1 to 1.4
Reference: von Oettingen et al., 1949

Type: $LC_{50}$
Species/strain: Mice/$B_6C_3F_1$
Exposure time: 6 hours
Value: 2250 ppm (4500 mg/m$^3$) for males; 8500 ppm (17,000 mg/m$^3$) for females
Method: Male and female mice were exposed to varying concentrations of chloromethane for 6 hours to determine the $LC_{50}$. GSH levels were determined in the liver, brain and kidney of both sexes. The effect of pre-treatment with DL-buthionine-S,R-sulfoximine (8 mmole/kg), an inhibitor of GSH synthesis two hours before exposure to chloromethane was investigated in the male mice.
GLP: Unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: In $B_6C_3F_1$ mice, which are highly susceptible to chloromethane, there was also a marked sex difference in lethality. Male mice were more susceptible to the lethal effects of a single 6-hour exposure to chloromethane (LC50 = 2250 ppm) than were female mice (LC50 = 8500 ppm). The lethality in male mice was decreased ($LC_{50}$ 3500 ppm) by pretreating with DL-buthionine-S, R-sulfoxime (8 mmoles/kg), an inhibitor of glutathione synthesis. During this pre-treatment period hepatic GSH decreased to 45% of control. Exposure to 2250-ppm chloromethane for 6 hours resulted in rapid depletion of glutathione in both sexes of mice. A dose-dependent depletion of glutathione occurred in the liver, kidneys and brain of both sexes. After 0.5-hour exposure, hepatic glutathione was reduced to 9% of controls in both sexes.
Reference: White et al., 1982.

Type:
Species/strain: Mice/$B_6C_3F_1$
Exposure time: 6 hours
Value:
Method: B6C3F1 male mice were exposed to 1500 ppm chloromethane 6 hr/day, 5 days/week for 2 weeks, with and without daily pretreatment with 2 mmol L-BSO/kg. The effectiveness of the different pretreatment in depleting CSH was determined by assaying GSH in liver, kidney, and brain as on protein sulfhydryl (NPSH) at various time points after pretreatment. Data for treatment groups were compared to control by Student's t test. Probability values less than 0.05 were considered to indicate significant differences.
GLP: Unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: "Previous data have demonstrated that chloromethane is toxic to $B_6C_3F_1$ mice under both acute and chronic exposure conditions, and that conjugation of chloromethane with glutathione (GSH) is a key step in the metabolism of chloromethane. This study examined the role of GSH in mediating the acute toxicity of chloromethane to liver, kidney, and brain of male $B_6C_3F_1$ mice.

The lethal effects of a single 6-hr inhalation exposure of $B_6C_3F_1$ males to 2500-ppm chloromethane were completely prevented by pretreatment with the GSH synthesis inhibitor, L-buthionine-S,R-sulfoximine (4 mmol L-BSO/kg, ip 1.5 hr prior to chloromethane exposure). GSH levels (measured as nonprotein sulfhydryl) in liver and kidney were depleted to 19 and 25% of control values, respectively, at the start of the exposure; the ratio of dead/exposed mice during the 18-hr post exposure declined from 14/15 mice to 0/10. Also, the LC50 for chloromethane increased from 2200 to 3200 ppm in male mice pretreated with BSO. The hepatic toxicity of chloromethane was detected by increased alanine aminotransferase (ALT) activities in serum 18 hr after a 6-hr exposure to 1500-ppm chloromethane (2147 $\pm$ 1327 IU/liter vs 46 $\pm$ 6 in controls). Liver toxicity was inhibited when $B_6C_3F_1$ males were depleted of GSH prior to chloromethane exposure by BSO pretreatment (43 $\pm$ 2), fasting (100 $\pm$ 47), or injection of diethyl maleate (42 $\pm$ 16). The effects of GSH depletion on chloromethane toxicity to brain and kidney were determined in $B_6C_3F_1$ males exposed to 1500 ppm chloromethane 6 hr/day, 5 days/week for 2 weeks, with and without daily pretreatment with 2 mmol L-BSO/kg. This dose of BSO depleted hepatic and renal GSH by 28 and 60%, respectively, at the start of chloromethane exposure. BSO-pretreated mice were protected from the central nervous system toxicity of chloromethane as assessed by microscopic examination of the granule cell layer of the cerebellum. BSO pretreatment also inhibited the renal toxicity of chloromethane as measured by incorporation of [$^3$H]thymidine ([$^3$H]TdR) into renal DNA, an indicator of cell regeneration after cortical necrosis. [$^3$H]TdR incorporation was 105 +/- 10, 337 +/- 40, and 60 +/- 15 dpm/ug DNA in nonexposed controls, chloromethane, and chloromethane + BSO treatment groups, respectively. These results indicate that GSH is an important component in the toxicity of cloromethane to multiple organ systems in $B_6C_3F_1$ mice. Reaction of chloromethane with GSH appears to constitute a mechanism of toxication, contrary to the role usually proposed for GSH in detoxifying xenobiotics."

Remarks: "In the present report, the acute toxic effects of chloromethane on the kidney were found to be more subtle than those produced in the central nervous system and liver."

Reference: Chellman et al., 1986b.

Species/strain: Cats; Dogs/beagle
Sex: Male
Route of Administration: Inhalation
Exposure period: 3 days
Frequency of treatment: 23-1/2 hours/day
Post exposure observation period Cats: 2 weeks Dogs: 4 weeks
Dose: 200 or 500 ppm
Control group: Yes
Concurrent no treatment
NOAEL: Dogs: 200 ppm (400 mg/m$^3$) Cats: 500 ppm (1000 mg/m$^3$)
LOAEL: Dogs: 500 ppm (1000 mg/m$^3$)
Results: According to McKenna's summary: "Male cats showed no effects attributable to chloromethane exposure. Male beagle dogs exposed to 500-ppm chloromethane exhibited neurological effects ranging from near normal presentation to severe upper motor neuron disease characterized by ataxia, paralysis and tremors. Pathological examination of these dogs revealed lesions in the brain stem and spinal cord consistent with the clinical neurological findings. The effects noted were observed immediately following exposure and even the most severely affected animal exhibited signs of reversibility of symptoms during the ensuing 4-week observation

period. Dogs exposed to 200-ppm chloromethane showed no effects attributable to exposure. Under the conditions of this study no-observable-effect-levels (NOEL) were judged to be 200 ppm for dogs and 500 ppm for cats."

Method: other: Male cats and dogs were exposed by inhalation for 23 ½ hours/day for 3 days to chloromethane at concentrations of 200 or 500 ppm. The post exposure observations period was 2 and 4 weeks for cats and dogs, respectively. According to McKenna's summary: "Parameters monitored included clinical observations; neurological exams; routine clinical chemistry, hematology and urinalysis; body weights and selected organ weights obtained at necropsy. Gross and microscopic pathology exams were performed on all animals.'

GLP: Unknown

Test substance: As prescribed, sections 1.1 to 1.4

Reference: McKenna et al., 1981a.

Species/strain: Rats/Sprague-Dawley

Sex: No data

Route of Administration: Inhalation

Exposure period: 2-3 days

Frequency of treatment: 24 hours/day

Post exposure observation period: Some sacrificed immediately; others in recovery for up to 12 days

Dose: 200, 500, 1000, or 2000 ppm

Control group: Yes
Concurrent no treatment

LOEL: 200 ppm (400 mg/m$^3$)

Results: The authors' summarized their study as follows: "Exposure to 2000 ppm of chloromethane for 48 or 72 hours resulted in 100% mortality either during or soon after the exposure period. The primary cause of death appeared to be kidney toxicity and subsequent renal failure. A less degree of liver toxicity was also evident. Exposure to 1000 ppm of chloromethane for 48 or 72 hours resulted in some mortality after the exposures. Surviving rats sacrificed immediately after exposure to 1000 ppm for 48 or 72 hours showed decreased body weights, and kidney toxicity was evident in the rats immediately after the exposure period. A lesser degree of liver toxicity was also present. Following the recovery period, most parameters were normal and definite signs of renal tubular regeneration was evident indicating an active process of repair from the toxicity. In addition, the epididymides were affected in male rats exposed to 500, 1000, or 2000 ppm for 48 or 72 hours and in those males that survived the recovery period. The effects included degeneration, inflammation, sperm granuloma formation, scarring and obstructive changes. Testicular atrophy was also present apparently occurring secondarily to the epididymal alterations. Exposure-related effects were minimal in male and female rats exposed to 200 ppm for 48 or 72 continuous hours and consisted of slight reversible liver effects."

Method: other: Rats were exposed continuously for 2-3 days to chloromethane at concentrations of 200, 500, 1000, or 2000 ppm. The authors' summarized their study as follows: "Some rats were immediately sacrificed after exposure and some were held for a recovery period of up to 12 days. Animal evaluations included general observations, body weights, organ weights, hematologic parameters, urinalysis parameters, clinical chemistry parameters, gross necropsy observations and histopathologic observations."

GLP: Unknown

Test substance: As prescribed, sections 1.1 to 1.4

Reference: Burek et al., 1981.

### 5.1.3 ACUTE DERMAL TOXICITY

### 5.1.4 ACUTE TOXICITY BY OTHER ROUTES OF ADMINISTRATION

## 5.2 CORROSIVENESS/IRRITATION

### 5.2.1 SKIN IRRITATION/CORROSION

Remarks: Standard irritation testing is not applicable to chloromethane as it exists as a gas.

### 5.2.2 EYE IRRITATION/CORROSION

Remarks: "Exposure of a rabbits eye to pure chloromethane gas at room temperature for ninety seconds caused only slight conjunctival hyperemia in two rabbits exposed for five days to concentrations from 250 to 465 ppm in air. There were no changes in the corneas, nor in pupillary reactions to light."
Reference: Grant, 1986. (as cited in HSDB, 1998)

## 5.3 SKIN SENSITISATION

Remarks: Standard sensitization testing is not applicable to chloromethane as it exists as a gas.

## 5.4 REPEATED DOSE TOXICITY

Species/strain: Rat/Fischer 344 and mice/$B_6C_3F_1$
Sex: Male/Female
Route of Administration: Inhalation
Exposure period: 13 weeks
Frequency of treatment: 6 hours/day, 5 days/week
Post exposure observation period: none
Dose: 375, 750 and 1500 ppm
Control group: Yes
Concurrent no treatment
NOAEL: 750 ppm (1500 mg/m$^3$)
LOAEL: 1500 ppm (3000 mg/m$^3$)
Results: Significant increases in SGPT activity were observed in male mice in the 1500-ppm dose group. These increases may be explained by the presence of histologic hepatic changes. One male mouse and one female rat at the 1500-ppm dose level each had evidence of hepatic infarction. All other changes in hematologic or hemochemical parameters were within the expected normal range and/or were changes for which a dose-response relationship could not be clearly established. Increased relative organ weights (liver) were observed in the 1500-ppm dose group. Both male and female rats of the 1500-ppm group had significantly lower body weights when compared to controls from week 3 through week 13 and males and females of the 750-ppm group from week 6 through week 12.
Method: other: In general conformance with OECD 413.
Observations were made with respect to food consumption, body weight changes, mortality, and physical effects. Hematology and clinical chemistry analyses were conducted on the animals at 13 weeks (prior to exsanguination) and subjected to a complete gross pathological examination. Tissues from the control and highest test level were examined histopathologically.

Selected organs were taken from all animals and selected organs weighed; all tissues were fixed in 10 percent neutral buffered formalin.

GLP: Unknown
Test substance: As prescribed, sections 1.1 to 1.4
Reference: CIIT (1979) by Battelle Columbus Laboratories.

Species/strain: Rat/Fischer 344
Sex: Male/Female
Route of Administration: Inhalation
Exposure period: 24 months (interim sacrifices at 6, 12 and 18 months)
Frequency of treatment: 6 hours/day, 5 days/week
Post exposure observation period: none
Doses: 50, 225 or 1000 ppm
Control group: Yes
Concurrent no treatment
NOAEL: 225 ppm (450 mg/$m^3$)
LOAEL: 1000 ppm (2000 mg/$m^3$)
Results: Rat survival was unaffected by exposure to any concentration. Ophthalmologic examinations revealed changes which were apparently due to a virus and which were also found in control animals, although at a lower incidence. Lenticular changes, which appeared in rats only at 18 months, may have been related to exposure.

No neurofunctional impairments were observed that are attributable to chloromethane exposure.

Clinical observations, clinical chemistry, hematology, and urinalysis were unaffected in rats exposed to all concentrations. Organ weights showed significant changes only in rats exposed to 1000 ppm. Increased relative heart weights were found in male rats exposed to 1000 ppm at 12, 18 and 24 months and in female rats at 12 and 18 months. Relative kidney weights were increased in male rats exposed to 1000 ppm at all sacrifice periods but female rats were unaffected. Male rats exposed to 1000 ppm had increased relative liver weights and female rats had decreased absolute weights. Testicular weights of male rats exposed to 1000 ppm were decreased when compared to the controls on both an absolute and relative basis. Relative lung weight was increased at all concentrations but only at the 6-month sacrifices.

The testes were the only organ of the rats considered to have significant chloromethane induced lesions. Bilateral and diffuse degeneration and atrophy of the seminiferous tubules of the testes were first noted in males exposed to 1000 ppm for 6 months. The effect increased in degree and in number of animals affected until the 18-month sacrifice. By 24 months, the effects of normal ageing prevented interpretation. Testicular size was reduced at 1000 ppm but no changes in the testes were detectable at either 50 or 225 ppm.
Remark: Therefore, on the basis of these results, it appears reasonable to conclude that 225-ppm is the NOAEL in this 2-year (lifetime) study in rats.
Method: other: In general conformance with OECD 453.
Body weight, clinical signs of toxic effects, and mortality were followed throughout the study. Blood and urine samples were taken for hematological, clinical chemical, and urine analysis from rats randomly preselected for necropsy at 6, 12, 18 and 24 months. The animals were then subjected to a complete gross pathological examination and a preselected battery of tissues taken and preselected organs weighed.
GLP: No

Test substance: As prescribed, sections 1.1 to 1.4
Reference: Chemical Industry Institute of Toxicology (CIIT), 1981 and 1983.

