SCOEL/REC/191
Chloromethane

Recommendation from the
Scientific Committee on Occupational Exposure Limits

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Directorate-General for Employment, Social Affairs and Inclusion
Directorate B —Employment
Unit B.3 — Health and safety

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RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR CHLOROMETHANE

8-hour TWA:	42 mg/m^3 (20 ppm)
STEL:	Not applicable
BLV:	Not applicable
Additional categorisation:	Not applicable
Notation:	Not applicable

This evaluation is based on ATSDR (1998 and 2009), DFG (1996 and 1998), IARC (1999), US EPA (2001), WHO (2000), OECD SIDS (2002), and a further literature search performed by SCOEL (December 2013).

The present Recommendation was adopted by SCOEL on 2016-07-06.

RECOMMENDATION EXECUTIVE SUMMARY

Key data

The primary toxic effect of chloromethane is neurotoxicity, which is directed towards the central nervous system. This effect is seen both on animal experimentation and in human casuistic findings. A subacute (11 days) study in female C57BL/6 mice with intermittent exposure (5.5 hours/day) to chloromethane identified a NOAEC of 150 ppm and a LOAEC of 400 ppm (Landry et al 1985; Section 7.3.2). These NOAEC/LOAEC figures were based on both functional and morphological (cerebellar granular cell layer degeneration) effects. For these experiments, a particular animal model (C57BL/6 mouse) had been chosen because of its high susceptibility to chloromethane-induced neurotoxicity. NOAEC figures derived from other repeated-dose studies of longer duration in several species, including a 2-year chronic carcinogenicity study in F-344 rats and B6C3F1 mice, were all higher than 150 ppm.

Reproductive toxicity

In the available experimental studies on reproductive toxicity (Section 7.8.2), the NOAEC was either 150 ppm (Hamm et al 1985) or higher.

Genotoxicity/carcinogenicity

Chloromethane is weakly mutagenic in *in vitro* tests; *in vivo*, however, genotoxicity effects are noticed only at very high and already toxic doses. But there is no evidence of DNA alkylation by chloromethane *in vivo*. The likely reason for this discrepancy is the rapid metabolism of chloromethane *in vivo*. A 2-year carcinogenicity study (exposure 6 hours/day, 5 days/week) in F-344 rats and B6C3F1 mice revealed renal tumours (cystadenomas and adenomas), but only in male mice of the highest exposed group (1 000 ppm). This was the reason for a classification for cancer (H351). However, based on a number of arguments (for details, see Section 7.9) it can be concluded that the formation of these tumours does not permit an extrapolation to the situation in exposed humans. No adverse effects were found in the 2-year study in rats or mice exposed to 225 ppm. A SCOEL carcinogenicity group is not assigned.

Outcome Considerations

Based on these data in total, SCOEL concludes that the experimentally derived NOAEC of 150 ppm can serve as the basis for the derivation of a recommended OEL based on experimental neurotoxicity, without the need of an adjustment to longer study durations (as the available chronic study resulted in even higher NAOEC values). There is no indication of a genotoxic or carcinogenic effect at this level or below. Starting from the NOAEC of 150 ppm in a particularly susceptible strain of mice, as mentioned above, the application of an uncertainty factor of 5 for possible human inter-individual variations and further application of SCOEL's preferred value approach (also accounting for possible interspecies differences in susceptibility) results in a recommended OEL of 20 ppm. Uncertainty regarding human inter-individual variability comes from the involvement of the human polymorphic glutathione S-transferase GSTT1-1 (chapter 8). The overall resulting 7.5-fold margin of safety to the lowest reported NOAEC for male fertility in rats appears sufficient with regard to the observed reversibility of this effect. Because the study providing the NOAEC was by inhalation, a factor for extrapolation to humans is not required.

Derived Limit Values

Some observations in occupationally exposed humans, described under Section 7.3.1, provide a high degree of confidence that this recommended OEL is indeed safe for the human workforce. An OEL of 20 ppm is also consistent with the notion of Löf et al (2000) that no irritation or central nervous system effects were observed in human volunteers exposed to chloromethane at 10 ppm for 2 hours, which was the only exposure condition in this study.

