METHYL CHLORIDE

Data were last reviewed in IARC (1986) and the compound was classified in *IARC Monographs* Supplement 7 (1987a).

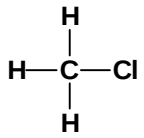
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 74-87-3
Chem. Abstr. Name: Chloromethane
IUPAC Systematic Name: Chloromethane
Synonym: Monochloromethane

1.1.2 *Structural and molecular formulae and relative molecular mass*



CH_3Cl Relative molecular mass: 50.49

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description:* Colourless gas with an ethereal odour and sweet taste (Budavari, 1996)
(*b*) *Boiling-point*: –24.0°C (Lide, 1997)
(*c*) *Melting-point*: –97.7°C (Lide, 1997)
(*d*) *Solubility*: Slightly soluble in water (303 mL/100 mL at 20°C); soluble in ethanol; miscible with acetone and diethyl ether (Budavari, 1996; Lide, 1997)
(*e*) *Vapour pressure*: 488 kPa at 20°C; relative vapour density (air = 1), 1.8 (Holbrook, 1993; Verschueren, 1996)
(*f*) *Reactivity*: Reacts with active metals (aluminium, magnesium, zinc) (Lewis, 1993)
(*g*) *Explosive limits*: Upper, 17.2%; lower, 8.1% by volume in air (American Conference of Governmental Industrial Hygienists, 1992)
(*h*) *Octanol/water partition coefficient (P):* log *P*, 0.91 (Hansch *et al*., 1995)
(i) *Conversion factor*: $mg/m^3 = 2.1 \times ppm$

1.2 Production and use

Production capacity for methyl chloride in the United States was reported to be 438 thousand tonnes in 1992 and 417 thousand tonnes in 1995 (Anon., 1992, 1995).

Methyl chloride is used in the production of tetramethyllead antiknock compounds for gasoline and methyl silicone resins and polymers, and as a catalyst carrier in low-temperature polymerization (e.g., butyl rubber), a refrigerant, a fluid for thermometric and thermostatic equipment, a methylating agent in organic synthesis, an extractant and low-temperature solvent, a herbicide, a topical antiseptic, and a slowing agent (IARC, 1986; Lewis, 1993).

The use pattern for methyl chloride in the United States in 1992 and 1995 was (%): methyl chlorosilanes used as intermediates for silicones, 80; methyl cellulose manufacture, 6; quaternary ammonium compounds, 5; agricultural chemicals, 5; butyl rubber production, 2; and miscellaneous, 2 (Anon., 1992, 1995).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 10 000 workers in the United States were potentially exposed to methyl chloride (see General Remarks). Occupational exposures to methyl chloride may occur in its production and in the production of silicones, methyl cellulose, quaternary ammonium compounds and other chemical agents. Data on workplace exposures to methyl chloride have been presented in a previous monograph (IARC, 1986).

1.3.2 *Environmental occurrence*

Thousands of tonnes of methyl chloride are produced naturally every day, primarily in the oceans. Other significant natural sources include forest and brush fires and volcanoes. Although the atmospheric budget of methyl chloride can be accounted for by volatilization from the oceanic reservoir, its production and use in the manufacture of silicones and other chemicals and as a solvent and propellant can make a significant impact on the local atmospheric concentration of methyl chloride. It has been detected at low levels in drinking-water, groundwater, surface water, seawater, effluents, sediments, in the atmosphere, in fish samples and in human milk samples (Holbrook, 1993; United States National Library of Medicine, 1998). Tobacco smoke contains methyl chloride (IARC, 1986).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 103 mg/m^3 as the 8-h time-weighted average threshold limit value for occupational exposures to methyl chloride in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

No international guideline for methyl chloride in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

Holmes *et al.* (1986) conducted a small study of 852 butyl rubber-manufacturing workers employed at some time between 1943 and 1978 in the United States who could have been exposed to methyl chloride. For all cancers, they observed standardized mortality ratios (SMRs) of 0.7 (95% confidence interval (CI), 0.4–1.0; *n* = 19) for white men and 0.6 (95% CI, 0.3–1.1; *n* = 11) for black men. SMRs for lung cancer were 0.7 (95% CI, 0.3–1.4; *n* = 7) for white men and 1.2 (95% CI, 0.4–2.6; *n* = 6) for black men.