Species/strain: Mice/$B_6C_3F_1$
Sex: Male/Female
Route of Administration: Inhalation
Exposure period: 24 months (interim sacrifices at 6, 12 and 18 months)
Frequency of treatment: 6 hours/day, 5 days/week
Post exposure observation period: none
Doses: 50, 225 or 1000 ppm
Control group: Yes
Concurrent no treatment
NOAEL: 225 ppm (450 mg/m$^3$)
LOAEL: 1000 ppm (2000 mg/m$^3$)
Results: $B_6C_3F_1$ mice in general were much more severely affected than rats.
The effects were very severe in the 1000-ppm groups, but were questionable in the 50 and 225-ppm groups since they were not always related to exposure concentration, nor were they seen at all sacrifice periods.
No changes were observed in mice during ophthalmic examination. Neurofunctional impairment (loss of clutch response), which was observed in the 1000-ppm groups at 18 and 21 months in males and 22 months in females, was statistically different than the controls. These observations, which were supported by histopathological observations in the 1000-ppm exposure groups, were not observed in the 50 or 225-ppm groups.
Growth of only the male mice exposed to 1000 ppm was depressed during the first 18 months. Clinical signs suggestive of disturbances of the central nervous system, such as tremors and paralysis, were observed. In male mice exposed to 1000 ppm, significantly elevated serum glutamic-pyruvic-transaminase (SGPT) values occurred at 6, 12, and 18 months and at 6 months in 50 and 225-ppm groups. In the 1000-ppm groups the increased values were associated with hepatocellular degeneration and necrosis. In female mice increases in SGPT found at 6 and 12 months in the 50, 225 and 1000-ppm groups did not correlate with any histopathology of the liver.
Relative heart weights in the 1000-ppm exposure group were increased in female mice (12 and 18 months) and male mice (12, 18 and 24 months). Female mice exposed to 1000 ppm generally displayed increased relative liver weights. Decreased absolute brain weights were observed at all time periods in male and female mice exposed to 1000 ppm and absolute and relative testicular weights were decreased at 18 and 24 months. In the two lower exposure groups, the only significant change in organ weights was an increase in the relative weight of the hearts of female mice exposed to 225 ppm for 24 months.
Hepatocellular changes were observed at 6 months in male mice exposed to 1000 ppm. These changes included centrilobular to midzonal hepatocellular vacuolization, karymegaly, cytomegaly, multinucleated hepatocytes, and degeneration. Females developed these changes to a lesser degree at 18 to 22 months.
Renal tubuloepithelial hyperplasia and karymegaly were seen in male mice exposed to 1000 ppm for 12 months and progressed in severity throughout the study. See Section 5.7 for discussion relating to carcinogenicity issue.
Renal cortical cysts were predominately seen in mice in the 1000-ppm group, whereas microcysts were noted most frequently in the 50-ppm group at 24 months. Both occurrences were different from controls but were not statistically significant.
Cerebellar lesions first appeared in male and female mice at the 18-month sacrifice from the 1000-ppm group. The lesion, which was characterized by degeneration and atrophy of the cerebellar granular layer, did not appear in

mice from any other exposure group or in the controls. Three of 7 males and 6 of 8 females from the 1000-ppm group were diagnosed as having the lesion at the 18-month sacrifice and 16 of 18 females terminated at 22 months had the lesion. Mice (1000 ppm) that died spontaneously between 0 and 17 months (9 of 20 females, 15 of 24 males) and between 18 and 22 months (35 of 37 females, 45 of 47 males) had a similar lesion. This lesion is considered to be related to chloromethane exposure.

At 18 months, axonal swelling and degeneration of minor severity were observed in the spinal nerves and cauda equina associated with the lumbar spinal cord. These effects were observed in all groups, including at a low incidence in the control group, and no dose-response relationship was established.

Injury to the testes was only apparent at 1000 ppm and was described as degeneration of the seminiferous tubules; the atrophy was not accompanied by decreased organ weight. This lesion was considered biologically significant and a result of chloromethane exposure.

Splenic alterations, ranging from lymphoid depletion to splenic atrophy, were present in male and female mice from the 1000-ppm group as early as 6 months and progressed throughout the study. Depletion was noted in only one control mouse during the study at the 6-month sacrifice. Splenic atrophy was noted in mice dying spontaneously between 0 and 17 months, but was not apparently increased over controls until the 18- to 24-month period. Both lesions are considered to be related to chloromethane exposure.

Remarks: While the Battelle investigators (CIIT, 1983) reported an apparent increase in non-tumorous renal cortical micro-cysts in the 50 and 1000-ppm groups, subsequent review indicates the purported increases were likely a procedural artifact due to multiple pathologists examining the tissues and using different nomenclature (Johnson, 1988). Johnson pointed out three reasons for this conclusion in his review:

1. The cysts did not occur in a dose-responsive manner.

2. Similar cysts are noted in control mice of this strain at approximately the same frequency in the Dow Toxicology Laboratory.

   In eight studies, the incidence varied from 0 to 14% with an overall mean of 6.6% (31/472). Furthermore, treated groups also had the same incidence range in the Dow studies.

3. Inconsistencies in histopathological terminology and lesion incidences in the study raise questions as to the validity of the purported effect. There are several inconsistencies in the histopathological terminology and diagnostic pattern among the various sacrifice intervals and even within a sacrifice interval, suggesting that either more than one pathologist examined the tissues or the terminology used for the lesion was inconsistent.

Remarks: Therefore, on the basis of these results, it appears reasonable to conclude that 225-ppm is the NOAEL in this 2-year (lifetime) study in mice.

Method: other: In general conformance with OECD 453.

Body weight, clinical signs of toxic effects, and mortality were followed throughout the study. Blood and urine samples were taken for hematological, clinical chemical, and urine analysis from mice randomly preselected for necropsy at 6, 12, 18 and 24 months. The animals were then subjected to a complete gross pathological examination and a preselected battery of tissues taken and preselected organs weighed.

GLP: No
Test substance: As prescribed, sections 1.1 to 1.4
Reference: CIIT, 1983; Johnson, 1988.

Species/strain: Rat/Fischer 344; Mice/C3H; Mice/C57/BL/6 and Mice/$B_6C_3F_1$
Sex: Male/Female
Route of Administration: Inhalation
Exposure period: Up to 12 days
Frequency of treatment: 6 hours/day
Post exposure observation period: none
Dose: Rats: 2000, 3500 or 5000 ppm
Mice: 500, 1000 or 2000 ppm
Control group: Yes
Concurrent no treatment
LOAEL: Rats: 2000 ppm (4000 mg/m$^3$) Mice: 500 ppm (1000 mg/m$^3$)
Results: All male $B_6C_3F_1$ mice exposed 2000 ppm were dead or moribund by day 2, and all male and female mice in the remaining 2000-ppm groups were moribund by day 5. Prior to death many of these mice exhibited ataxia, and hematuria with the latter occurring mainly in females. Treatment associated lesions in mice included hepatocellular degeneration and necrosis, degeneration and necrosis of proximal convoluted tubules and/or basophilic tubules in the renal cortex, and focal areas of necrosis of the internal granular layer of the cerebellum. Brain lesions were most severe in female C57/BL/6 mice, while hepatocellular degeneration was most severe in male C57/BL/6 mice and $B_6C_3F_1$ strains. Approximately 50% of the male and female rats exposed to 5000 ppm were killed *in extremis* on day 5. The principal clinical signs, which were confined to the 5000 and 3500-ppm groups, included severe diarrhea, incoordination of the forelimbs, and in a small number of animals, hind limb paralysis and convulsions. In rats, lesions were observed in the liver, kidney and brain, which resembled those seen in mice, but were generally less severe. Lesions observed in tissues examined only in rats included vacuolar degeneration of the zona fasciculata of the adrenal glands. Mice testes were not examined histologically but all groups of rats had testicular degeneration, with a clear exposure-concentration related response for the severity of the lesion. In affected testicles, the lesion did not involve all seminiferous tubules equally. The principal changes were reduced numbers of late-stage spermatids, with none in severely affected tubules, separation of spermatocytes and early-stage spermatids, with sloughing of these cells into the lumen, formation of irregular, apparently membrane-bound vacuoles in the germinal epithelium, and variable formation of multinucleate giant cells. Giant cells appeared to be formed by fusion of early-stage spermatids. In severely affected tubules only a thin layer of cells remained adjacent to the basement membrane.
Method: To determine the potential for toxicity following repeat dose exposure, rats and mice were exposed to chloromethane (2000, 3500, or 5000 ppm in rats; 500, 1000 or 2000 ppm in mice) for 6 hours/day for up to 12 days. Concurrent control groups were included, but received no treatment. Animals were observed daily for signs of toxicity. Animals that died or were found moribund and all sacrificed animals were subjected to complete necropsy and extensive histopathological examination of selected organs (liver, kidneys and brain). The testes examined in rats only and sperm parameters evaluated.
GLP: Unknown
Test substance: As prescribed, sections 1.1 to 1.4
Reference: Morgan et al., 1982.

Species/strain: Mice/C57/BL/6
Sex: Female
Route of Administration: Inhalation
Exposure period: 2 weeks
Frequency of treatment: 6 hours/day, 5 days/week
Post exposure observation period: none
Dose: 1500 ppm (3000 mg/m$^3$)
Control group: Unknown
Results: From the authors' abstract: "Focal and diffuse malacia, involving the cerebellar inner granular layer was found while renal lesions were minimal or absent. The cerebellar lesions were most frequently found in the ventral paraflocculus, and less often in other regions of the cerebellum. The earliest ultrastructural changes were seen in the nuclei of scattered cerebellar granule cells, with progression from slight confluence of heterochromatin, to complete nuclear condensation of karyorrhexis. More severely affected areas exhibited severe watery swelling and disruption of granule cell perikarya with less severe changes in other cell types. Blood vessels appeared normal, even in areas of severe malacia. It was concluded that the lesions in the mouse cerebellum closely resemble chloromethane induced brain lesions previously described in guinea pigs, and that these lesions are not secondary to the renal toxicity of chloromethane."
Method: Female C57BL/6 mice were exposed to 1500 ppm chloromethane for 6 hours/day, 5 days/week for 2 weeks. Control animals were exposed to room air in a similar chamber. After the final exposure the mice were anesthetized and the whole body perfused via the left ventricle with 10% dextran-40 in 0.9% sodium chloride for one minute, followed by a fixative solution containing 4% formaldehyde, and 1% glutaraldehyde in 0.1 M Sorenson's phosphate buffer. Each mouse was perfused with 20 mL of this fixative. After perfusion the whole body was immersed in fresh fixative at 4$^o$C for 2 days. The brain was then removed and rinsed twice with freshly prepared cold phosphate buffer and stored in this buffer overnight to remove residual glutaraldehyde. The cerebellum was then sliced transversely and examined for gross abnormalities. The posterior half of the cerebellum was embedded in paraffin, 5 µm-thick sections cut, stained with hematoxylin and eosin and examined by light microscopy. One mm-thick blocks were cut from the posterior face of the anterior half of the cerebellum, and trimmed to produce blocks approximately 2 x 3 x 1 mm, which permit easy orientation when sectioned. These blocks were rinsed in fresh phosphate buffer, post-fixed in 1% osmium tetroxide and embedded in Epon-araldite. One to 3 µm-thick sections were cut and stained with toluidine blue (TB) for light microscopy. Ultra-thin sections were cut from selected areas of the Epon-aralidte blocks, stained with lead citrate and uranyl acetate and examined in a Philips 400 transmission electron microscope.

A transverse block was cut from the kidneys of each animal, embedded in paraffin and 5 µm-thick paraffin sections were cut, and stained with hematoxylin and eosin or periodic acid-Schiff's stain (PAS).
GLP: Unknown
Test substance: As prescribed, sections 1.1 to 1.4
Reference: Jiang et al., 1985.

Species/strain: Mice/C57/BL/6
Sex: Female
Route of Administration: Inhalation
Exposure period: 11 days
Frequency of treatment: 22 hours/day or 5.5 hours/day (see doses below)

Post exposure observation period:
Dose: 15, 50, 100, 150, 200 or 400 ppm for 22 hours/day
150, 400, 800, 1600 or 2400 ppm for 5.5 hours/day
Control group: Yes
Concurrent no treatment
NOAEL: 22-hour exposure: 50 ppm (100 mg/m$^3$);
5.5-hour exposure: 150 ppm (300 mg/m$^3$)
LOAEL: 22-hour exposure: 100 ppm (200 mg/m$^3$)
5.5-hour exposure: 400 ppm 800 mg/m$^3$)
Remark: See Section 5.10A for complete discussion of results
Method: other: Female C57BL/6 mice were exposed intermittently and continuously to chloromethane gas in a neurotoxicity study (Landry et al., 1985). This strain and sex were chosen because it had been found to be particularly sensitive to the neurotoxic effects of chloromethane (Morgan et al., 1982). The female mice were scheduled for 11 days of exposure, either 22 hours per day to 15, 50, 100, 150, 200 or 400 ppm or 5.5 hours per day to 150, 400, 800, 1600 or 2400 ppm. Separate groups were exposed for neurofunctional testing and pathology. In addition, all moribund mice were necropsied and, together with the pathology group, received extensive histologic examination with particular emphasis on the nervous system.
GLP: Unknown
Test substance: As prescribed, sections 1.1 to 1.4
Reference: Landry et al., 1985.

Species/strain: Mice/CD-1; Rats/Sprague-Dawley; Dogs/Beagle
Sex: Male/Female
Route of Administration: Inhalation
Exposure period: 64-66 exposures in 93-95 days
Frequency of treatment: 6 hours/day, 5 days/week
Post exposure observation period: none
Dose: Mice/ Rats: 50, 150 or 400 ppm; Dogs: 400 ppm
Control group: Yes
Concurrent no treatment
NOAEL: 400 ppm (800 mg/m$^3$)
Results: From the authors' study: "All parameters were unaffected by chloromethane exposure except for the following:
Male rats exposed to 400-ppm chloromethane had decreased urinary specific gravity measurement when compared to controls. A decrease in urinary specific gravity was also seen in female rats exposed to 150, but not 400 ppm, chloromethane. The effects on specific gravity of the urine were not associated with any renal pathology, either gross or microscopic.
Male rats and female mice of the 400 ppm exposure group had a slight but statistically significant increase in mean liver to body weight ratio.
A similar increase in relative liver weight was suggested by the data from male mice exposed to 400 ppm chloromethane as well as mice of both sexes exposed to 150 ppm. However these findings were not supported by subsequent pathological evaluation or other clinical laboratory indicators of liver function.
No specific target organ toxicity or unequivocal toxic manifestations of chloromethane were observed in rats, mice or dogs exposed to concentrations as high as 400 ppm. In the absence of further supporting or confirmative evidence, the observations noted above were not interpreted as manifestations of toxicity of the test material."

Method: other: Male and female mice, rats and dogs were exposed to chloromethane (50, 150, or 400 ppm in mice and rats; 400 ppm in dogs) for 6 hours/day, 5 days/week for 93-95 days. From the authors' study: "Parameters monitored during the course of this experiment included clinical signs of toxicity: a battery of sensory and motor function tests; mortality; body weights; routine hematology, urinalysis, and clinical chemistry tests; selected organ weights; gross and microscopic pathology."

GLP: Unknown
Test substance: As prescribed, sections 1.1 to 1.4
Reference: McKenna et al., 1981b

Species/strain: Mice/ $B_6C_3F_1$
Sex: Male
Route of Administration: Inhalation
Exposure period: Exposed 5 days/week for 2 weeks
Frequency of treatment: 6 hours/day
Post exposure observation period: none
Dose: 1500 ppm (3000 mg/m$^3$)
Control group: Yes; Concurrent no treatment
Results: "Previous data have demonstrated that chloromethane is toxic to $B_6C_3F_1$ mice under both acute and chronic exposure conditions, and that conjugation of chloromethane with glutathione (GSH) is a key step in the metabolism of chloromethane. The effects of GSH depletion on chloromethane toxicity to brain, liver and kidney were determined in $B_6C_3F_1$ males exposed to 1500 ppm chloromethane 6 hr/day, 5 days/week for 2 weeks, with and without daily pretreatment with 2 mmol L-BSO/kg. This dose of BSO depleted hepatic and renal GSH by 28 and 60%, respectively, at the start of chloromethane exposure. BSO-pretreated mice were protected from the central nervous system toxicity of chloromethane, as assessed by microscopic examination of the granule cell layer of the cerebellum. BSO pretreatment also inhibited the renal toxicity of chloromethane as measured by incorporation of [3H]thymidine ([3H]TdR) into renal DNA, an indicator of cell regeneration after cortical necrosis. [3H] TdR incorporation was 105 $\pm$ 10, 337 $\pm$ 40, and 60 $\pm$ 1 five dpm/microgram DNA in non-exposed controls, chloromethane, and chloromethane + BSO treatment groups, respectively. These results indicate that GSH is an important component in the toxicity of chloromethane to multiple organ systems in $B_6C_3F_1$ mice. Reaction of chloromethane with GSH appears to constitute a mechanism of toxication, contrary to the role usually proposed for GSH in detoxifying xenobiotics.
Remarks: "Chloromethane-induced target organ toxicity following acute exposure (up to 2000 ppm, 6 hr/d, for 12 days) of rats and mice was similar to that seen in the 2 year study (Morgan et al., 1982); hepatic, cerebellar, and renal lesions were observed in male $B_6C_3F_1$ mice."
Remarks: "The kidney -lesion consisted of both proximal tubular degeneration/necrosis and tubular basophilia; the basophilia was suggested to result from a compensatory proliferative response following cell damage and necrosis."
Remarks: "Laurent et al., (1983) reported that cortical cells in rat kidney underwent a compensatory, proliferative response after administration of low doses of gentamycin which produced no marked histopathological evidence of damage; the cellular proliferation appeared to result from a regenerative process after focal, gentamycin-induced necrosis. The increased incorporation of [radiolabel] into renal DNA which occurred in chloromethane-exposed $B_6C_3F_1$ mice also appears to result from compensatory cell proliferation in response to cell death. Chloromethane induces both tubular necrosis and basophilic foci in the kidney cortex of $B_6C_3F_1$ mice (Morgan et al., 1982), features that are consistent with a regenerative cellular response following cell death. Furthermore, autoradiography has confirmed a high rate of cell turnover in

chloromethane-induced basophilic foci (20% of cells in S-phase vs less than 1 % in controls) (Jiang et al., 1984)."