Therefore, an OEL (8-hour TWA) of 20 ppm is recommended for chloromethane. There are no data to derive a STEL.

Biological Monitoring

As explained in Section 7.1.5, there is presently no proven strategy for a biological monitoring.

Measurement and analysis

Analytical measurement systems exist to determine the recommended levels with an appropriate level of precision and accuracy.

Notations

Not relevant

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RECOMMENDATION REPORT

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

Name:	Chloromethane
Synonyms:	Monochloromethane, methyl chloride, chloromethyl
Molecular formula:	CH3Cl
Structural formula:	
EC No.:	200-817-4
CAS No.:	74-87-3
Molecular weight:	50.49 g/mol
Conversion factors:	1 ppm = 2.09 mg/m3
(20 °C, 101.3kPa)	1 mg/m3 = 0.477 ppm

2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonized classification and labelling Chloromethane is provided by ECHA (ECHA 2015), as summarized in Tables 1 and 2.

Table 1: Chloromethane: Classification according to part 3 of Annex VI, table 3.1 (list of harmonized classification and labelling of hazardous substances of Regulation (EC) No 1272/2008 (ECHA 2015)

Index no.	Internat. Chemical Identification	EC no.	CAS no.	Classification		Labelling			Notes
				Hazard Class & Category Code (s)	Hazard statement code (s)	Pictogram Signal Word Code (s)	Hazard statement code (s)	Suppl. Hazard statement code (s)	
602-001-00-7	Chloromethane; methyl chloride	200-817-4	74-87-3	Press.Gas Flam. Gas 1 Carc. 2 STOT RE 2	 H220 H351 H373	GHS02 GHS08 GHS04 Dgr	 H220 H351 H373		Note U

Table 2: Chloromethane: Classification according to part 3 of Annex VI, table 3.2 (list of harmonized classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC of Regulation (EC) No 1272/2008; DSD classification (table 3.2) (ECHA 2015)

Classification	Risk Phrases	Safety Phrases	Indication of danger	Concentration Limits	
				Concentration	Classification
F+; R12 **Carc. Cat. 3; R40** **Xn; R48/20**	12 40 48/20	(2) 9 16 33	 F+ Xn		

3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

Chloromethane is a hazardous chemical agent in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

Chloromethane is not a carcinogen or mutagen for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC.

4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

Occupational exposure limits for Chloromethane exist in a number of countries, as shown in Table 3. An IOELV (indicative occupational exposure limit value) has been adopted at EU level, and national limit values will exist in all Member States. The values presented below are presented as examples and are not an exhaustive listing of all limit values within the EU and other countries.

Table 3: Existing OELs for Chloromethane; adapted from the GESTIS database (GESTIS 2015)

EU-countries	TWA (8 hrs)		STEL (15 min)		
	ppm	mg/m³	ppm	mg/m³	References
Austria	50	105	200	420	GKV (2011)
Belgium	50	104	100	210	RD (2014)
Denmark	25	52	50	104	BEK (2011)
European Union	20	42			SCOEL (2014)
Finland	50	100	75	160	MoSH (2012)
France	50	105	100	210	INRS (2012)
Germany (AGS)	50	100	100	200	BAUA (2006)
Germany (DFG)	50	100	100	200	DFG (2015)
Hungary		105		420	MHSFA (2000)
Ireland	50	105	100	210	HSA (2011)
Latvia		0,1			GESTIS (2015)
Poland		20			MLSP (2002)
Spain	50	105	100	210	INSHT(2011)
Sweden	10	20	20	40	SWEA (2011)
United Kingdom	50	105	100	210	HSE (2011)
Non EU-countries					
Australia	50	103	100	207	Safe Work Australia (2011)
Canada (Ontario)	50		100		Ontario Ministry of Labour (2013)
Canada (Québec)	50	103	100	207	IRSST(2010)
China		60		120	GESTIS (2015)
New Zealand	50	103	100	207	HS (2013)
Norway	25	50			NLIA (2011)
South Korea	50	105	100	205	GESTIS (2015)
Switzerland	50	105	100	210	SUVA (2015)
USA (OSHA)	100		200		OSHA (2006)

5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

5.1. Occurrence and use

Chloromethane (also commonly known as methyl chloride) is a clear, colourless gas and it is both an anthropogenic and naturally occurring chemical (WHO 2000, ATSDR 2009).