Ott *et al.* (1985) conducted a cohort mortality study of 1919 men employed for one or more years between 1940 and 1969 at a chemical manufacturing facility in the United States. This cohort included 226 workers assigned to a unit which produced chlorinated methanes (methyl chloride, dichloromethane (see this volume), chloroform (see IARC, 1987b), carbon tetrachloride (see this volume) and tetrachloroethylene (see this volume)). Exposure levels were not reported. The follow-up period was from 1940 to 1979 and follow-up was 94% complete. The SMR for all causes was 0.6 (95% CI, 0.5–0.9; *n* = 42) based on United States rates and that for all cancers was 0.7 (95% CI, 0.3–1.3; *n* = 9). There were three pancreatic cancer cases (0.9 expected), two of whom had worked for less than five years and the third for six years. [The Working Group noted that the mixture of exposures and the lack of information regarding exposure levels limits the ability to draw conclusions regarding the carcinogenicity of methyl chloride.]

3. Studies of Cancer in Experimental Animals

A study in which methyl chloride was tested for carcinogenicity in mice and rats by inhalation exposure was reported only in an abstract. Although an excess of kidney tumours was reported in male mice exposed to the highest dose, the incomplete reporting precluded an evaluation of this finding. The results in female mice and in male and female rats were reported to be negative (IARC, 1986).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Following inhalation of labelled methyl chloride as a single breath, 29% of the dose was exhaled within 1 h. Among six volunteers inhaling methyl chloride, blood concentrations were proportional to the exposure concentration, but for two volunteers the concentrations were two to three times higher than for the others. The four with lower

concentrations eliminated methyl chloride more rapidly, their metabolic rate constants (K_m) being five- to seven-fold higher than for the other two (e.g., 0.284 versus 0.039 at an exposure concentration of 21 mg/m^3 [10 ppm]) (IARC, 1986).

S-Methylglutathione was identified in erythrocytes incubated with [^{14}C]methyl chloride, but no methylation of haemoglobin was detected. *S*-Methylcysteine bound to serum albumin was identified following incubation of plasma with methyl chloride (IARC, 1986). In one study, erythrocytes from 12/20 donors metabolized methyl chloride to *S*-methylglutathione, in contrast to the findings with a number of non-human species (see below) (Peter *et al*., 1989a,b). Selective inhibition experiments suggest that CYP2E1 is a major catalyst of the oxidation of methyl chloride in human liver (Guengerich *et al*., 1991).

4.1.2 *Experimental systems*

Immediately following inhalation of labelled methyl chloride by rats, up to 20% of the label was incorporated into tissue macromolecules. After 6 h, the total level of non-volatile label was highest in liver and kidney and lower in testes. Within 24 h, about 64% of the label was exhaled, 32% found in urine and about 4% in faeces. About 50% of the radiolabel was expired as [^{14}C]CO_2. Following oral administration, radioactivity in hepatic proteins was associated with methionine and serine.

Urinary metabolites are *S*-methylthioacetic acid sulfoxide, *N*-acetyl-*S*-methyl-L-cysteine and *N*-(methylthioacetyl)glycine, which are metabolites of *S*-methyl-L-cysteine and *S*-methylglutathione. These last two compounds were found after incubation of methyl chloride with rodent liver, kidney and brain homogenates. The methyl group of methyl chloride is metabolized via *S*-methyl-L-cysteine to formate which is found in urine and blood of rats, whereas formaldehyde is found in rat liver microsomes and blood of mice and rabbits (IARC, 1986).

Erythrocytes from rats, mice, bovines, pigs, sheep and rhesus monkeys were unable to metabolize methyl chloride, in contrast to the conjugation reaction described for erythrocytes from a majority of human samples (Peter *et al*., 1989a,b). However, CYP2E1 present in kidney microsomes of male mice oxidized methyl chloride to formaldehyde and the quantity formed was dependent upon the hormonal status of the animals. Significantly lower oxidation rates were found with female mouse kidney microsomes for both methyl chloride and chlorzoxazone, a specific substrate for CYP2E1. In liver microsomes, there was no sex difference in methyl chloride oxidation rates, which were about two-fold higher than those with male mouse kidney preparations. Rat kidney microsomes did not convert methyl chloride into formaldehyde (Dekant *et al*., 1995).