Remarks: "The cell proliferation induced by chloromethane may be an important factor in the development of renal tumors. This hypothesis is supported by data indicating that a direct, genotoxic mechanism of carcinogenesis is unlikely, since chloromethane is an extremely weak direct-acting mutagen in bacteria and mammalian cells (Fostel et al., 1985; Working et al., 1986) and since alkylation of mammalian DNA has not been detected after *in vivo* exposure to chloromethane (Kombrust et al., 1982a; Peter et al., 1985).

Remarks: "In the present study however, exposure to 1500 ppm chloromethane also induced cell proliferation in kidneys of female $B_6C_3F_1$ mice, which did not exhibit tumors in the 2-year bioassay. It is possible that at the lower concentrations of chloromethane used in the 2-year bioassay (997, 224, and 51 ppm), male $B_6C_3F_1$ mice are more susceptible than females to the renal toxicity of chloromethane. This explanation is supported by the observations of Morgan et al. (1982), who reported an increased incidence of basophilic renal tubules in $B_6C_3F_1$ males relative to females after 12 consecutive days of exposure to 500 or 1 000 ppm chloromethane; in contrast, no sex difference was observed at 2000 ppm. Alternatively, factors other than cell proliferation may also be important in the sex-specific induction of kidney tumors by chloromethane in $B_6C_3F_1$ mice."

Method: other: The effects of GSH depletion on chloromethane toxicity to brain, liver and kidney were determined in $B_6C_3F_1$ males exposed to 1500 ppm chloromethane 6 hr/day, 5 days/week for 2 weeks, with and without daily pretreatment with 2 mmol L-BSO/kg.

GLP: Unknown

Test substance: As prescribed, sections 1.1 to 1.4

Reference: Chellman et al., 1986b.

Species/strain: Rats/Fisher 344; Mice/ $B_6C_3F_1$

Sex: Male

Route of Administration: Inhalation

Exposure period: Exposed 6 days

Frequency of treatment: 6 hours/day

Post exposure observation period: none

Dose: 1000 ppm (2000 mg/m$^3$)

Control group: Yes; Concurrent no treatment

Results: The authors concluded that the tumor formation in male mice (1) cannot be attributed to any obvious biochemical sex differences in enzymatic transformation with respect to FDH, (2) the absence of the characteristic formaldehyde-induced genetic damage suggested that the metabolically formed formaldehyde was not likely to be the effective carcinogen, and (3) there was a significant species difference between mice and rats; due to the higher activity of GST, especially in the kidneys, mice are more susceptible to the GSH-depleting effect of chloromethane.

Method: other: The purpose of this study was to determine whether chloromethane induced renal tumors in male mice was mediated by the metabolic intermediate, formaldehyde. DNA-lesions (crosslinks and single strand breaks), glutathione-S-transferase (GST), and formaldehyde dehydrogenase (FDH) activity were measured.

GLP: Unknown

Test substance: As prescribed, sections 1.1 to 1.4

Reference: Jäger et al., 1988.

## 5.5 GENETIC TOXICITY IN VITRO

## A. BACTERIAL TEST

Type: *Salmonella typhimurium* reverse mutation assay
System of testing: TA 98, TA100, TA1535, TA1537, TA1538
Concentration: 25,000 -200,000 ppm
Metabolic activation: With and without
Results:
Genotoxic effects:
With metabolic activation: positive
Without metabolic activation: positive
Method: other: In general conformance with OECD 471
GLP: Unknown
Test substance: As prescribed, sections 1.1-1.4
Remarks: Chloromethane has been shown to be mutagenic in *Salmonella typhimurium* in the presence or absence of S9 metabolic activation from the livers of Aroclor-induced rat livers. The test concentrations were high, ranging from 25,000 to 200,000 ppm in the air surrounding the test plates (desiccator test for exposure to gases).
Reference: Simmon et al., 1977 and 1978.

Type: *Salmonella typhimurium* reverse mutation assay
System of testing: TA98, TA100, TA1535 and TA1537
Concentration: 1%, 4%, 7%
Metabolic activation: With and without
Results:
Genotoxic effects:
With metabolic activation: positive
Without metabolic activation: positive
Method: other: In general conformance with OECD 471
GLP: Unknown
Test substance: As prescribed, sections 1.1-1.4
Remarks: Chloromethane caused a positive response (> 2-fold increases in revertants/plate relative to controls) in strains TA1535 and TA100 at all concentrations tested, both in the presence and absence of metabolic activation.
Reference: Haskell Laboratories (1978) (as cited in HSDB, 1998).

Type: *Salmonella typhimurium* reverse mutation assay
System of testing: TA1535
Concentration: 5000 to 207,000 ppm
Metabolic activation: With and without
Results:
Genotoxic effects:
With metabolic activation: positive
Without metabolic activation: positive
Method: other: In general conformance with OECD 471
GLP: Unknown
Test substance: As prescribed, sections 1.1-1.4
Reference: Andrews et al., 1976.

Type: *Salmonella typhimurium* reverse mutation assay
System of testing: TM677
Concentration: 50,000 - 300,000 ppm
Metabolic activation: Without
Results:
Genotoxic effects:
Without metabolic activation: positive
Method: other: In general conformance with OECD 471 (with modification)

GLP: Unknown
Test substance: As prescribed, sections 1.1-1.4
Remarks: A concentration-dependent increase in 8-azaguanine-resistant fraction was observed *in S. typhimurium* TM677 exposed to chloromethane at 37°C for 3 hours. Exposure concentrations were 50,000 to 300,000 ppm. Lethality increased with increasing concentrations while viability was reduced to half at 200,000 ppm and the induced mutant fraction had increased from 0.9 x $10^4$ for controls to 7 x $10^4$ for exposed.
Reference: Fostel et al., 1985.

## B. NON-BACTERIAL IN VITRO TEST

Type: Gene mutation assay
System of testing: Human: TK6 lymphoblastoid cells
Concentration: 1-5% chloromethane
Metabolic activation: Without
Results:
Genotoxic effects:
Without metabolic activation: positive
Method: other: In general conformance with OECD 476
GLP: Unknown
Test substance: As prescribed, sections 1.1-1.4
Remarks: TK6 lymphoblastoid cells were used for a gene mutation assay, sister-chromatid exchange (SCE) assay and alkaline elution (results of latter two assays are noted below). Using $^{14}C$ analysis, it was determined that the media, which was exposed to a known concentration of chloromethane, contained 0.73 mM chloromethane per each % of chloromethane in the atmosphere. After exposure to 1-5% chloromethane gas for 3 hours, the efficiency of colony formation and mutant fraction were determined. There was a dose-dependent increase in the trifluorothymidine-resistant fraction of TK6 human lymphoblast cells with all concentrations above 1% elevated above control cultures. Growth after exposure to 5% lagged behind the controls indicating a cytotoxic or cytostatic effect on the cells. At the time of plating all cultures displayed 50-70% plating efficiency.
Reference: Fostel et al., 1985.

Type: Sister chromatic exchange assay
System of testing: Human: TK6 lymphoblastoid cells
Concentration: 1-5% chloromethane
Metabolic activation: Without
Results:
Genotoxic effects:
Without metabolic activation: positive
Method: other: In general conformance with OECD 479
GLP: Unknown
Test substance: As prescribed, sections 1.1-1.4
Remarks: Chloromethane induced a statistically significant concentration-related increase in sister-chromatid exchange.
Reference: Fostel et al., 1985.

Type: Alkaline Elution
System of testing: Human: TK6 lymphoblastoid cells
Concentration: 1-5% chloromethane
Metabolic activation: Without
Results:
Genotoxic effects:
Without metabolic activation: negative

Method: other: In general conformance with OECD 482
GLP: Unknown
Test substance: As prescribed, sections 1.1-1.4
Remarks: Alkaline elution of the DNA from TK6 cells exposed to 1, 3, and 5% chloromethane showed no increase in strand breakage over DNA from control TK6 cells.
Reference: Fostel et al., 1985.

Type: Cell transformation
System of testing: Syrian primary hamster embryo cells
Concentration: 3000 - 50,000 ppm
Metabolic activation: Without
Results:
Genotoxic effects:
Without metabolic activation: positive
Method: other: In general conformance with OECD 476
GLP: Unknown
Test substance: As prescribed, sections 1.1-1.4
Remarks: Transformation of Syrian Hamster embryo cells by SA7 adenovirus was reported by Hatch et al. (1983) to be increased after exposure of the cells to 3000 to 50,000 ppm (6.2 to 103.5 g/m$^3$) of chloromethane for 20 hours. The relevance of this isolated test is not clear.
Reference: Hatch et al., 1983.

Type: Unscheduled DNA synthesis assay
System of testing: Rat: hepatocytes, spermatocytes, tracheal epithelial cells
Concentration: 1-10%
Metabolic activation: Without
Results:
Genotoxic effects:
Without metabolic activation: + in hepatocytes and spermocytes
Method: other: In general conformance with OECD 482
GLP: unknown
Test substance: As prescribed, sections 1.1-1.4
Reference: Working et al., 1986 (as cited in ATSDR, 1990).

## 5.6 GENETIC TOXICITY IN VIVO

Type: Sex-linked recessive lethal test
Species/strain: *Drosophilia*
Sex: Male
Route of Administration: Inhalation
Exposure period: 50 minutes to 2 hours
Doses: 200,000 ppm
Results:
Genotoxic effects: positive
Method: other: In general conformance with OECD 477
Treated and control male drosophila from a wild-type stock (Canton-S) were mated with females from a laboratory stock called "Basc". Exposures were to 200,000 ppm and ranged from 2 hours. Treated male flies were mated 72 hours after exposure to 3 virgin "Basc" females. Each male was transferred 3 days later to 3 new virgin females. The transfer process was repeated twice more. Early broods, those from sperm ejaculated less than seven days post-exposure were discarded so that only sperm, which was pre-meiotic at the time of exposure, was used.
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4

Remarks: Exposures were to 200,000 ppm and ranged from 2 hours, which gave 90% mortality to 50 minutes, which apparently allowed survival. Narcosis occurred in all exposures. The investigators concluded chloromethane was a "potent" mutagen in Drosophila melanogaster, inducing sex-linked recessive lethals in all post-meiotic germ cell developmental stages equally. Further, they considered it a direct-acting mutagen based on these exposures to 200,000 ppm for 50 minutes.
Reference: University of Wisconsin, 1982a.

Type: Sex-linked recessive lethal test
Species/strain:. *Drosophilia*
Sex: Male
Route of Administration: Inhalation
Exposure period:
Doses: 373,000, 375,000 and 786,000 ppm.hr (ppm x hrs of exposure)
Results:
Genotoxic effects: positive
Method: other: In general conformance with OECD 476.
The ability of chloromethane to induce sex-linked recessive lethal mutations in the post-meiotic germ cells was evaluated in *Drosophila* males (wild-type stock, Canton-S). Based on preliminary toxicity determinations, flies (60-71/group) were treated with chloromethane at 373,000, 375,000, and 786,000 ppm-hr (ppm x hrs of exposure). The surviving flies (70, 54 and 50 at low-, mid-, and high-dose levels, respectively) were mated with 3 sets of 3 virgin "Basc" females for 72 hrs each.
GLP: Unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: The ability of chloromethane to induce sex-linked recessive lethal mutations in the post-meiotic germ cells was evaluated in *Drosophila* males (wild-type stock, Canton-S). Based on preliminary toxicity determinations, flies (60-71/group) were treated with chloromethane at 373,000, 375,000, and 786,000 ppm-hr (ppm x hrs of exposure). The surviving flies (70, 54 and 50 at low-, mid-, and high-dose levels, respectively) were mated with 3 sets of 3 virgin "Basc" females for 72 hrs each. Percent mortalities during exposure and prior to mating on increasing dose level were 1, 10 and 29%, respectively. Percent sterility for the 3 broods ranged from 4, 7, and 16% at the low-dose level to 26, 40, and 56% at the high-dose level. Chloromethane was clearly mutagenic at all dose levels tested and in all germ cell stages tested. All multiple lethals, except one, were found likely to be independent lethals.
Percent lethals ranged from 1.45% at low-dose level to 2.17% at high-dose level versus a range of 0.06-0.15% for the controls.
Reference: University of Wisconsin, 1982b (as cited in HSDB, 1998).

Type: Unscheduled DNA synthesis assay
Species/strain: Rat hepatocytes, spermatocytes and tracheal epithelial cells
Sex: Male
Route of Administration: Inhalation
Exposure period: 6 hours/day; 5 days
Doses: 3000-3500 ppm
Results:
Genotoxic effects: Hepatocytes: negative
Spermatocytes: negative
Tracheal epithelial cells: negative
Method: other: In general conformance with OECD 482
GLP: Unknown

Test substance: As prescribed, sections 1.1 to 1.4
Remarks: Inhalation exposure to chloromethane *in vivo* (3000-3500 ppm 6 hr/day for 5 successive days) failed to induce DNA repair in any cell type.
Reference: Working et al., 1986.

Type: Unscheduled DNA synthesis assay
Species/strain: Rat hepatocytes, spermatocytes and tracheal epithelial cells
Sex: Male
Route of Administration: Inhalation
Exposure period: 3 hours/day
Doses: 15,000 ppm
Results:
Genotoxic effects: Hepatocytes: marginally positive
Spermatocytes: negative
Tracheal epithelial cells: negative
Method: other: In general conformance with OECD 482
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: *In vivo* exposure to 15,000-ppm chloromethane for 3 hr also failed to induce unscheduled DNA synthesis in tracheal epithelial cells and spermatocytes, but did cause a marginal increase in UDS in hepatocytes.
Reference: Working et al., 1986.

Type: Alkaline Elution
Species/strain: Mice
Sex: Male/Female
Route of Administration: Inhalation
Exposure period: 8 hours
Doses: 1000 ppm
Results:
Genotoxic effects: negative
Method: other: method of Sterzel et al. (1984)
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Results: Immediately after termination of the exposure, nuclei were prepared from hepatic and renal tissues in treated and control mice. The alkaline elution assay was performed according to the method of Sterzel et al. (1984). The alkaline elution assay pointed to DNA-protein crosslinks in the kidneys of male mice exposed to chloromethane. The effect was not observed in renal tissue from female mice or in hepatic tissue from either sex.
Remarks: An indication of DNA-protein crosslinks after chloromethane exposure was only found in renal tissue of male mice and coincides with tumor formation in the kidney of this species. Possibly, cytochrome P-450-dependent dehalogenation of chloromethane results in the production of formaldehyde (Ulsamer et al., 1984) which is known for its ability to cause DNA-protein crosslinks.
Remarks: A comparison between the present study and the study by Jäger et al. (1988), which found no DNA-protein crosslinks in the kidney of male mice following chloromethane exposure (1000 ppm, 6 hr/d, 6 d), suggests that formaldehyde-induced lesions in the kidney are rapidly and efficiently repaired. In the study by Jäger et al., mice were sacrificed 6 hr after cessation of the final exposure, while in the present study animals were euthanized immediately after cessation of exposure.
Remarks: The results of (Jäger et al., 1988) are consistent with these findings; DNA-protein crosslinks found in renal tissue of male mice may in fact be due to the action of formaldehyde. The question of the relevance of these lesions for renal carcinogenicity is difficult because of their rapid repair.