Most of the naturally occurring chloromethane is formed in the oceans by natural processes (e.g. marine phytoplankton), from biomass burning in grasslands and forested areas (e.g. forest fires), occur from combustion of grass, wood, charcoal, and coal and is also present in some lakes and streams. It is also released to the air as a product of tropical plants (Yokouchi et al 2002, 2000, 2007) and wood-rotting fungi (Saxena et al 1998) and to soil from wood-rotting fungi (Moore et al 2005). It breaks down very slowly in plain water and when comes in contact with soil it does not stick to the soil and most of it moves to the air (ATSDR 1998).

Most of the chloromethane that is released to the environment (estimated at up to 99%) comes from natural sources (ATSDR 1998; Budavari 1996). According to IARC (1986) and ATSDR (2009) only a minor amount is released to the atmosphere during:

- its production and use in industry (used as an intermediate in production of vinyl chloride and other chemicals where remains as impurity);
- incineration of municipal and industrial wastes (used for its inhibitory effect on combustion; Philbrick et al 1993);
- municipal waste landfills (highlighting his past presence in consumer products e.g., propellants for aerosol cans, old refrigerators; ATSDR 1998);
- cigarette smoke (Novak et al 2008).

As a result of its natural and anthropogenic occurrence, chloromethane is a ubiquitous low-level constituent of air and is probably found at very low concentration in many drinking water supplies that have used chlorine treatment for disinfection (ATSDR 1998).

The natural levels of chloromethane are about 700 parts per trillion in ambient air. Monitoring near non-industrial anthropogenic sources or near industrial plants producing or using this chemical have shown much higher levels; however it is consistent with the level reported in ATSDR (2009) stating the chloromethane concentration is about 500 ppt (parts per trillion) in typical urban air.

Considering its solubility, chloromethane is expected to exist principally in the air and is not expected to be present in the aquatic or terrestrial compartments at high concentration.

When detected, it has been observed at low concentrations in water (< 222 ng/l; OECD 2002), possibly due to the rapid volatilization.

Chloromethane is not readily biodegradable but may be degraded by adapted bacteria and under anaerobic conditions (OECD 2002).

5.2. Production and use information

Synthetic chloromethane may be manufactured by the following processes (Key 1980; OECD 2002; Ahlstrom and Steele 1979):

- chlorination of methane: by heating a mixture of methane and chlorine to over 400°C. It produces by-products containing high chlorinated compounds such as methylene chloride and chloroform which demand is declining so it is usually only used when these other products are also desired;
- methanol hydrochlorination: which is the preferred approach, that is carried out through two different industrial processes:
    - a liquid-phase process in which an excess of an hydrous HCI vapor is bubbled through boiling methanol with or without a zinc chloride catalyst; afterwards chloromethane product is vaporized from the reactor, scrubbed and stripped of HCl;
    - a vapor-phase process in which methanol vapor and an excess of anhydrous HCl vapor pass together over a catalyst (gamma alumina or cuprous or zinc chloride on pumice or activated carbon) at 180-200 °C. The chloromethane product is distilled twice to remove excess HCl and unreacted methanol.
- Another noncommercial process, is reported in (IHS 1994), in which excess methanol reacts with cheap by-product aqueous HCl in the liquid phase. A series of continuous stirred-tank reactors is used and no catalyst is used

In the chemical industry, the compound serves for different purposes:

- as a key intermediate in the production of silicones (to make methylate silicon);
- as an intermediate methylating compound (i.e. production of methyl cellulose; Lewis 1997);
- in the production of agricultural chemicals as a pesticide or fumigant and herbicide (HSDB 1998);
- as a catalyst carrier in low-temperature polymerization (production of methyl cellulose, quaternary amines and butyl rubber; ATSDR 1998);
- manufacture of tetramethyl lead (in the past) (ATSDR 1998, US EPA 2015);
- in refrigerators (now replaced by other chemicals; US EPA 2000);
- as a foam-blowing agent (ATSDR 1998);
- manufacturing process for vinyl chloride (OECD 2002);
- adhesives and sealant chemicals (US EPA 2015);
- extractant for oils, fats and resins (ILO 1983);
- local anesthetic (Budavari 1996);
- fluid for thermometric and thermostatic equipment (Lewis 1997).