Similar sex and species differences have been described for glutathione *S*-transferase activity. The activities of glutathione-*S*-transferase (using dichloronitrobenzene as a substrate) were two- to three-fold higher in the livers of male B6C3F$_1$ mice, compared with female mice and Fischer 344 rats of both sexes, and about seven-fold higher than in male mouse kidney. Neither hepatic nor renal formaldehyde dehydrogenase showed any sex difference in either species, but the activities in mouse liver were about two-fold

higher than those in rat liver. Exposure of mice to 1000 ppm [2100 mg/m^3] methyl chloride for 8 h did not result in any increase in formaldehyde concentration in either liver or kidney, leading the authors to conclude that formaldehyde is unlikely to be the cause of renal carcinogenicity in male mice (Jäger *et al*., 1988). This supports the suggestion that it is the glutathione pathway which is toxicologically significant, since glutathione depletion has been shown to reduce the toxicity of methyl chloride (Chellman *et al*., 1986a).

4.2 Toxic effects

4.2.1 *Humans*

Liver cirrhosis has been described as an effect of long-term exposure to methyl chloride fumes. Non-fatal cases also developed renal damage and nervous system dysfunction (IARC, 1986).

4.2.2 *Experimental systems*

Long-term exposure of many animal species to methyl chloride induced renal damage, hyperaemia, lung haemorrhage and various nervous system effects, ranging from apathy and anorexia to convulsions or paralysis. In mice and rats, exposure by inhalation induced renal and hepatocellular necrosis and degeneration and testicular damage. Adrenal degeneration occurred in rats and cerebellar lesions were induced in mice and guinea-pigs.

Inhalation of methyl chloride decreased non-protein thiol concentrations in rodent liver, kidney, lung, brain and testis. It also induced lipid peroxidation in mice (IARC, 1986).

The effect of glutathione depletion upon methyl chloride toxicity has been assessed in inhalation experiments in male B6C3F$_1$ mice that were pretreated with buthionine sulfoximine, an inhibitor of glutathione synthesis, or diethyl maleate. Depletion reduced the lethality of methyl chloride and reduced its toxicity to liver (as indicated by serum alanine aminotransferase activity), central nervous system (as indicated by cerebellar histology) and kidney (as indicated by cortical cell regeneration following necrosis) (Chellman *et al*., 1986a). Methyl chloride toxicity was also reduced in Fischer 344 rats by treatment with 3-amino-1-[*meta*-(trifluoromethyl)phenyl]-2-pyrazoline, an inhibitor of cyclooxygenase/lipoxygenase. Thus, intraperitoneal injection of the inhibitor at 10 mg/kg bw 1 h before and 1 h after exposure to 15 750 mg/m^3 methyl chloride for 6 h per day for two days reduced lethality from 8/12 to 0/6 and epididymal granuloma formation from 4/4 to 0/6. The effect of the inhibitor on the toxicity of 10 500 mg/m^3 methyl chloride for 6 h per day for five days was to abolish hepatocellular cloudy swelling, renal cortical degeneration, necrosis of the internal granular layer of the cerebellum and degenerative changes in the testes and epididymis; only vacuolar degeneration of the adrenal cortex persisted. Neither the distribution nor the metabolism (quantities of expired methyl chloride or radiolabelled CO_2 or urine) of [^{14}C]methyl chloride was significantly altered by the anti-inflammatory agent (Chellman *et al*., 1986b).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Exposure by inhalation to methyl chloride causes fetal growth retardation and impaired male reproductive capacity in rats and malformations of the heart in fetal mice (IARC, 1986). The preimplantation losses described in rats in which the males were exposed to 6300 mg/m^3 methyl chloride for 6 h per day for five days were due to a failure of fertilization rather than preimplantation embryonic death. A concentration of 2100 mg/m^3 had no effect upon fertilization (Working & Bus, 1986).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

Methyl chloride was mutagenic to bacteria and induced chromosomal aberrations in plants. It induced unscheduled DNA synthesis in cultured rat hepatocytes and, in rats exposed *in vivo*, there was a small increase in unscheduled DNA synthesis in hepatocytes but not in tracheal epithelial cells or spermatocytes. DNA strand breaks were induced by methyl chloride in the kidney cells of exposed mice. In cultured mammalian cells, it induced mutations and sister chromatid exchanges and enhanced viral cell transformation. It induced dominant lethal effects in rats. The last effect appears to be due to a failure of the males to fertilize the females, rather than to preimplantation embryonic death and can be partially inhibited by treatment with an anti-inflammatory agent (Chellman *et al*., 1986c).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to methyl chloride may occur in its production, and in the production of silicones and various other chemical products. Methyl chloride is produced naturally, primarily in oceans, and it is widely detected in ambient air and water.