Reference: Ristau et al., 1989.

Type: Alkaline Elution
Species/strain: Mice
Sex: Male/Female
Route of Administration: Inhalation
Exposure period: 8 hours
Doses: 1000 ppm
Results:
Genotoxic effects: negative
Method: other: method of Sterzel et al. (1984)
Male $B_6C_3F_1$ mice were exposed to a single inhalation dose of 1000-ppm chloromethane for 8 hours. The animals were sacrificed immediately after exposure or at 5 or 48 hours after exposure. Other male mice were exposed to 1000 chloromethane for 6 hours/day for 4 days and sacrificed at 0 or 5 hours after the end of exposure. In order to distinguish between single strand breaks (SSB), DNA/DNA crosslinks (DDC) and DPC, some of the samples were subjected to ionizing radiation and/or treatment with proteinase-K prior to alkaline elution.
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: This study was conducted in order to understand the possible role of DNA protein cross links (DPC) in the formation of renal tumors, After treatment with X-rays, DNA from mice sacrificed immediately after exposure to chloromethane was eluted at a slower rate than DNA from control mice; after digestion with proteinase-K, the elution profiles of irradiated DNA from exposed mice and untreated animals were almost identical. These findings suggested the presence of DPC in the kidneys of exposed mice. No evidence of DPC was found in renal tissue from exposed mice killed 5 hours later. However, enhanced elution rate of DNA from treated mice compared to DNA from controls pointed to low levels of SSB. Neither DPC nor SSB were observed in mice killed at 48 hours after chloromethane exposure. A slight indication of DPC was noted in animals that had been treated with chloromethane for 4 days and killed immediately after the last exposure. Low levels of SSB were detectable in mice that had been exposed to chloromethane for 4 days and sacrificed 5 hours after the last exposure. The authors conclude that DPC may contribute directly to the local tumorigenic effect of chloromethane in kidneys of male mice on the one hand; on the other hand incomplete and delayed repair of chloromethane-induced DNA lesions may also contribute to the formation of renal tumors.
Reference: Ristau et al., 1990.

Type: DNA Binding
Species/strain: Fischer 344
Sex: Male
Route of Administration: Inhalation
Exposure period: 6 hours
Doses: 500 or 1500 ppm
Results:
Genotoxic effects: negative
Method: other: In general conformance with OECD 482
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: Kornbrust et al. (1982a) exposed rats by inhalation to $^{14}C$-labeled chloromethane in order to assess incorporation into macromolecules. Rats were given 6-hour exposures to either 500 or 1500 ppm of the gas. Radioactivity, which accumulated in lipid, RNA, DNA, and protein isolated

from lung, liver, kidney, testes, brain, muscle, and intestine, was associated with acid- insoluble material. Most of the activity was in labeled protein and lipid, although the concentration of $^{14}C$ was found to be over 10-fold higher in nucleic acids when compared on a molar basis of nucleotide to amino acid residue. Radioactivity in purine bases was not due to methylation. This is consistent with rapid metabolism to formate discussed subsequently.

Kornbrust et al. showed further that pretreatment of the rats with cycloheximide reduced the amount of radioactivity associated with tissue protein by 42-58% indicating that most of the incorporation was due to normal protein synthesis. Pretreatment with methotrexate, which inhibits folate-dependent formate metabolism inhibited the incorporation of $^{14}CH_3Cl$ into lipid, acid-insoluble material, RNA, and DNA by 47, 64, 65 and 93%, respectively, and pretreatment with methanol inhibited $^{14}CH_3Cl$ uptake by acid-insoluble material by 66%. These investigators concluded that these findings were consistent with incorporation due to the radioactivity entering the one-carbon pool. However, since ethanol, 4-methylpyrazole and 3-amino-1,2,4-triazole failed to inhibit $^{14}CH_3Cl$ incorporation, the chloromethane did not appear to be metabolized to methanol *per se*. Methanol itself inhibited $CO_2$ evolution indicating metabolism via single-carbon pathways is of major quantitative significance, and supports the conclusion that direct alkylation is negligible.

References: Kornbrust et al., 1982a.

Type: DNA Binding
Species/strain: Rat/Fisher 344 and Mice/$B_6C_3F_1$
Sex: Male/Female
Route of Administration: Inhalation
Exposure period: 6 hours for rats; 4 hours for mice
Doses: 720 ppm
Results:
Genotoxic effects: negative
Method: other: In general conformance with OECD 482
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: Peter et al. (1985) extended the work of Kornbrust et al. by using $^{14}CH_3Cl$ of high radioactivity and by using Fischer 344 rats and $B_6C_3F_1$ mice of both sexes. Based on body weight, mice were found to metabolize $^{14}C$-labeled chloromethane 2.5 to 3.5 times more rapidly than rats.

It was shown that although there was considerable incorporation of $^{14}C$ activity in DNA and RNA, it was not due to methylation but was due rather to incorporation of one-carbon metabolic fragments. Because tumors of the kidneys of male mice were the only tumors increased in the 1981 lifetime studies in rats and mice, a search was made for radioactivity in possible DNA alkylation products. Despite maximizing sensitivity by pooling samples, activity was found only in the natural purines (adenine and guanine) with no indication of the methylation products (7-N-methylguanine or $0^6$-methylguanine). Non-alkylating incorporation of radioactivity was particularly high in the DNA of mouse kidney, "suggesting a high turnover to $C_1$ bodies (formaldehyde, formate) in this tissue." In rats, which did not develop kidney tumors, more radioactivity was found in hepatic DNA than in renal DNA.

Reference: Peter et al., 1985.

Type: Dominant lethal test
Species/strain: Rat
Sex: Male

Route of Administration: Inhalation
Exposure period: 6 hours/day; 5 days
Doses: 875, 1584 or 3330 ppm
Results:
Genotoxic effects: positive
Method: other: In general conformance with OECD 478
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: Each group consisted of 27 male rats. Twenty males were selected from each group and placed individually with two virgin females for one week. This was repeated for 8 weeks. Each female was scored for pregnancy, living fetuses, early and late fetal deaths and corpora lutea. The group exposed to 3330 ppm was seriously injured and many deaths occurred. Rats exposed to 875 or 1584 ppm appeared normal except for one rat with diarrhea in the low group and four rats with diarrhea in the intermediate group on the second day of exposure. No effect was observed in the lowest exposure group but a positive dominant lethal effect occurred in a dose-related manner in the two higher groups. Fertility in the 8th week post-exposure had returned to normal indicting the reversibility of the effect.
Reference: Rushbrook, 1982.

Type: Dominant lethal test
Species/strain: Sprague Dawley
Sex: Male
Route of Administration: Inhalation
Exposure period: 6 hours/day; 5 days
Doses: 1000, 2000 or 3000 ppm
Results:
Genotoxic effects: positive
Method: other: In general conformance with OECD 478
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: The mutagenicity of chloromethane was evaluated in the dominant lethal assay using three groups of 20 male Sprague Dawley rats receiving whole body exposures to nominal concentrations of test material at 1000, 2000 and 3000 ppm in a dynamic air flow chamber for 6 hours/day for five consecutive days. Following exposure, each male was mated with two virgin females per week for eight consecutive weeks. All rats in the control, 1000-ppm and 2000-ppm groups appeared normal throughout the study. Eight of the males in the 3000-ppm breeding group were found dead. Females mated with males from the two highest dose levels exhibited significant differences (t-test) from the negative controls during some part of the first four mating weeks for: fertility index, average implants/ pregnant female, average live implants/pregnant female, average dead implants/pregnant female, dead implants/total implants, average corpora lutea/pregnant female and average preimplantation loss/pregnant female. Dominant lethal effects were more pronounced and observed over a longer time period in the 3000-ppm group relative to the 2000-ppm group, and a dose response relationship was observed.
Reference: SRI International, 1984 (as cited in HSDB, 1998).

Type: Dominant lethal test
Species/strain: Rat/Fischer 344
Sex: Male
Route of Administration: Inhalation
Exposure period: 6 hours/day; 5 days
Doses: 1000 or 3000 ppm

Results:
Genotoxic effects: negative
Method: other: In general conformance with OECD 478;
Groups of 40 male rats each were exposed to 0, 1000, or 3000 ppm chloromethane 6 hr/day for 5 consecutive days, or received a single ip injection of 0.2 mg triethylenemelamine (TEM)/kg as a positive control. Each male was bred to a single female weekly for 8 weeks, and the standard criteria of dominant lethal tests were recorded.
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: Male rats exposed to 1000 ppm were able to fertilize female rats at a rate comparable to control males. Male rats exposed to 3000 ppm 6 hours per day for 5 consecutive days were infertile two weeks after exposure and remained below control animals for at least 8 weeks. The authors concluded pre-implantation losses were observed and were considered due to genotoxic effects on sperm in the vas deferens and epididymis at the time of exposure. Subsequent study has shown the apparent genetic effect to be the probable consequence of severe inflammation of the epididymis with the release of reactive oxygen intermediates which produce chromosomal aberrations, transformations and mutations in the sperm. Treatment with an anti-inflammatory agent Burroughs-Welcome BW755C inhibited the inflammation caused by chloromethane. Females bred to treated males given BW755C did not exhibit the characteristic elevation in post-implantation embryonic death rate "leading to the conclusion the chloromethane -induced dominant lethal mutations, rather than being caused by a direct interaction of the chemical with the germ cell DNA, were a consequence of its induction of inflammation in the epididymis."
Reference: Working et al., 1985a and 1985b.

Type: Dominant lethal test
Species/strain: Rat/Fischer 344
Sex: Male
Route of Administration: Inhalation
Exposure period: 6 hours/day; 5 days
Doses: 3000 ppm
Results:
Genotoxic effects: negative
Method: other: In general conformance with OECD 478
GLP: unknown
Test substance: As prescribed, sections 1.1 to 1.4
Remarks: This study assessed the possible relationship between chloromethane -induced epididymal inflammation and the formation of dominant lethal mutations in sperm of Fischer 344 rats. Groups of 40 males were exposed to chloromethane (3000 ppm 6 hr/day for 5 days), with or without concurrent treatment with the anti-inflammatory agent 3-amino-1-(m-(trifluoromethyl)phenyl)-2-pyrazoline (BW 755C; 10 mg/kg, ip 1 hr pre- and post exposure); BW 755C was shown previously to inhibit chloromethane-induced epididymal inflammation. Control groups (n= 20) were untreated, injected as described above with BW 755C, or injected on the afternoon of day 5 with triethylenemelamine (0.2 mg/kg), a known dominant lethal mutagen. The dominant lethal mutations induced by chloromethane appear to be a consequence of its induction of inflammation in the epididymis. These data demonstrate the potential genotoxicity of inflammatory processes *in vivo*.
Reference: Chellman et al., 1986a.

Remarks: Subsequent investigations (Working and Chellman, 1989) have revealed that chloromethane -induced preimplantation loss was a result of cytotoxic rather than genotoxic effects on sperm, with a significant decrease in the count of motile sperm of normal morphology in exposed males during weeks 2 to 8 after treatment. In fact, examination of the fertilization rate during these weeks using a system of embryo recovery and culture revealed that the entire elevated rate of preimplantation loss detected in the dominant lethal assay was the result of failure of fertilization; it had no genetic component at all. Post-implantation death is considered a more reliable indicator of dominant lethality than is preimplantation loss. In the chloromethane dominant lethal assay, such increased post-implantation loss was detected only when the fertilizing sperm had been present at the site of chloromethane -induced acute inflammation in the cauda epididymis. Inflammatory cells, such as those in the chloromethane -exposed epididymis, are known to produce a variety of genetic lesions in the DNA of neighboring cells. Therefore, male rats were concurrently exposed to chloromethane and treated with an anti-inflammatory agent (BW755C) to inhibit the epididymal inflammation.

## 5.7 CARCINOGENICITY

Species/strain: Rat/Fischer 344
Sex: Male/Female
Route of Administration: Inhalation
Exposure period: 24 months (interim sacrifices at 6, 12 and 18 months)
Frequency of treatment: 6 hours/day, 5 days/week
Post exposure observation period: none
Doses: 50, 225 or 1000 ppm
Control group: Yes; Concurrent no treatment
Results: Sperm granulomas were noted in three male rats at 1000 ppm:
two at 6 months and one at 24 months. Their presence cannot be directly attributed to chloromethane exposure. Other lesions noted in rats, such as C-cell carcinoma, pituitary adenomas, and mandibular lymph node hyperplasias, were not related to chloromethane exposure.

Additional results of this study are presented in Section 5.4 (Repeat Dose).

Remark: There were no carcinogenic effects attributable to chloromethane in rats under the conditions of this study.
Method: other: In general conformance with OECD 453
Male and female rats were exposed by inhalation to chloromethane for 6 hours/day, 5 days/week at concentrations of 50, 225 or 1000 ppm for 24 months. Interim sacrifices were scheduled at 6, 12 and 18 months. A control group was treated concurrently (0 ppm). The usual parameters for a lifetime toxicity-oncogenicity study were measured. Body weight, clinical signs of toxic effects, and mortality were followed throughout the study. Blood and urine samples were taken for hematological, clinical chemical, and urine analysis from rats randomly preselected for necropsy at 6, 12, 18 and 24 months. The animals were then subjected to a complete gross pathological examination and a preselected battery of tissues taken and preselected organs weighed.
GLP: No
Test substance: As prescribed, sections 1.1 to 1.4
Reference: CIIT, 1983.

Species/strain: Mice/$B_6C_3F_1$
Sex: Male/Female
Route of Administration: Inhalation

Exposure period: 24 months (interim sacrifices at 6, 12 and 18 months)
Frequency of treatment: 6 hours/day, 5 days/week
Post exposure observation period: none
Doses: 50, 225 or 1000 ppm
Control group: Yes; Concurrent no treatment
Results: Renal tubuloepithelial hyperplasia and karymegaly were seen in male mice exposed to 1000 ppm for 12 months and progressed in severity throughout the study. Renal tumors were noted in 1000-ppm male mice sacrificed or dying between 12 and 21 months, including renal cortical adenoma, renal cortical adenocarcinoma, papillary cystadenoma, papillary cystadencarcinoma and tubular cystadenoma. The only renal neoplasms noted at concentrations less than 1000 ppm occurred in two 225-ppm male mice at the 24-month terminal sacrifice. The occurrence of these neoplasms was not statistically significant.

Renal cortical cysts were predominately seen in mice in the 1000-ppm group, whereas microcysts were noted most frequently in the 50-ppm group at 24 months. Both occurrences were different from controls but were not statistically significant.

Remarks: While the Battelle investigators (CIIT, 1983) reported an apparent increase in non-tumorous renal cortical micro-cysts in the 50 and 1000-ppm groups, subsequent review indicates the purported increases were a likely procedural artifact due to multiple pathologists examining the tissues and using different nomenclature (Johnson, 1988). Johnson pointed out three reasons for this conclusion in his review:

1. The cysts did not occur in a dose-responsive manner.
2. Similar cysts are noted in control mice of this strain at approximately the same frequency in the Dow Toxicology Laboratory.

In eight studies, the incidence varied from 0 to 14% with an overall mean of 6.6% (31/472). Furthermore, treated groups also had the same incidence range in the Dow studies.

3. Inconsistencies in histopathological terminology and lesion incidences in the study raise questions as to the validity of the purported effect.