Historically (30 years ago or longer) chloromethane was widely used as a refrigerant and significant human exposures were associated with leaking refrigerators (ATSDR 1998).

More recently, according to ATSDR (1998) and OECD (2002) nearly all commercially produced chloromethane was used as a chemical intermediate for the production of chemicals, mainly silicones (72% of the total chloromethane used). In 2012, according to Research and Market (2014) almost 49.9% of the total chloromethane demand was associated to silicone manufacturing. Other products that are made from reactions involving chloromethane include agricultural chemicals (8%), methyl cellulose (6%), quaternary amines (5%), and butyl rubber (3%).

According to WHO (2000), the total global release of chloromethane from all sources was estimated to be about 5×10^6 tonnes per year. The contribution from natural sources had been estimated to be well over 90% of the total release.

5.3. Occupational exposure

Occupational exposures to chloromethane may occur in the chemical industry during production and use for the synthesis of other chemicals, such as silicones, methyl cellulose, quaternary ammonium compounds (IARC 1999).

An anthropogenic source of chloromethane may be cigarette smoke. Novak et al (2008) collected smoke samples from burning cigarettes in special smoking adaptors into 2-l canisters and analysed the smoke for chloromethane using gas chromato¬graphy. The chloromethane concentrations were about 30–500 ppm (1.5–5.3 mg/cigarette) as compared to about 500 ppt in typical urban air (ATSDR 2009).

5.4. Routes of exposure and uptake

Chloromethane does not concentrate in sediments, or in animals and fish in the food chain so it is not generally found in food but has been found in drinking water and in the air at very low levels (US EPA 2015). Chloromethane can enter the body mainly through the lungs (breathing air that contains chloromethane vapour) or through digestive tract (drinking contaminated water. Inhalation of contaminated air is the most likely route of exposure especially those living near a hazardous waste site.

39% of chloromethane does not get changed in the body and is breathed out in the air. The rest is changed in the body to other breakdown products that mostly leave in the urine.

Contact with liquid chloromethane is rare, but could occur in an industrial accident from a broken metal container. Prolonged skin contact with liquid chloromethane is unlikely, because it turns into a gas very quickly at room temperature. It is not known how much chloromethane liquid or gas will enter the body through contact with the skin, but the amount is probably very low (ATSDR 1998).

6. MONITORING EXPOSURE

Chloromethane can be monitored in the air of the workplace by applying the NIOSH method 1001, which is a fully evaluated method applicable for STEL determinations (NIOSH 1994).

In this method chloromethane is sampled from the air in the workplace by adsorption onto a solid sorbent, followed by extraction of chloromethane with an organic solvent. The chloromethane-containing extract can then be analysed by gas chromatography (GC), using flame ionisation detection (FID) as shown in Table 4.

Table 4: Overview of sampling and analytical methods for monitoring chloromethane in the workplace.

Method	Sorbent	Desorption solution	Analysis	Recovery (%)	LOQ	Concentration range	References
NIOSH 1001	Coconut shell charcoal	CH_2CL_2	GC-FID	105	0.01 mg/sample	0.1 to 1 mg/sample*	NIOSH (1994)

* The working range is 31 to 320 ppm (66 to 670 mg/m^3) for a 1.5-L air sample

7. HEALTH EFFECTS

In humans, brief exposures to high levels of chloromethane can have serious effects primarily on the central nervous system, including convulsions and coma (von Oettingen et al 1949). Other effects include dizziness, blurred or double vision, fatigue, personality changes, confusion, tremors, uncoordinated movements, slurred speech, nausea and vomiting. Such symptoms develop within a few hours after exposure and may persist for several months. No information is available regarding chronic effects of chloromethane in humans (US EPA 2000).