5.2 Human carcinogenicity data

Two small cohort studies evaluated the mortality experience of workers employed in facilities using or producing methyl chloride. No clear mortality excess occurred, and the small size and mixed exposures of these studies limited their utility for assessing the carcinogenicity of methyl chloride.

Table 1. Genetic and related effects of methyl chloride

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SAF, *Salmonella typhimurium* TM677, forward mutation, 8-azaguanine resistance	+	NT	10% atm	Fostel *et al*. (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	2.5% atm	Simmon *et al*. (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	1% atm	JETOC (1997)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	0.5% atm	Andrews *et al*. (1976)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	0.1% atm	JETOC (1997)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.5% atm	JETOC (1997)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	0.5% atm	JETOC (1997)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	+	+	10% atm	JETOC (1997)
TSC, *Tradescantia* species, pollen grains, chromosomal aberrations	+	NT	0.92% atm	Smith & Lotfy (1954)
T7S, Cell transformation, SA7 virus/Syrian hamster embryo cells *in vitro*	+	NT	0.6% atm	Hatch *et al*. (1983)
URP, Unscheduled DNA synthesis, Fischer 344 rat primary hepatocytes *in vitro*	+	NT	1% atm	Working *et al*. (1986)
UIA, Unscheduled DNA synthesis, Fischer 344 rat primary spermatocytes *in vitro*	+	NT	1% atm	Working *et al*. (1986)
DIH, DNA strand breaks, cross-links human lymphoblast line *in vitro*	–	NT	5% atm	Fostel *et al*. (1985)
GIH, Gene mutation, human lymphoblast line, *tk* locus *in vitro*	+	NT	2% atm	Fostel *et al*. (1985)
SIH, Sister chromatid exchange, human lymphoblast line *in vitro*	+	NT	1% atm	Fostel *et al*. (1985)
DVA, DNA strand breaks, cross-links in male $B6C3F_1$ mouse kidney cells *in vivo*	+		1000 ppm inh 8 h × 1	Ristau *et al*. (1990)
UPR, Unscheduled DNA synthesis, Fischer 344 rat hepatocytes *in vivo*	(+)[c]		15000 ppm inh 3 h × 1	Working *et al*. (1986)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
UVR, Unscheduled DNA synthesis, Fischer 344 rat spermatocytes *in vivo*	–[c]		15000 ppm inh 3 h × 1	Working *et al*. (1986)
UVR, Unscheduled DNA synthesis, Fischer 344 rat tracheal epithelial cells *in vivo*	–[c]		15000 ppm inh 3 h × 1	Working *et al*. (1986)
DLR, Dominant lethal test, Fischer 344 rats *in vivo*	+		3000 ppm inh 6 h/d × 5	Working *et al*. (1985)
DLR, Dominant lethal test, Fischer 344 rats *in vivo*	+		3000 ppm inh 6 h/d × 5	Chellman *et al*. (1986c)
BVD, Binding (covalent) to DNA, Fischer 344 rat liver cells *in vivo*	+		9 µmol po × 1	Xu *et al*. (1993)

[a] +, positive; (+), weak positive; –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; atm, atmosphere; inh, inhalation; po, oral
[c] Negative for exposure to 3500 ppm, 6 h/d, up to five days

5.3 Animal carcinogenicity data

No adequate data were available to the Working Group.

5.4 Other relevant data

The toxicokinetics of methyl chloride have been studied in human volunteers. It can be converted by human erythrocytes to *S*-methylglutathione, a metabolite also observed in animal studies; alternatively, it is metabolized by CYP2E1. Carbon dioxide is a major metabolite.

Methyl chloride causes toxicity in rodents in the liver, kidney and central nervous system. It may deplete glutathione in tissues.

Methyl chloride is mutagenic to bacteria. It was genotoxic in a number of mammalian cell systems *in vitro* and gave positive results in the dominant lethal test in rats *in vivo*.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity of methyl chloride to humans.

There is *inadequate evidence* for the carcinogenicity of methyl chloride in experimental animals.

Overall evaluation

Methyl chloride is *not classifiable as to its carcinogenicity to humans (Group 3).*

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