There are several inconsistencies in the histopathological terminology and diagnostic pattern among the various sacrifice intervals and even within a sacrifice interval, suggesting that either more than one pathologist examined the tissues or the terminology used for the lesion was inconsistent.

Additional results of this study were presented in Section 5.4 (Repeat Dose).

Remarks: Chloromethane induced renal tumors in male mice at the highest concentration tested (1000 ppm).

Remarks: In this bioassay, there was considerable mortality in all groups of male mice, particularly in those of the highest exposure group. A plausible reason for this was the occurrence of dominance fighting among male mice that were caged together, with attendant injuries of the genitals and ascending infections of the urinary tract (Bolt and Gansewendt, 1993).

Remarks: When considering the possible mechanisms of tumor production by chloromethane, "some impact of the ascending infections of the urinary tract observed in the bioassay ought to be considered" (Bolt and Gansewendt, 1993).

Method: other: In general conformance with OECD 453
Male and female mice were exposed by inhalation to chloromethane for 6 hours/day, 5 days/week at concentrations of 50, 225 or 1000 ppm for 24 months. Interim sacrifices were scheduled at 6, 12 and 18 months. A control group was treated concurrently (0 ppm). The usual parameters for a lifetime toxicity-oncogenicity study were measured. Body weight, clinical signs of

toxic effects, and mortality were followed throughout the study. Blood and urine samples were taken for hematological, clinical chemical, and urine analysis from mice randomly preselected for necropsy at 6, 12, 18 and 24 months. The animals were then subjected to a complete gross pathological examination and a preselected battery of tissues taken and preselected organs weighed.

GLP: No
Test substance: As prescribed, sections 1.1 to 1.4
Reference: CIIT, 1983, Johnson, 1988.

Remark: In their review of the mechanisms of carcinogenicity of methyl halides, Bolt and Gansewendt (1993) conclude the following: "Chloromethane induces renal tumors only in male ($B_6C_3F_1$) mice, under the highest concentrations tested of 1000 ppm. For these particular conditions and this experimental system, the following arguments must be considered:

- The exposure concentration (1000-ppm) is close to a concentration (1500-ppm) that led, under repeated exposure, to a clear enhancement of the replication rate in the target tissue.

- The exposure conditions cause a glutathione depletion in the target tissue to <5% of the pre-exposure values [and results in enhanced lipid peroxidation in kidneys]. This [glutathione depletion] removes the co-factor of the glutathione-dependent primary metabolic pathway of chloromethane. The enzyme activities for the alternative oxidative (P-4501) pathway in the target tissue are sex-specific, higher in male than in female mice. This alternative pathway leads directly to formaldehyde.

- The glutathione depletion in the target tissue also removes the cofactor for FDH [formaldehyde dehydrogenase], the enzyme inactivating formaldehyde.

- DNA-protein cross-links, a lesion typical of formaldehyde, appear in the target tissue of male but not female mice, immediately after a single exposure to 1000-ppm chloromethane. Under these conditions, there also are indications of DNA single-strand breaks.

- In a long-term bioassay that showed renal tumors in male mice, retrograde infection of the urinary tract was noted. Inflammation processes also accompany liberation of reactive oxygen species and enhanced cell replication.

- In contrast to the closely related compounds methyl bromide and methyl iodide, chloromethane does not methylate DNA, as demonstrated by two independent DNA-binding assays in vivo.

These very different arguments indicate that the formation of tumors in the chloromethane bioassay took place under conditions that preclude extrapolating the risk factors to man."

"Although this compound is clearly mutagenic *in vitro*, two independent DNA-binding studies show that it does not alkylate DNA of putative target organs in rodents. The mechanism of mutagenicity of chloromethane is not known."

"Carcinogenicity has been studied in rats and in mice. There are a number of reasons why the tumor formation observed in these bioassays (renal tumors only in male mice and only at the highest dose level) might not be extrapolated to realistic situations of human exposure. It is probably important for the risk assessment of chloromethane to determine the mechanisms by which it can produce renal tumors and to demonstrate (as has been demonstrated for other chemicals) that such a mechanism is not operative at low concentrations to which people are exposed."

Reference: Bolt and Gansewendt, 1993.

Species/strain: Mouse
Sex: Male/Female
Route of Administration: Inhalation

Remarks: "The biotransformation of several low molecular weight xenobiotics known to be substrates of P4502El has been implicated in the male mouse-specific nephrotoxicity and/or carcinogenicity of dimethylnitrosamine, chloroform, and acetaminophen (Smith et al., 1983, 1984; Branchflower et al., 1984; Smith and Hook, 1984; Hong et al., 1987; Hu et al., 1993)."

Remarks: "This enzyme, likely cytochrome P4502El, seems to be involved in renal chloromethane biotransformation in the mouse since microsomes obtained from the castrated mouse incubated with chloromethane produced significantly lower amounts of formaldehyde. The rates of formaldehyde formation from chloromethane observed in the kidney microsomes from the female mouse were similar to that observed in kidney microsomes from the castrated male; testosterone pretreatment increase the capacity for chloromethane biotransformation of renal microsomes from the female mouse to those seen in the male."

Remarks: "Interestingly, the mouse renal cytochrome P4502El was not induced by the classical P4502El inducer ethanol (Koop et al., 1989; Koop and Tierney, 1990), but could be inhibited by approximately 50% by the cytochrome P4502El inhibitor (Guengerich et al., 1991) diethyldithiocarbamate."

Remarks: 'The concentrations of the P4502El protein in mouse kidney were also influenced by the hormonal status of the animal - castration of the male significantly reduced P4502El protein concentrations; in the female, testosterone pretreatment elevated renal P4502E1 concentrations to those seen in the naive male. Testosterone pretreatment was also reported to increase total renal cytochrome P450 content of the female mouse to that of the male (Branchflower et al., 1984). No sex differences and no effect of testosterone pretreatment on the biotransformation of chloromethane were observed in liver microsomes from the mouse; the hepatic enzyme could be induced by ethanol pretreatment and was inhibited by >75% by diethyldithiocarbamate."

Remarks: "Strain differences in the capacity of renal microsomes from the male mouse were observed. The extent of chloromethane oxidation observed in microsomes of the male of different strains was correlated to differences in the rates of oxidation of chlorzoxazone ($r^2$=0.87) and in the P4502El protein content as determined by immunoblotting ($r^2$=0.90)."

Remarks: "Kidney microsomes from both male and female rat did not biotransform chloromethane to detectable concentrations of formaldehyde, had a very low capacity to oxidize chlorzoxazone, and also did not respond to ethanol pretreatment. In rat liver microsomes, no sex-difference in the capacity to oxidize chloromethane and chlorzoxazone was observed; cytochrome P4502El activity could be increased by ethanol pretreatment more than two-fold and was inhibited by >80% by diethyldithiocarbamate. Moreover, the P4502El protein concentrations determined by immunoblotting were not significantly different."

Remarks: "Sex-dependent differences in the capacity for the oxidative metabolism of other cytochrome P4502E1 substrates such as chloroform and 1,1-dichloroethene and a role for androgens in the renal bioactivation of these male mouse-specific nephrotoxins have been observed previously (Smith et al., 1983, 1984; Branchflower et al., 1984; Smith and Hook, 1984; Speerschneider and Dekant, 1995).

"Our results have shown that a sex- and species-specific oxidation in the mouse also occurs with chloromethane. Previous work comparing the relative concentrations of cytochrome P4502El protein in kidney microsomes from mice have shown that sex differences seen are not only due to different activities of the cytochrome P4502El, but due to different concentrations of it in the kidney of the male and female mouse (Speerschneider and Dekant, 1995). Species differences in renal P4502El content and chloromethane oxidation were only seen in the mouse; in rat the renal biotransformation of chloromethane was not observed and renal activities of cytochrome P4502El were very low. This, the species and target-organ specific biotransformation may account for the sex and species-specific tumorigenicity of chloromethane.

"The product of chloromethane oxidation, formaldehyde, is genotoxic in bacteria (Heck and Casanova-Schmitz, 1983); however, the role for genotoxicity in the tumorigenicity of chloromethane in the kidney has not been established. Toxic effects caused by formaldehyde in the proximal tubule cells and the high capacity of the kidney for regenerative cell proliferation (Short et al., 1987; Goldsworthy et al., 1990; Short and Swenberg, 1991) may be major contributors to tumorigenicity in the kidney of the male mouse exposed to chloromethane.

"An increased rate of formaldehyde production from chloromethane in kidney microsomes from the male mouse was also observed earlier, but was not implicated in chloromethane tumorigenicity since the rates for formaldehyde production observed in this study were much higher in the liver (Jäger et al, 1988). However, the use of microsomes from homogenates of the kidney, an organ which contains a variety of different cell types, may underestimate the metabolic capacities of the target cell for the toxicity of chloromethane, the proximal tubular epithelial cells (Dekant and Vamvakas, 1992; Anders and Dekant, 1993). This cell type contains most of the renal cytochrome P4502El, thus forming high concentrations of formaldehyde in the target cell of toxicity (Hu et al., 1990). Moreover, after inhalation exposure, this cell type is exposed to high concentrations of chloromethane present in the systemic circulation due to the high blood flow to the kidney and the tubular epithelial cells.

"Since renal cytochrome P4502E1 was not detected in several human kidney samples from both the male and female donor (Speerschneider and Dekant, 1995), a risk assessment for chloromethane based on its tumorigenicity to the kidney of the male mouse seems to be inappropriate."

Method: other
GLP: Unknown
Test substance: As prescribed, sections 1.1 to 1.4
Reference: Dekant et al., 1995.

## 5.8 TOXICITY TO REPRODUCTION

Type: Fertility
Species/strain: Rat/ Fischer 344
Sex: Male
Route of Administration: Inhalation
Exposure period: Exposed for 5 days, not exposed for 3 days, exposed again for 4 days
Frequency of treatment: 6 hours/day

| | |
|---|---|
| Doses: | 3500 ppm |
| Control group: | Yes; Concurrent no treatment |
| Results: | Testicular lesions (delay of spermiation, germinal epithelial vacuolisation, and cellular exfoliation) and bilateral epididymal granulomas were observed in most animals with onset at day 9 or 11 following the initiation of exposure. Animals examined at 19 days post-exposure showed lesions with a greater degree of severity. In animals killed 70 days following exposure, 70-90% of the seminiferous tubules lacked any germinal cells and varying degrees of recovery of spermiation were observed in 10-30% of the tubules. The authors' had proposed that chloromethane acts centrally to lower circulating testosterone. Nonprotein sulfhydryls were depleted in liver, testis, and epididymis after chloromethane exposure, but not in whole blood. This finding indicated that sulfhydryl depletion was not due to direct alkylation, but was enzymatically mediated. Sulfhydryl depletion did not correlate with lesion development. It was concluded that the initial testicular effects of chloromethane are directed at either the late stage spermatids or the Sertoli cells with a resultant delay in spermiation. |
| Method: | Experiments were carried out in rats to characterize the development of the testicular and epididymal lesions and any associated effects on reproductive hormones. Adult F-344 rats were exposed to 3500 ppm chloromethane 6 hr/day for 5 days, not exposed for 3 days, and exposed again for 4 days. The 3-day break in exposures was used because of the poor condition of rats surviving 5 consecutive days of exposure. Tissue processing: For light microscopy, six or eight treated and two control animals were killed on Days 5, 7, 9, 11, 13, 15, 19 and 70 after starting exposures. Animals were anesthetized and perfused through the ascending aorta with 0.1% procaine HCl in Ringer's balanced salts; this step was followed by perfusion with Karnovsky's fixative.<br>Testes and epididymides were removed and stored in fixative for up to 2 weeks. A 2-mm thick transverse section from one testis of each animal and longitudinal sections from the head and tail of the ipsilateral epididymis and processed for staining. The following criteria were used in evaluating the tissue sections: lesions were judges "minimal" if less than 10% of tubules in the most vulnerable stage were affected in <50% of the rats. "Moderate" severity was accorded to pathology affecting 20-50% of the tubules in > 50% of the animals, while "severe" lesions affected >50% of the tubules in >50% of the animals. For hormone analysis, the pituitary gland was removed and stored in Karnovsky's fixative and mixed blood from the neck wound following decapitation was assayed for serum testosterone. For subsequent challenge studies, other chloromethane-exposed or control animals were injected sc with either 100 IU human chorionic gonadotropin to test for Leydig cell function, 100 ng/kg luteinizing hormone releasing hormone ethylamide to test for pituitary function, or saline vehicle. Two hours after injection, animals were killed and sera were assayed for free testosterone. Tissue non-protein sulfhydryl content (NPSH) was determined for testes, caput epididymis, cauda epididymis, liver and heart blood. Statistical analyses were performed by Student's t Test. |
| GLP: | Unknown |
| Test substance: | As prescribed, sections 1.1 to 1.4 |
| Reference: | Chapin et al., 1984. |

| | |
|---|---|
| Type: | Two-generation study |
| Species/strain: | Rat/ Fischer 344 |
| Sex: | Male/Female |
| Route of Administration: | Inhalation |
| Exposure period: | 6 hours/day in 80 females/group: 10 weeks prior to mating (5 days/week); then 7 days/week for 2 weeks during mating and to gestation day (GD) 18; |

exposure discontinued from GD18 to postnatal day (PND) 4; and exposure resumed from PND 4 to PND 28.
6 hours/day in 40 males/group: 10 weeks prior to mating (5 days/week); then 7 days/week for 2 weeks during mating; 10 males necropsied and remaining 30 mated to 60 previously unexposed females.
$F_1$ pups exposed to the same concentration as their parents for 10 weeks and then mated.

Frequency of treatment: See exposure period
Post exposure observation period: See exposure period
Premating exposure period: male: 10 weeks, female: 10 weeks
Duration of the test: To lactation and weaning
Doses: 150, 475 and 1500 ppm
Control group: Yes; Concurrent no treatment
NOAEL Parental: 150 ppm (300 mg/m$^3$)
NOAEL F1 Offspring: 150 ppm (300 mg/m$^3$)
NOAEL F2 Offspring: 150 ppm (300 mg/m$^3$)
LOAEL Parental: 475 ppm (statistically significant reduced male fertility)
Results: General parental toxicity: Severe testicular degeneration (10/10) and granulomas of the epididymis (3/10) were observed only in the 1500 ppm group males necropsied after the first mating period. No litters were born to the males exposed to 1500 ppm and mated to either exposed or unexposed female rats (0 litters/87 exposed plus unexposed females) despite equal evidence of copulation plugs in all groups. There were no significant differences in the number of litters born to 150-ppm groups but fewer litters were born to the 475-ppm groups than to controls. When bred 10 weeks after cessation of exposure 5/20 1500-ppm $F_0$ males had regained their ability to sire normal litters. $F_0$ males exposed to 475 ppm were as fertile as control males (15/20 475 ppm vs. 13/20 controls).

After weaning, the $F_1$ pups from 475, 150 and 0 ppm were exposed to the same concentration as their parents for 10 weeks and mated. There was a tendency toward decreased fertility only in the 475-ppm group. No effect on reproduction was seen in the 150-ppm group at any time.

Toxicity to offspring: No differences in litter size, sex ratio, pup viability, or pup growth were found among the 475, 150 or control $F_0$ groups.

Method: other: In general conformance with OECD 416
GLP: Unknown
Test substance: As prescribed, sections 1.1 to 1.4
Reference: Hamm et al. (1985).