7.1. Toxicokinetics (absporption, distribution, metabolism, excretion)

In general, chloromethane is readily taken up via the lungs and rapidly metabolised in the human and animal organism (Andersen et al 1980). Most elimination does not take place via the lungs. In man, 29 % of the absorbed substance is exhaled during the first hour (Morgan et al 1970). During 120–135 minutes after subcutaneous injection of the substance into rats, about 27 % is exhaled unchanged; 70 % is metabolised within 20–330 minutes (Soucek 1961). In dogs, 80 % of a dose administered by intravenous injection disappears from the blood very rapidly and a total of 90 % within the first hour (Sperling et al 1950). This points to a rapid metabolism.

7.1.1. Human data

In man there appears to be genetic differences in the capacity for chloromethane metabolism.

In a laboratory investigation, 6 male test persons were exposed to chloromethane concentrations of 50 or 10 ppm for 6 hours, and the levels of the substance in blood and alveolar air were determined during and after the exposures (Nolan et al 1985). In 2 of the 6 persons, the blood levels were markedly higher (by a factor of 2–3) during the exposure and decreased much more slowly after the exposure than in the rest of the

collective; the results also suggested the existence in the human population of two groups differing in their capacity for chloromethane metabolism. Incubation of chloromethane with human haemolysate revealed in about 60–70 % of the population ("metabolisers") an enzymatic conversion to S-methylglutathione, which was absent in the remaining 30–40 % ("non-metabolisers") (Peter et al 1989a). Erythrocytes from rats, mice, cattle, pigs, sheep and rhesus monkeys did not carry out this conjugation step. Other studies (Schröder et al 1992) showed that the erythrocytes from persons who carry out the conjugation contain an isoenzyme of glutathione transferase with high specificity for C1 and C2 substrates such as methyl halogenides and ethylene oxide; this isoenzyme was later identified as the human glutathione-S-transferase theta 1 (GSTT1-1) (Bolt and Thier 2006).

These studies, together with those of van Doorn et al (1980; see Section 7.1.4) and Nolan et al (1985), demonstrate that the human population can be divided into groups of fast metabolisers, medium metabolisers and non-metabolisers, along with the genetic deletion polymorphism of the enzyme GSTT1-1. Because of this unique polymorphism, these populations have been further investigated in the development of physiologically-based pharmacokinetic (PBPK) models, in order to assess the reliability of such models in general (Johanson et al 1999, Jonsson et al 2001) and to see how the genetic polymorphism affects the metabolism and disposition of chloromethane in humans in vivo (Löf et al 2000).

Löf et al (2000) exposed 24 volunteers, 8 with high, 8 with medium and 8 with no GSTT1-1 activity to 10 ppm chloromethane for 2 hours. The concentration of chloromethane was measured in inhaled air, exhaled air and blood. The experimental data was used in a 2-compartment model with pathways for exhalation and metabolism. The relative respiratory uptake averages were 60 % (243 µmol), 49 % (148 µmol) and 16 % (44 µmol) in the high, medium and no GSTT1-1 activity groups, respectively. During the first 15 minutes of exposure, the concentration of chloromethane in blood rose rapidly and then reached a plateau. The blood concentrations of chloromethane were similar in all three groups during the 2-hour exposure. At the end of exposure, the blood concentrations declined rapidly in the high and medium metabolising groups, but declined more slowly in the group lacking GSTT1-1 activity. The half-times were 1.7, 2.8 and 3.8 minutes, respectively, for the first phase and 44, 48 and 60 minutes, respectively, for the second phase. Metabolic clearance was 4.6 and 2.4 l/min in the high and medium GSTT1-1 groups, but nearly absent in the non-metabolising group. The rate of exhalation clearance was similar among the three groups, but the non-metabolism group had much higher concentrations of chloromethane in exhaled air after exposure.