Type: Fertility
Species/strain: Rat/ Fischer 344
Sex: Male
Route of Administration: Inhalation
Exposure period: 5 days
Frequency of treatment: 6 hours/day
Duration of the test: Up to 3 weeks
Doses: 3000 ppm
Control group: Yes; Concurrent no treatment
Results: This study assessed the possible relationship between chloromethane-induced epididymal inflammation and the formation of dominant lethal mutations in sperm of Fischer 344 rats. The dominant lethal mutations induced by chloromethane appear to be a consequence of its induction of inflammation in the epididymis.
Method: other: Groups of 40 males were exposed to chloromethane (3000 ppm 6 hr/day for 5 days), with or without concurrent treatment with the anti-inflammatory agent 3-amino-1-m-(trifluoromethyl)phenyl)-2-pyrazoline (BW 755C; 10 mg/kg, ip 1 hr pre- and post-exposure); BW 755C was

shown previously to inhibit chloromethane -induced epididymal inflammation. Control groups (n= 20) were untreated, injected as described above with BW 755C, or injected on the afternoon of day 5 with triethylenemelamine (0.2 mg/kg), a known dominant lethal mutagen.

GLP: Unknown
Test substance: As prescribed, sections 1.1 to 1.4
Reference: Chellman et al., 1986a.

Type: Fertility
Species/strain: Rat/ Fischer 344
Sex: Male
Route of Administration: Inhalation
Exposure period: 5 days
Frequency of treatment: 6 hours/day
Doses: 1000 and 3000 ppm
Control group: Yes
Concurrent no treatment

Results: Male rats exposed to 1000 ppm were able to fertilize female rats at a rate comparable to control males. Male rats exposed to 3000 ppm 6 hours per day for 5 consecutive days were infertile two weeks after exposure and remained below control animals for at least 8 weeks. Testes weights were significantly decreased in the 3000-ppm group for 3-8 weeks post-exposure. More than 50% of the animals in the 3000-ppm group showed sperm granulomas in the epididymis, along with a significant decrease in testicular spermatid head counts, delay in spermiation, epithelial vacuolisation, luminal exfoliation of spermatogenic cells and multinucleated giant cells. In addition, sperm isolated from the vas deferens showed significantly decreased numbers and an increased incidence of abnormal sperm head morphology at 1-week post-exposure. At 3-weeks post-exposure, a significant decrease in sperm motility and increased incidence of headless tails were observed. Most of these observations were reversed by 16-weeks post-exposure. The authors concluded that the pre-implantation losses were due to genotoxic effects on sperm in the vas deferens and epididymis at the time of exposure. In a follow -up study male rats were treated as noted above or received a single injection of triethylenemelamine (TEM; a known dominant lethal mutagen) as a positive control for genotoxicity. At weeks 1-3 post-exposure preimplantation losses in the 3000-ppm group did not exceed the number of unfertilised ova that was noted for the TEM group. Subsequent study has gone on to show that the apparent genetic effect is instead due to the severe inflammation of the epididymis with the release of reactive oxygen intermediates; this is a cytotoxic, rather than genotoxic, effect. Treatment with an anti-inflammatory agent Burroughs-Welcome BW755C inhibited the inflammation caused by chloromethane. Females bred to treated males given BW755C did not exhibit the characteristic elevation in post-implantation embryonic death rate "leading to the conclusion the chloromethane-induced dominant lethal mutations, rather than being caused by a direct interaction of the chemical with the germ cell DNA, were a consequence of its induction of inflammation in the epididymis."

Method: Studies were performed to assess the effects of inhaled chloromethane on sperm quality and testicular histopathology in the rat. Adult male F-344 rats were exposed to 1000 or 3000 ppm chloromethane 6 hr/day for 5 days or received an ip injection of 0.2 mg TEM/kg on the afternoon of Day 5. Five males from a control group and each of the three treatment groups were killed weekly for 8 weeks, and five more from the control and 3000 ppm groups at Week 16 post exposure.

GLP: Unknown

Test substance: As prescribed, sections 1.1 to 1.4
Reference: Working et al., 1985a and 1985b; Working and Bus, 1986; Working and Chellman, 1989.

## 5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

Species/strain: Rat/Fischer 344
Sex: Female
Route of Administration: Inhalation
Duration of the test: To day 20 of pregnancy
Exposure period: Days 7-19 of gestation
Frequency of treatment: 6 hours/day
Doses: 100, 500 and 1500 ppm
Control group: Yes; Concurrent no treatment
NOAEL Maternal Toxicity: 500 ppm (1000 mg/m$^3$)
NOAEL teratogenicity: 1500 ppm (3000 mg/m$^3$)
Results: Maternal general toxicity: Exposure to 1500 ppm resulted in decreased food consumption, weight gain, and body weight gain.
Pregnancy/litter data: There was an absence of effect on implantations, resorptions, dead fetuses, live fetuses, and sex ratio.
Foetal data: Fetal body weight was reduced in both sexes at 1500 ppm as was female fetal crown-to-rump length. Skeletal ossification was delayed at 1500 ppm only, indicative of toxicity, but no teratological malformations were increased at any concentration in the rat fetuses.
Method: other: In general conformance with OECD 414
Groups of 25 bred Fischer 344 rats were exposed 6 hours per day to 0, 100, 500 or 1500 ppm chloromethane gas on gestation days 7-19, and sacrificed on day 20 of gestation and examined for maternal reproductive and fetal parameters.
GLP: Unknown
Test substance: As prescribed in 1.1-1.4
Remarks: There was no evidence of teratogenicity in the groups exposed to 100 or 500 ppm. Maternal and fetal toxicity were grossly apparent at 1500 ppm. Reduced maternal weight gain and depressed body weight was found at sacrifice. Fetal body weight was reduced in both sexes at 1500 ppm as was female fetal crown-to-rump length. There was an absence of effect on implantations, resorptions, dead fetuses, live fetuses, and sex ratio, supporting the conclusion that the effect on the fetuses at 1500 ppm was secondary to maternal and possibly fetal toxicity (Bus et al., 1980). Skeletal ossification was delayed at 1500 ppm only, indicative of toxicity, but no teratological malformations were increased at any concentration in the rat fetuses.
Reference: Wolkowski-Tyl et al., 1983b.
Species/strain: Rat/Fischer 344
Sex: Female
Route of Administration: Inhalation
Duration of the test: Rats were sacrificed 0, 2, 4 and 8 hours post-exposure
Exposure period: Gestation day 19 of gestation
Frequency of treatment: 6 hours
Doses: 1500 ppm
Control group: Yes; Concurrent no treatment
Results: Evaluated maternal and fetal non-protein sulfhydryl (NPSH) levels in treated animals compared to sham-exposed rats.
Maternal general toxicity: Maternal liver and kidney NPSH were maximally depressed to 14.9 and 27.4% of control value immediately after exposure. Two hours later values had risen to 36.4 and 67.4% of controls with return to control levels at 8 hours. Maternal blood NPSH was unaffected.

Foetal data: Placental NPSH was unaffected. Fetal placental NPSSH was 87.5% of control immediately after exposure and returned to control levels by 4-hour post-exposure. Fetal liver and carcass NPSH were 79.4% and 72.7% of control at the end of exposure and maximally depressed to 66.8 and 71.0% at 2 hours post-exposure. At 8 hours they were 86.5 and 92.6% of controls, respectively.

Method: Pregnant female rats were exposed to chloromethane at 1500 ppm (control rats were not exposed) for six hours on gestation day 19 and sacrificed at 0, 2, 4 or 8 hours post-exposure to evaluate the effect of chloromethane-exposure on maternal and fetal non-protein sulfhydryl levels in the blood and tissues.

GLP: Unknown

Test substance: As prescribed in 1.1-1.4

Reference Bus et al., 1980.

Species/strain: Mouse (female C57BL/6 mice bred to C3H male mice to produce $B_6C_3F_1$ offspring)

Sex: Female

Route of Administration: Inhalation

Exposure period: Days 6-17 of gestation

Frequency of treatment: 6 hours/day

Doses: 100, 500 and 1500 ppm

Control group: Yes; Concurrent no treatment

NOAEL Maternal Toxicity: 500 ppm (1000 mg/m$^3$)

NOAEL teratogenicity: 100 ppm (200 mg/m$^3$)

Results: Maternal general toxicity: Severe maternal toxicity forced premature sacrifice of 1500-ppm groups on days 10-14 of gestation. Urogenital bleeding and central nervous system dysfunction began in one mouse on the 4th day of exposure to 1500 ppm (9th day of gestation). A specific lesion of the internal granular layer of the cerebellum was seen microscopically in the mouse dams exposed to 1500 ppm after 4-day exposure. The effect was not seen after 90 days of repeated exposure to 1500 ppm suggesting that the added stress of pregnancy may have enhanced the production of the lesion in the brain of this mouse strain. In addition to the mouse with vaginal bleeding after 4 days, one animal appeared to be walking on tip-toes and after subsequent exposures, tremors, a hunched appearance, difficulty in righting, disheveled fur, and bloody urine were frequently observed. The dams exposed to 1500 ppm were therefore terminated at 6-9 days and tissues taken from uterus, kidneys, lungs and brain in addition to the usual organs and tissues saved for teratogenic evaluation. In the dams, only the brains of the 1500-ppm group, which were discussed previously, showed histological changes. Maternal water and food consumption was increased relative to controls in the 500-ppm group and days 6-14 of gestation and water consumption only during days 14-18. Neither maternal body weight nor weight gain were altered at either 500 or 100 ppm.

Pregnancy/litter data: The reproductive parameters studied which were primarily dependent upon what occurred during the pre-exposure period, were not affected in the 500 or 100-ppm groups of mice nor, where data were available, in the 1500-ppm groups.

Foetal data: Fetal development parameters, which were dependent upon the exposure period, were also normal except for a reported small but statistically significant increase in heart defects in the 500-ppm group only. According to the authors' abstract, "The anomaly, a reduction or absence of the atrioventricular valve, chordae tendinae, and papillary muscle, was observed on the left side (biscuspid valve) in three fetuses and on the right side (tricupsid valve) in six fetuses (three male and three females)." Contrary to what might be expected, ossification was apparently faster in exposed fetuses and was associated with increasing dosage. The trend was not statistically significant however.

Method: other: In general conformance with OECD 414
GLP: Unknown
Test substance: As prescribed in 1.1-1.4
Reference: Wolkowski-Tyl et al., 1983a.
Species/strain: Mouse (female C57BL/6 mice bred to C3H male mice to produce $B_6C_3F_1$ offspring)
Sex: Female
Route of Administration: Inhalation
Exposure period: Days 6-18 of gestation
Frequency of treatment: 6 hours/day
Doses: 250, 500 and 750 ppm
Control group: Yes; Concurrent no treatment
NOAEL Maternal Toxicity: 500 ppm (1000 mg/m$^3$)
NOAEL teratogenicity: 250 ppm (500 mg/m$^3$)
Results: Maternal general toxicity: Dams exposed to 750 ppm exhibited ataxia commencing on gestation day 12 and they became hypersensitive to touch and sound, as well as exhibiting tremors and convulsions. Six dams exposed to 750 ppm died and one was sacrificed *in extremis* prior to the scheduled sacrifice. There was a significant decrease in body weight in the 750 ppm group, a decrease in weight gain and a decrease in absolute weight gain (weight gain minus gravid uterine weight). The other two lower exposure groups showed no change in the above parameters.

Pregnancy/litter data: Reproduction indices were unaffected except for a significant exposure-related increase in the number and percentage of affected (non-live plus malformed) fetuses per litter with the incidence of affected fetuses in the 750-ppm group significantly higher than controls.

Foetal data: The investigators reported that they had seen an increase in fetal heart malformations in the 500 and 750-ppm groups (which showed maternal toxicity), but not at 250 ppm. The authors' summary states, "There was a statistically significant increase in the incidence of heart defects in the 500 and 750-ppm group relative to controls. Of 37 fetuses in the study with heart defects, 23 were female, 14 were males. The heart defects observed included: absent or abnormal tricuspid valve; reduced number of papillary muscles and/or chordae tendinae in the right side; small right ventricle; globular heart, and white spots in the left ventricle wall. Multiple malformations were observed in one fetus from the 500-ppm group and three in fetuses in the 750-ppm group." The primary lesion consisted of a reduction in the number of papillary muscles, sometimes with reduced chordae tendinae of the tricuspid valve on the right side of the heart. This lesion was reported in 14 of 400 fetuses (3.5%) at 750 ppm and in 7 out of 444 fetuses (1.6%) at 500 ppm versus 2 fetuses out of 433 (0.5%) in controls.

Method: other: In general conformance with OECD 414
GLP: Unknown
Test substance: As prescribed in 1.1-1.4
Remarks: According to John-Green et al. "The normal anatomy of the tiny papillary muscles in the mouse heart and the variability of their appearance complicate a definitive diagnosis concerning chloromethane induced structural alterations." These authors noted that the reported incidence of malformations was low in the first study (Wolkowski-Tyl et al., 1983a) and even lower in the second study (Wolkowski-Tyl et al., 1983b); that the "second study confirmed the existence of an anomaly of the tricuspid valve only"; and the "nature of the lesion was somewhat different."
Reference: Wolkowski-Tyl et al., 1983b.
Species/strain: Mouse (female C57BL/6 mice bred to C3H male mice to produce $B_6C_3F_1$

offspring)
Sex: Female
Route of Administration: Inhalation
Exposure period: Gestation day 11.5 to 12.5 (day 0 was the day the copulatory plug was found)
Frequency of treatment: Phase I: 24 hours/day; Phase II: 24 hours/day; also 6 litters evaluated following exposure to 1000 ppm for 12 hours
Doses: Phase I: 12 litters from 250-300 ppm exposure to dams and 11 control litters;
Phase II: 7 litters from 300-ppm exposure to dams and 5 control groups;
Also evaluated 6 litters from dams exposed to 1000 ppm
Control group: Yes; Concurrent no treatment
Method: other: Female C57BL/6 mice were bred to C3H male mice to produce $B_6C_3F_1$ offspring. Females were exposed from Gestation day 11.5 to 12.5 (day 0 was the day the copulatory plug was found). The frequency of treatment for Phase I: 24 hours/day; Phase II: 24 hours/day; also 6 litters evaluated following exposure to 1000 ppm for 12 hours. The dose levels for Phase I: 12 litters from 250-300 ppm exposure to dams and 11 control litters; Phase II: 7 litters from 300-ppm exposure to dams and 5 control groups; also evaluated 6 litters from dams exposed to 1000 ppm.
GLP: Unknown
Test substance: As prescribed in 1.1-1.4
Remarks: The study was an attempt to extend the earlier studies by intensifying the exposure (24 consecutive hours) at the key period of development days 11.5 to 12.5. As a result of more serious toxic effects from the 24-hour exposure, it was necessary to lower the exposure concentration to 250-300 ppm, considerable lower than the concentrations used by Wolkowski-Tyl. It is possible the 24-hour exposure period selected may not have been the most critical (Tyl, 1985).
Those mice fetuses from the second phase were read “blind” by the investigators who, according to the summary “became increasingly aware of the considerable interanimal variability in appearance of the papillary muscles and the inherent difficulty in confirming their presence owing to their small size and the delicate and precise dissection required to view them.”
Reference: John-Green et al., 1985.

## 5.10 OTHER RELEVANT INFORMATION

### A. Specific toxicities (Neurotoxicity, Immunotoxicity, etc.)

Type: NEUROTOXICITY
Remarks: Nineteen guinea pigs were exposed to 2% (20,000 ppm) chloromethane 10 minutes per day, 6 times per week for 7-70 days.
According to the available abstract, the exposures were given "in a pressurized chamber” but it is not clear if the pressure was above atmospheric. Samples of cerebellum, cerebrum, mesencephalon, brain stem, spinal medulla, and spinal ganglia were stained for light microscopy and some sections were examined after staining for electron microscopy. Six guinea pigs showed ataxia and paresis after 17 exposures but four did not show toxic symptoms until after 25 exposures. Numerous changes in the granular layer are described. Focal necrosis and edema was seen after 21 days. Later alterations in the Purkinje cells were observed and electron microscopy showed increased density of nuclear chromatin of granular cells. There was swelling of cytoplasm with vacuolar degeneration. The number of synaptic vesicles decreased and changes in the Purkinje cell axons were seen later.
References: Kolkmann and Volk, 1975.

Remarks: Female C57BL/6 mice were exposed intermittently and continuously to chloromethane gas in a neurotoxicity study (Landry et al., 1985). This strain and sex were chosen because it had been found to be particularly sensitive to the neurotoxic effects of chloromethane (Morgan et al., 1982). The female mice were scheduled for 11 days of exposure, either 22 hours per day to 15, 50, 100, 150, 200 or 400 ppm or 5.5 hours per day to 150, 400, 800, 1600 or 2400 ppm. Separate groups were exposed for neurofunctional testing and pathology. In addition, all moribund mice were necropsied and, together with the pathology group, received extensive histologic examination with particular emphasis on the nervous system. Mice exposed to 15, 50 or 100 ppm for 22 hours per day showed no overt effect nor did mice exposed 5.5 hours per day to 150, 400 or 800 ppm. Mice exposed 22 hours per day to 400 ppm were incapacitated after 2 days. Exposure to 400 ppm, 22 hours per day was lethal after 4 days as was 200 ppm 22 hours per day after 5 days. Mice exposed to 150 ppm 22 hours per day were sacrificed in a moribund condition after 10.5 days. The 200-ppm group exposed 22 hours per day were severely affected after 3 days but were not moribund. They were ataxic, but could move forward rapidly although they would frequently fall on their sides. The following table, adapted from Landry, et al. summarizes their results:

SUMMARY OF NEUROMOTOR PERFORMANCE AND CEREBELLAR HISTOPATHOLOGY IN MICE EXPOSED TO CHLOROMETHANE (adapted from Landry et al., 1985)

| **Exposure Conc. (ppm)-interval** | **Performance Decrement** | **Cerebellar Lesions**[a] | **In-life Observations** | **Histopathology Liver** | **Histopathology Kidney** |
|---|---|---|---|---|---|
| 0-C | None | None | Normal appearance | Normal | Normal |
| 15-C | None | None | Normal appearance | Normal | Normal |
| 50-C | None | None | Normal appearance | Normal | Normal |
| 100-C | None | Slight (100%) | Normal appearance (possible body weight decrease) | Slight | Normal |
| 150-C | Severe (after 4 days) | Moderate (100%) | Moribund in 10 days | | |
| 200-C | Incapacitated (after 4 days) | Severe (100%) | Lethal in 5 days | | |
| 400-C | Incapacitated (after 2 days) | Severe (100%) | Lethal in 4 days | Focal Necrosis | Normal |
| 0-I | None | None | Normal appearance | Normal | |
| 150-I | None | None | Normal appearance | Normal | |
| 400-I | Questionable on Day 4 | Slight (33%) | Normal appearance | Slight | Normal |
| 800-I | Slightly (only on Day 4) | Slight (67%) | Normal appearance | Slight | Normal |
| 1600-I | Moderate (only on Day 4) | Slight 65%) | Slightly stiff legs (Day 11) | Slight | Normal |
| 2400-I | Moderate on Day 4, incapacitated by Day 8 | Slight to moderate (100%) | Red urine (at 4-7 days); sick (by 5 days); moribund (by 9 days) | Slight | Very slight |

[a]At termination of the respective exposure groups, the percentages affected are provided in parentheses. The lesions consisted primarily of granular cell layer degeneration. C = 22 hours/day; I = 5.5 hours/day."

The no-effect level for 22-hour "continuous" exposure appeared to be 50 ppm. "Intermittent" 5.5-hour daily exposures to 150 ppm were also without affect.The investigators could not develop clear concentration-time relationships for performance decrements since injury to the liver and kidneys at higher exposure levels produced illness and decreased the ability of the mice to perform on the rotating rod. Injury was observed in the livers of mice exposed to 100 ppm or more, for 22 hours per day but none at 15 or 50 ppm. In mice exposed to 150 ppm 5.5 hours per day, liver injury was slight and appeared to be glycogen depletion without degeneration or necrosis. Kidney injury was observed only in the 2400-ppm group exposed 5.5 hours per day.

References: Landry et al., 1985.

Type: IMMUNOTOXICITY

Remark In animals, the only effects that could possibly be considered immunological effects were lymphoid depletion of the spleen and splenic atrophy observed in mice exposed to 1000-ppm chloromethane for up to 2 years (CIIT 1981). The lymphoid depletion was first observed in mice killed after 6 months of exposure, while the splenic atrophy was observed in mice killed after 18 months. The lower exposure level in this study (225 ppm) cannot be considered a NOAEL for immunological effects, however, because more sensitive tests for immune function were not conducted. In addition, cats exposed continuously to chloromethane for 3 days had higher incidences of brain lesions than did control cats (McKenna et al., 1981a). The lesions, however, were consistent with infection or post-vaccinal reaction (the cats were vaccinated for panleukopenia by the supplier). Exacerbation of viral-induced central nervous system disease could not be ruled out. It is not known whether the exacerbation would represent an immunological effect.

Reference: As cited in ATSDR, 1990.

## B. Toxicodynamics, toxicokinetics

## 5.11 EXPERIENCE WITH HUMAN EXPOSURE

Type: ODOR THRESHOLD

Remarks: A report by Stahl (1973), as cited in the IARC Monograph (1986), that chloromethane has an odor threshold of 10 ppm seems extremely doubtful. Torkelson and Rowe (1981) concluded that chloromethane has a weak odor and inadequate warning properties based on the frequency with which excessive exposures had occurred. Putz-Anderson et al. (1981a) reported that neither 100 nor 200 ppm had an odor that they felt needed masking during performance tests on 56 human subjects. The subjects were no more successful than chance in guessing whether they were being exposed to 0, 100 or 200 ppm. It is safe to conclude that at concentrations likely to be encountered inside or outside the work place, chloromethane will have no odor.

Reference: As noted above.

Type: OCCUPATIONAL EXPOSURE

Remarks: A study was conducted in four chemical plants in the United States to determine the workplace concentrations by evaluating the personal 8 hour time-weighted average (TWA) of chloromethane. In the three plants that produced chloromethane the 8-hour TWAs ranged from non-detectable (less than 0.1 ppm) to 12.7 ppm TWA (Cohen, et al., 1980). In the fourth plant where chloromethane was used as a blowing agent in the production of foam, the 8-hour TWAs ranged from 3.0-21.4 ppm. Currently, the typical operational exposures seen in the plants of Dow Corning are less than 0.5 ppm as an 8-hour TWA; most exposures were at non-detectable levels (Heffel, 2000). Currently, personal monitoring indicates employee exposures at less than 1 ppm for an 8-hour TWA at the GE Silicones manufacturing plant (Browning, 2000).

References: Noted above.

Type: TOXICOKINETICS

Results: After inhalation as a single breath of $^{38}$C-chloromethane by volunteers, 29% of the inhaled radioactivity was excreted in expired air within one hour. The urinary excretion was < 0.01% /min. Chloromethane was shown to be slower in excretion than predicted based on the blood: air partition coefficient, suggesting it reacts with substances in the bloodstream.

References: Morgan et al., 1970.

Type: TOXICOKINETICS - VOLUNTEER STUDY

Results: When studied in humans, absorption appears to be quite similar to animals. The most extensive data were obtained by Nolan, et al. (1985) who exposed six human volunteers for six hours on separate days to 10 and 50 ppm of the gas. Plateaus were reached for blood and expired air concentrations within one hour and, as in animals, were proportional to the inhaled concentrations. Consistent with earlier reports (Stewart et al., 1977; Putz-Anderson et al., 1981a), the six subjects fell into two distinct groups, one group having twice the blood and three times the expired air concentrations of the second group. Nolan et al. questioned the toxicological significance of the difference that they felt was due to a demonstrated two-fold difference in the rates at which the two groups metabolized chloromethane.

Results: Nolan et al. (1985) showed that in contrast to rats and dogs, special handling was necessary or chloromethane *per se* quickly disappeared from human blood. Sealed human blood samples (headspace analysis) had to be heated to 100°C for one minute in order to prevent enzymatic breakdown of the chloromethane. They also observed that chloromethane was eliminated in the breath at a slower rate in those volunteers with the higher venous blood and expired air concentrations. They concluded the difference was due to greater metabolism in the group with the lower blood concentrations, but that it was of questionable toxicological significance. Nolan et al. observed that since there are two major pathways by which chloromethane is metabolized it "suggests that differences in species or individual sensitivity are unlikely to be a simple function of the overall metabolic rate. Thus, in the absence of data on the relative importance of these pathways, it is premature to speculate that one group may be more sensitive than the other." (Nolan et al., 1985). Chloromethane was rapidly eliminated and metabolized by both groups and thus has a low potential to accumulate in either group during prolonged or repeated exposure. Contrary to a report by van Doorn et al. (1980), S-methylcysteine was not increased in urine by either exposure concentration. Hence it is doubtful that this substance can be used as a measure of exposure to chloromethane (Nolan et al., 1985).

References: Nolan et al., 1985.

Type: HUMAN METABOLISM

Results: Redford-Ellis and Gowenlock (1971a, 1971b) studied the reaction of chloromethane with blood, and preparations of liver, brain and kidney *in vitro*. In plasma, $^{14}CH_3Cl$ radioactivity was found only in albumin. On hydrolysis the major reaction produced was S-methylcysteine with only small amounts of 1- and 3-methyl-histidine.

Results: In erythrocytes about 40% of the radioactivity was bound to glutathione as S-methylglutathione. The reaction appeared to be enzymatically catalyzed. Methylglutathione was also found in liver, kidney and brain homogenates.

S-methylcysteine was also present. Both substances appeared to be the result of metabolic action.

References: Redford-Ellis and Gowenlock, 1971a and 1971b.

Results: van Doorn et al. (1980) measured the concentration of methylthio-compounds in the urine of workers exposed to chloromethane. They identified the formation of S-methylcysteine (S-MC), however, there was considerable fluctuation of concentration within the group. For example, two of the workers excreted low amounts of S-MC compared to the other four. The authors proposed that their data are consistent with the existence of two populations with regard to chloromethane metabolism, with "poor-converters" (low urinary S-MC) possible being more susceptible to the toxic effects of chloromethane than "converters".

References: van Doorn et al. (1980).

Type: ACCIDENTAL EXPOSURE

Results: It is impossible to precisely determine the concentrations and conditions that have caused acute human injury and death. While it would appear that man is not markedly different from laboratory animals, humans probably are not as sensitive as $B_6C_3F_1$ mice. The most common consequences of excessive single or repeated exposures have been functional changes in the central nervous system. These have often been described as drunkenness as from ingested ethanol, but are much longer in persistence. The symptoms of overexposure may include a staggering gait, weakness, drowsiness, double vision, headache, apathy, anorexia, nausea, vomiting, abdominal pain, diarrhea, personality changes, spasms, tremors, loss of memory, paralysis, confusion, unconsciousness and death. Other organ systems can be affected in persons showing marked central nervous system changes; these include the kidneys, liver, and particularly the lungs (von Oettingen, 1955). Changes reported in other systems are less certain and may be secondary or coincidental to chloromethane exposure. Although recovery appears to be complete, it is often prolonged and at least one report indicates adverse affects may be permanent (Gudmundsson, 1977). Permanency may depend upon the degree of injury and the ability of the subject to compensate for the injury.

Human experience prior to 1955 was summarized by von Oettingen who found reports of 19 fatalities in the literature (von Oettingen, 1955). Exposure concentrations were not available. Seventeen had died following a severe single exposure and two died suddenly after a few repeated exposures. As noted by von Oettingen, there have been reports of a sweetish or offensive odor in the breath of the victims. Given the weak odor of chloromethane itself, odor would appear to be due to a metabolite or reaction product of the victim.

At least 200 nonfatal cases were found and summarized by von Oettingen. A multitude of symptoms was reported which are consistent with those summarized previously. Treatment appears to be supportive with no specific antidotes or therapy. Obviously, all exposure must cease if adverse affects are suspected, and the subject must be kept free of exposure until complete recovery is assured.

More recent articles confirm von Oettingen's summary of human response and findings in animal studies, but add little quantitative data regarding human exposure (Spevak et al., 1976; Thorderson et al., 1965; Hartman et al., 1955; Gudmundsson, 1977; Leurini et al., 1982; MacDonald, 1964; Borovska et al., 1976; Gummert, 1961; Thomas, 1960; Bettigelli and Perini, 1955). Leurini et al. (1983) described a complex case of an apparent victim with Type II diabetes, liver cirrhosis, and porphyria cutanea as well as excessive alcohol consumptions; hence, the report is of very limited value.

Lanham (1982) presented a case report of a husband and wife exposed over a period of time to chloromethane emitted from fresh polystyrene foam panels purchased and stored in their house prior to installation as insulation. The panels were normally off-gassed (seasoned) for a period of time before they were distributed, but in this case they were apparently inadequately seasoned before being put in the house. The house was a recently constructed, electrically heated, energy efficient structure with an air exchange (turnover) of only 0.06 changes/hour. Both husband and wife were well educated but apparently unaware of the significance of their symptoms which included complete exhaustion and labyrinthitis, blurred vision, fatigue, vertigo, nausea, vomiting, tremors and unsteadiness of gait. Exposure occurred over several days. Air concentrations were still over 200 ppm when measurements were made subsequent to the exposure. The couple appeared to recover completely with late-afternoon fatigue being a persistent effect.

One report which describes the effects of prolonged repeated industrial exposure is particularly useful since the authors were able to make estimates of exposure concentrations in addition to duration of exposure (Scharnweber et al., 1974). Six cases are summarized. Cases 1 and 2 had prolonged and repeated exposure to up to 300 ppm. Cases 3 and 6 had 12- to 16-hour exposures of about 265 ppm for two to three weeks. All six cases appeared to recover but 2-3 months were required for several subjects. These authors cite industrial experience indicating no apparent effect in plastic foam plants where exposures averaged less than 100 ppm but that when exposures average 200 ppm or more, reversible CNS symptoms were observed.

Another study of human response (Repko et al., 1976) is so seriously flawed that it is of doubtful value. While the investigator claims to have measured a decrement in performances in workers exposed repeatedly to a mean concentration of 33.6 ppm, it is not possible to draw this conclusion based on the study protocol and the data. First the control group was much younger than the exposed population; second, the controls were measured at a different time (late in the study) and not at the same location. Third, the workers had previous exposures to higher concentrations of chloromethane in the work place and hence if any effects were observed, it could have been influenced by previous exposure. Thus this study adds little to knowledge of chloromethane's effects.

References: As noted above.

Type: VOLUNTEER STUDY

Results: Industrial experience has shown the central nervous system to be the most sensitive organ system in humans. Therefore there have been attempts to measure decrements in performance following single and reported exposure of volunteers to chloromethane gas.

The most extensive studies are those of Stewart et al. (1977) conducted for the National Institute for Occupational Safety and Health. Healthy adults of both sexes were exposed to chloromethane gas in a carefully designed, controlled-environmental chamber. The subjects were from Caucasian middle-class working population and recruited by a private employment agency.

The experimental goal was primarily to measure expired air, blood, and urine during and after exposure. However, extensive neurological, physiological, behavioral, clinical, and medical tests were included. The following parameters were measured on all or some of the subjects during one or more exposure regimes.

Breath samples (alveolar air) for chloromethane
Blood samples for chloromethane
Blood carboxyhemoglobin
Methyl alcohol in urine
Complete blood count (CBC)
Clinical chemistry (23 values)
Twelve lead electrocardiograms
Blood pressure
Temperature
Subjective signs and symptoms
Urinalysis
Continuous medical surveillance during exposure
Neurological studies (modified Rhomberg, heel-to-toe equilibrium, spontaneous electroencephalograms (visual evoked response)
Cardiopulmonary function (Spirometry), minute volume, forced expiratory volume
Carbon monoxide diffusion
Cognitive Testing (Ten and Thirty Second Estimation of Time, Marquette Time Estimation Test, Coordination Test, Arithmetic Test, Inspection Test)
Electromyograms
Subjective response

Stewart et al. (1977) gave male and female subjects single and repeated exposures to 0, 20, or 100 ppm of chloromethane gas. Exposures were for 1, 3, or 7'h hours and were given to some subjects on five consecutive days. In addition, similar exposures were given to 150 ppm on two successive days the following week.