Jonsson et al (2001) used the toxicokinetic data from the GSTT1-1 deficient, non-metabolising group from the Löf et al (2000) study to assess population PBPK models by Markov-chain Monte Carlo simulation in a hierarchical population model.

7.1.2. Animal data

By the major glutathione-dependent metabolic pathway, chloromethane is broken down to formate (Kornbrust and Bus 1982), and finally to CO_2 (Kornbrust and Bus 1982, Landry et al 1983); some of the carbon enters the C1 pool (tetrahydrofolic acid) of intermediary metabolism and is built into biological macromolecules. Formaldehyde is produced as an intermediate in the metabolism of chloromethane (Bus 1982). Kornbrust and Bus (1982) investigated the liver, kidneys, lungs and testes of rats exposed to 14C-chloromethane, also after pre-treatment with cyclohexamide, methotrexate and methanol. The results suggest that most, if not all, of the protein-bound radioactivity derived from 14C-chloromethane had entered the protein by metabolic incorporation of formic acid arising in C1 metabolism.

The main metabolic pathway begins with the enzymatic conjugation of chloromethane with glutathione (Dodd et al 1982, Landry et al 1983). A later metabolite, S-methylcysteine, has been identified in the urine of persons exposed to chloromethane

(van Doorn et al 1980). In rats, not only S-methylcysteine but also N-acetyl-S-methylcysteine, methylthioacetic acid sulphoxide and N-(methylthio¬acetyl)glycine have been identified as metabolites of 14C-chloromethane; all of these metabolites can be considered to arise as a result of primary glutathione conjugation (Landry et al 1983).

By contrast, the oxidative conversion of chloromethane to formaldehyde (via cytochrome P450) is considered to be a minor metabolic pathway (Bus 1982, Hallier et al 1990, Kornbrust and Bus 1982).

It has been proposed that methanethiol (methyl mercaptan) is the metabolite responsible for the neurotoxic effects of chloromethane (Kornbrust and Bus 1984). This metabolite was shown to be formed in incubations of rat intestinal contents with S-methyl-glutathione or S-methylcysteine (Peter et al 1989b) and thus could be formed in vivo in the intestine after biliary excretion of such metabolites of the glutathione-dependent pathway.

Exposure of rats or mice to chloromethane at 2 500 ppm for 1–6 hours resulted in a marked dose-dependent and time-dependent glutathione depletion in a number of organs (Bolt et al 1988, Kornbrust and Bus 1984). Exposure of mice to chloromethane concentrations of 2 000–2 500 ppm for 6 hours resulted in a marked increase in lipid peroxidation, determined as ethane exhalation and as levels of thiobarbituric acid reactive material in the liver, kidneys and brain (Kornbrust and Bus 1984).

7.1.3. In vitro data

Species differences in the GSTT1-1 activity for chloromethane in liver and kidney tissues from mice, rats, hamsters and all three phenotypes of humans were studied in vitro (Thier et al 1998). No GSTT1-1 activity was found in either tissue of the non-metabolising phenotypic human subjects. The GSTT1-1 activity in the liver and kidney tissue from the high GSTT1-1 humans were twice as high as in the low metabolising group, and 2–7 times higher in the liver tissues than in the kidney tissues of either group. The GSTT1-1 enzyme activities in decreasing order were: mice > high GSTT1-1 humans > rat > low GSTT1-1 humans > hamster > GSTT1-1 deficient humans.

7.1.4. Toxicokinetic modelling

There are no data available.

7.1.5. Biological monitoring

The use of excreted metabolites for biological monitoring of persons occupationally exposed to chloromethane is hampered by the genetic polymorphism of the human GSTT1-1, which leads to large individual differences in parent compound and metabolite excretion (see Section 7.1.1). In a small occupational study, S-methylcysteine in the urine of 6 individuals, who were exposed at an industrial workplace to very similar chloromethane levels, was analysed. It was demonstrated that 2 persons, unlike the other 4, excreted practically no S-methylcysteine at all (van Doorn et al 1980). In the exposure chamber study by Löf et al (2000), the phenotype difference in urinary extraction of S-methylcysteine was small, although statistically significant. Yet, non-conjugators had nearly tenfold higher breath levels of chloromethane than medium and fast conjugators, following 2 hours of exposure at 10 ppm (Löf et al 2000). In view of these inter-individual differences, a proven strategy for biological monitoring cannot be recommended at present.