The following is a summary of the exposure schedule used by Stewart et al. for male and female test subjects:

**METHYL CHLORIDE EXPOSURE SCHEDULE: MALE SUBJECTS**

| | | | **Number of Subjects Exposed** | | |
|---|---|---|---|---|---|
| **Weeks** | **Days** | **PPM** | **7 1/2 hr** | **3 hr** | **1 hr** |
| 1 | 4-5 | 0 | 3-4 | 4 | 2 |
| 2 | 1-5 | 100 | 3-4 | 2-4 | 2 |
| 3 | 1-4 | 20 | 4 | 1-2 | 3 |
| 4 | 4-5 | 0 | 4 | 1 | 1-3 |
| 5 | 1-5 | Fluctuating (100 ppm avg.) | 4 | 0-1 | 1-3 |
| 6 | 1-2<br>3 | 150<br>0 | 4<br>4 | 1<br>1 | 1-2<br>1 |

**METHYL CHLORIDE EXPOSURE SCHEDULE: FEMALE SUBJECTS**

| | | | Number of Subjects Exposed | | |
|---|---|---|---|---|---|
| **Weeks** | **Days** | **PPM** | **7 1/2 hr** | **3 hr** | **1 hr** |
| 1 | 5 | 0 | 4 | 4 | 2 |
| 2 | 1-5 | 100 | 4 | 3 | 2 |
| 2 | 1 | 0 | 4 | 3 | 2 |

The authors concluded that their subjects fell into two distinct groups based on their blood and breath analysis values and that a minority of subjects had chloromethane blood and breath levels two to six times higher in concentration than did seven of ten male and eight of nine female subjects. The investigators found no deleterious response at any magnitude of exposure, even after five repeated exposures two weeks in a row, followed by two 7-hour exposures to 150 ppm the following week. While there were distinct differences in the blood and expired air concentrations in the subjects, there was no build-up in concentrations as a result of repeated daily exposures to as high as 150 ppm. They concluded that measurement of expired air (breath) was of little value in measuring exposure to chloromethane because of its rapid elimination from the body.

Sixty minutes after repeated 7 1/2 hour exposures to 100 ppm, the alveolar air contained only 1 to 4 ppm and after 23 hours was below their limit of analytical sensitivity.

References: Stewart et al., 1977.

Type: VOLUNTEER STUDY

Results: A study of the possible combined effects of chloromethane and diazepam (Valium) on human performance was reported by Putz-Anderson et al. (1981). Each of 56 volunteers (17 female) was randomly assigned to one of six groups comprising the combinations of diazepam (10 mg by ingestion) and placebo and one of the two levels of chloromethane (100 ppm or 200 ppm) plus control. Each individual was tested in an environmental room on three tasks involving components of eye-hand coordination, mental alertness and time discrimination. Both pretreatment and treatment data were obtained. Diazepam produced a significant 10% impairment of task performance, whereas the effect of 200 ppm (3 hrs) of chloromethane was marginal (average performance impairment of 4.5%). When the two agents were combined, total impairment was equal to the sum of the two individually induced doses. Large inter-individual differences in breath and blood levels were found for chloromethane.

As reported by Stewart et al. (1977) and later confirmed by Nolan et al. (1985), blood and expired air concentrations in an individual were highly correlated and the subjects studied by Putz-Anderson fell into two distinct sub-groups in regard to blood and expired air concentrations. A few individuals had much higher levels than the majority.

References: Putz-Anderson et al., 1981a.

Type: VOLUNTEER STUDY

Results: Industrial workers are frequently exposed to organic solvents such as chloromethane and also voluntarily ingest quantities of alcohol or caffeine, which affect the nervous system. Behavioral effects of such substances alone and when combined were assessed. Volunteers (84) were randomly assigned to 1 of 6 treatment groups. Each individual was then tested before and during the treatment or control procedures on three performance tasks. An alcohol dose sufficient to register blood levels of 0.08% produced a significant impairment of 10% on all three tests, which included eye-hand coordination and alertness. A caffeine dose equivalent to two cups of coffee (200 mg) produced a small but significant impairment on only the eye-hand coordination test. Participates who were exposed to chloromethane for 3.5 hr at levels equivalent to the current legal standard did not experience any significant impairments on the tests. When the solvent was combined with each drug individually, the effect was essentially equivalent to the sum to the separate effects; no behavioral interaction was found.

Reference: Putz-Anderson et al., 1981b (as cited in HSDB, 1998).

Type: EPIDEMIOLOGY

Results: Table 4-4 taken from the epidemiological study by Holmes et al. (1986) summarizes the limited data on causes of death in 852 exposed workmen including carcinogenic deaths. There was no increase in deaths due to cancer in this study population, but the study has only limited statistical power. External causes of death were too few to calculate significance. In general, less than expected mortality occurred in every category and no cause of death was in statistical excess. The authors noted the small size and low power of their study.

**TABLE 4-4**

**Observed and Expected* Deaths From Selected Causes Among White Male Butyl Rubber Workers First Employed In Butyl Rubber Operations During the Period 1943-1950 by Potential for Exposure to Methyl Chloride**

| Cause of Death | Low | | Medium | | High | |
|---|---|---|---|---|---|---|
| (ICD-8th rev) | Obs/Exp | SMR[a] | Obs/Exp | SMR | Obs/Exp | SMR |
| All causes (001-998) | 7/12.6 | 56 | 16/22.1 | 72 | 69/77.5 | 89 |
| Malignant neoplasms (140-209) | 1/2.4 | 42 | 2/4.4 | 45 | 10/15.5 | 65 |
| Circulatory system diseases (390-458) | 3/6.3 | 48 | 10/11.0 | 91 | 43/40.0 | 108 |
| External causes of death (800-998) | 2/1.5 | 133 | 3/2.3 | 30 | 7/7.0 | 100 |

*Expected numbers are based on calendar time and age-specific mortality rates of U.S. white males.

[a](Observed/expected) x 100. (Holmes, et al., 1986).

References: As noted above.

Type: OCCUPATIONAL EXPOSURE

Results: A study conducted in four plants in the United States with differing processes for using chloromethane showed 8 hour TWAs ranging from non-detectable (less than 0.1 ppm TWA) to 21.4 ppm TWA (Cohen, et al., 1980). Several Health Hazard Evaluation reports from NIOSH described chloromethane concentrations up to 300 ppm (Ruhe, 1976; Gorman, 1981; Markel, 1983; NIOSH Current Intelligence Bulletin 43, 1984). Generally, however, the exposure levels were well within the OSHA standards for TWAs, ceilings and peak levels applicable at that time (100 ppm TWA, 200 ppm ceiling and 300 ppm peak).

Results: Another report reviews 6 cases of worker illnesses related to chronic exposures to over 200 ppm TWA chloromethane. Workers were exposed occupationally to relatively low levels (275 ppm [550 mg/m$^3$]) for 2-3 weeks before the onset of typical symptoms (Scharnweber, et al., 1974).

Reference: As cited in ATSDR, 1990.

Remarks: The potential for significant exposure in industrial operations is most likely related to leaks, accidental releases and maintenance efforts. Accidents or malfunctions in transportation and product transfer systems also offer a potential for significant exposure. For all of these routes potentially significant exposure would result in relatively short-term exposures, and prudent use of personal protection equipment should preclude potentially serious overexposures.

Type: ACCIDENTAL OVEREXPOSURE

Results: In this study, the authors investigated mortality and cancer patterns among a group of individuals accidentally exposed to chloromethane 32 years earlier. This group of 24 persons had survived the immediate intoxication, which had occurred on a trawler during a fishing trip. The authors selected a reference group, which contained five times as many individuals as the study group, from registers of crews, and they controlled for age, occupation, social class, and lifestyle factors. The authors established a record linkage through personal identification numbers with the national death register and cancer register, thus securing 100% follow-up. The Mantel-Haenszel point estimate (M-H) was 2.2, and the 95% confidence interval (CI) was 1.3-3.1 for all causes of death. There was an excess of deaths from cardiovascular diseases (M-H = 2. 1, 95% Cl = 1.2-3.8). This excess mortality was more prominent among deckhands who had been subject to higher exposure; risk ratios (RRs) were elevated for all causes of death (RR = 2.5, 95% Cl = 1.0-5.7), as well as for cardiovascular diseases (RR = 3.9, 95% Cl = 1.0- 14.4). In addition, the authors noted elevated risks for all cancers (M-H = 1.5, 95% Cl = 0.3-5.6) and for lung cancer (M-H=2.7, 95% Cl = 0.1-52.6). The authors discussed their results in the context of a possible relationship between the incidence of cardiovascular disease and exposure to chloromethane, although any relationship between the two, based on their data, appeared marginal.

Reference: Rafnsson and Gudmundsson, 1997.

Type: MECHANISM OF TOXICITY

Remarks: A previous clinical case report of blindness after simultaneous exposure to chloromethane and chloramine gases (Minami et al., 1992) stimulated Minami et al. to further investigate the toxicity mechanism in this exposure (Minami et al., 1993 - see Section 4.8). The findings of the magnetic resonance imaging (MRI) in the brain of the patient taken one month after the exposure indicated that the changes appeared in basal ganglia and cerebral cortex which consisted of cholinergic neurons. They employed enzymological and pharmacological methods to investigate the relevance of chloramine and the metabolites of chloromethane to the neuronal cholinergic factors such as acetylcholinesterase (AChE) and cholinergic receptors (nicotinic and muscarinic acetylcholine receptors; nAChR and mAChR, respectively). Chloramine competitively inhibits AChE activity, and formaldehyde, one of the metabolites of chloromethane, potentiates the inhibitory action. Another metabolite of chloromethane, formate, did not show such an effect. Chloramine also inhibits non-competitively the ACh action on nAChR of frog skeletal muscle. Attenuatory action of chloramine ($10^{-5}$-$10^{-4}$ M) on muscle contraction due to the inhibition of nicotinic ACh action exceeds the augmentatory action of chloramine (more than $10^{-5}$ M) on the contraction due to the enzyme (AChE) inhibition. Chloramine augments the muscarinic action of ACh through AChE inhibition. Chloramine also has a positive inotropic action, and the beta-blocker, propranolol, cancels this action, and has a weak modificational action on heart muscle contraction through AChE inhibition.

Reference: Wang and Minami, 1996 (as cited in Toxline, 1996).

Type: MECHANISM OF TOXICITY

Remarks: Interindividual variation in the *in vitro* conjugation of chloromethane with glutathione by erythrocyte glutathione transferase was investigated in 208 healthy males and females from the southern and central parts of Sweden. It was found that 11.1 % of the individuals lacked this activity, whereas 46.2% had intermediate activity and 42.8% had high activity. This distribution of three phenotypes is compatible with the presence of one functional allele with a gene frequency of 0.659 and one defect allele with a gene frequency of 0.341. The proportion of non-conjugators in this Swedish material was considerably smaller than that previously found in Germany (Peter et al., 1989). The polymorphic distribution of another glutathione transferase, GST mu, was determined in the same individuals with a PCR method. No connection between the genotype for GST mu (GSTM1) and the glutathione conjugation with chloromethane in erythrocytes was found.

Reference: Warholm et al., 1994.

Type: MECHANISM OF TOXICITY

Remarks: Laurate and arachidonate omega and (omega-1)-hydroxylase activities, cytochrome P450 2E1 (CYP2E1), and CYP4A content were measured in 18 human kidney microsomal samples. The rates of laurate and arachidonate were found to be very different from those measured in human liver samples, with a laurate omega/omega-1 ratio of approximately 22 in human kidney vs 0.75 in human liver.

lmmunoblot analysis of the 18 human kidney microsomal samples identified 1 CYP4A electrophoretic band, but CYP2E1 was not detectable in human kidney, contrary to liver. Laurate and arachidonate omega-hydroxylase activities were significantly correlated with CYP4A content (r = 0.86 and 0.75, respectively). Polyclonal antirat CYP2El antibody did not affect omega-hydroxylase activity, whereas the polyclonal antirat CYP4Al antibody inhibited it by 60%. These results suggest that, in contrast to other species, human kidney microsomes do not contain significant amounts of CYP2E1, but possess CYP4A and fatty acid omega-hydroxylase activity.

Reference: Amet et al., 1997.

Type: MECHANISM OF TOXICITY

Remarks: A new system has been developed to determine enzyme activities of glutathione transferase theta (GSTTI -1) based on radiometric product detection resulting from the enzymatic reaction of chloromethane with 35S-labelled glutathione. In principle, the method is universally applicable for determination of glutathione transferase activities towards a multiplicity of substrates. The method distinguishes between erythocyte GSTT1-1 activities of human 'non-conjugators', 'low conjugators' and 'high conjugators'. Application to cytosol preparations of livers and kidneys of male and female Fischer 344 and $B_6C_3F_1$ mice reveals differential GSTT1-1 activities in hepatic and renal tissues. These ought to be considered in species-specific modelings of organ toxicities of chlorinated hydrocarbons.

Reference: Thier et al., 1998a.

Type: MECHANISM OF TOXICITY

Remarks: Glutathione transferase (GST) TSTT1-1 is involved in the biotransformation of several chemicals widely used in industry, such as butadiene and dichloromethane (DCM). The polymorphic hGSTT1-1 may well play a role in the development of kidney tumors after high and long-term occupational exposure against trichloroethylene. Although several studies have investigated the association of this polymorphism with malignant diseases little is known about its enzyme activity in potential extrahepatic target tissues. The known theta-specific substrates, chloromethane, dichloromethane and 1,2-epoxy-3- (p-nitrophenoxy) propane (EPNP), were used to assay GSTT1 -1 activity in liver and kidney of rats, mice, hamsters and humans differentiating the three phenotypes (non-conjugators, low conjugators, high conjugators) seen in humans. In addition GSTT1-1 activity towards MC and DCM was determined in human erythrocytes. No GSTT1-1 activity was found in any tissue of non-conjugators (NC). In all organs high conjugators (HC) showed twofold higher activity towards chloromethane and DCM than low conjugators (LC). The activity in human samples towards EPNP was too close to the detection limit to differentiate between the three conjugator phenotypes. GSTTI-1 activity towards chloromethane was two to seven-times higher in liver cytosol than in kidney cytosol. The relation for chloromethane between species was identical in both organs: mouse > HC > rat > LC > hamster > NC. In rats, mice and hamsters GSTT1-1 activity in liver cytosol towards DCM was also two to seven times higher than in the kidney cytosol. In humans this activity was twice as high in kidney cytosol than in liver cytosol. The relation between species was mouse > rat > HC > LC > hamster > NC for liver, but mouse > HC > LC/rat > hamster/NC for kidney cytosol. The importance to heed the specific environment at potential target sites in risk assessment is emphasized by these results.

Remarks: "Altogether the presented results show that DCM and chloromethane may be regarded as very specific substrates of GSST1-l."

Remarks: "Although the GSST1-1 activity toward chloromethane and DCM is much lower in kidney than in liver cytosol in all animal species investigated, the inverse has been observed in human samples regarding DCM, but not chloromethane metabolism."

Remarks: "...no CYP2E1 [P4502E1] activity was detected in human kidney samples supported by the lack of protein as determined by immunological investigations (Amet et al., 1997)."

Remarks: "The data presented here show that species differences can vary for tissues and for substrates independent of each other and explain why target organs can differ between species. These results emphasize the importance to consider specific conditions at possible target sites when extrapolating from animals to the humans situation."

Reference: Thier et al., 1998b.

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