7.2. Acute toxicity

7.2.1. Human data

The inconspicuous odour of chloromethane and the mostly mild symptoms of acute toxicity provide little warning of the incipient intoxication, which results after prolonged inhalation of the substance. In the literature, several hundred descriptions of cases of chloromethane poisoning and more than 30 deaths are described (Greim, 1996Henschler 1992). Part of these cases refer to earlier use of chloromethane as a refrigerant in home and industrial refrigerators, where leaks occurred (ATSDR 1998).

Pre-narcotic symptoms (headaches, dizziness, confusion, marked sleepiness) and gastrointestinal disorders (nausea and vomiting) are followed by a symptom-free interval of 0–2 days. The subsequent illness is characterised clinically by neurotoxic symptoms. Personality changes originating in organic changes in the brain, tremor, tonic-clonic spasms, hiccough and transient paralysis are observed. The eyes can also be affected. The symptoms (amblyopia, strabismus, double vision, accommodation disorders and ptosis) are similar to those of methanol intoxication (Greim 1996).

Early observations also point to effects on the heart as myocardial damage with characteristic ECG changes (Gummert 1961, Walter and Weis 1951), on the liver as enlargement (Roche et al 1956), jaundice (Weinstein 1937), pathological liver function parameters (Chalmers et al 1940, Sayers et al 1929) and focal parenchymal degeneration (Kegel et al 1929), on the kidney as symptoms of nephritis (Mendeloff 1952, Roche et al 1956, Verrière and Vachez 1949) and histopathological changes such as congestion, haemorrhage, focal degeneration and tubular necrosis (Dunn and Smith 1947, White and Somers 1931) and on the lungs as hyperaemia, congestion and haemorrhage (Nuckolls 1933, Schwarz 1926, White and Somers 1931).

When a chloromethane intoxication is not lethal, the lesions in the central nervous system and of parenchymatous organs can regress completely. Frequently, however, there are permanent defects. Most of the numerous occupational intoxications were acute; measurements of workplace concentrations were not carried out. There are only few reports of chronic intoxications (Mackie 1961, Noetzel 1952, Roche and Bouchet 1948) and details of exposure concentrations are not available for these either.

In the previously mentioned exposure chamber study in which 24 volunteers were exposed to 10 ppm chloromethane for 2 hours, the subjects did not experience any irritation or central nervous system effects (Löf et al 2000). Symptoms were recorded by ratings on 0–100 mm Visual Analogue Scales.

7.2.2. Animal data

It appears that the mechanism of the acute toxic action of chloromethane differs between animal species. In rats, N-acetyl cysteine can serve as an antidote against acute methyl halide poisoning, so that reduction in the glutathione level seems to amplify the acutely lethal effects (Peter et al 1985a). In addition, pre-treatment of rats with the non-steroidal anti-inflammatory agent BW755C prevents the death of animals acutely exposed to otherwise lethal concentrations of chloromethane (Working and Bus 1986a). In mice (B6C3F1), however, depletion of glutathione with L-buthionine-S,R-sulphoximine (BSO) protects the animals from the lethal effects of acutely toxic doses of chloromethane (Chellman et al 1986).

In rats, it was demonstrated that the composition of the diet affected the survival. The LC50 increased by a factor of 3 when the casein level in the diet was increased from 20 % to 35 %. Addition of cysteine or methionine increased the LC50 by a factor of 14 even with the low casein diet (Smith and von Oettingen 1947a).

7.3. Specific Target Organ Toxicity/Repeated Exposure

7.3.1. Human data

In a 4-month study, average workplace concentrations of chloromethane were determined as 30 ppm with peak concentrations up to 440 ppm. Symptoms of toxicity were not seen. In another factory where the workers were exposed to mixtures of chloromethane with chlorofluorocarbons, 9 employees – at concentrations in the workplace air of 26–1 500 ppm – complained of symptoms such as weakness, inebriation, unsteadiness, lack of concentration and effects on the tongue. At concentrations between 2 and 500 ppm, 141 persons "were said to be free of symptoms" (Dow Chemical Co. 1986).

7.3.2. Animal data

7.3.2.1. Inhalation

Early studies (Smith and van Oettingen 1947a, b) on mortality in 6 different species (guinea pig, mouse, rat, dog, monkey, rabbit) under/after repeated chloromethane exposures (6 hours/day, 6 days/week, up to 64 weeks) to 500, 1 000, 2 000 or 4 000 ppm showed lethalities occurring under all conditions, except in rats exposed to 500 ppm where no lethal effect was noted (see detailed table in Greim 1996).

McKenna et al (1981a) performed a study where groups of three male beagle dogs (aged 7–8 months) or three male cats (aged 8–9 months) were exposed for approximately 23.5 hours/day for 3 days (i.e. 72-hour treatment regimen) to chloromethane concentrations of 0, 200 or 500 ppm. After 48 hours of treatment, 500-ppm dogs appeared more tranquil, with one animal exhibiting intermittent tremor and slight excess salivation, but all were judged alert and responsive. Immediately after 72 hours of treatment, control and 200-ppm dogs were comparable. However, all 500-ppm dogs appeared weak and displayed a range of adverse effects that varied in severity from animal to animal. These included hind- and forelimb stiffness and incoordination, occasional slipping and falling, inability to sit up or walk, limb tremor, and excessive salivation. Improvement was noted in all 500-ppm dogs by post-exposure day 10, which continued until termination on day 27. Neurological evaluations and gross and histopathology revealed no treatment-related abnormalities in control or 200-ppm dogs, whereas each of the three 500-ppm dogs exhibited various clinical deficiencies (posterior paresis, opisthotonus, extensor tonus, and intention tremor). By 26 days post exposure, spinal reflexes and postural reactions were normal, balance was maintained normally, and walking with intermittent ataxia was observed. All three 500-ppm dogs displayed lesions in the brain and spinal cord (vacuolisation, swollen eosinophilic axons, axon loss, demyelinisation, and microglial cells that contained phagocytosed debris), which were characterised as generally "very slight" to "slight" and multifocal in nature. The lesions were localised to the brain stem and the lateral and ventral funiculi of the spinal column, and were not observed in the cerebrum, cerebellum or peripheral nerves. During the first 48 hours of exposure, the 200- and 500-ppm cats evidenced a decline in appetite, which then recovered, and after 24 hours they appeared less active than controls, but were always alert and displayed no signs of inactivity or sluggishness upon removal from the exposure chamber. Throughout the 2-week recovery period, 200- and 500-ppm cats were comparable to controls. Brain and/or spinal cord lesions were found in control (1/3), 200-ppm (1/3), and 500-ppm (3/3) cats. Several characteristics of these lesions led the authors to speculate that they were likely the result of a post-vaccinal reaction, a viral infection, or both; however, it was recognised that exposure to 500 ppm chloromethane could possibly have exacerbated such a disease process. The findings of this study indicate a NOAEC of 200 ppm for a continuous (nearly) 72-hour exposure to chloromethane, and a LOAEC of 500 ppm based principally upon a spectrum of clinically and histopathologically observable neurological effects seen in male beagle dogs.

In a second study by the same investigators, there was no evidence of brain or spinal cord lesions in male beagle dogs exposed for 6 hours/day, 5 days/week for a total of 64-66 exposures to concentrations of 0, 50, 150 or 400 ppm (McKenna et al 1981b).

The histopathological effects (e.g. cerebellar lesions) were also seen at levels of 500 ppm chloromethane and higher, in shorter-term studies which were evaluated by US EPA (2001). US EPA (2001) concluded that the results in total lent support to the NOAEC and LOAEC values derived from the key study of Landry et al (1983), which is described below.

In a subacute study in mice, Landry et al (1985) evaluated the relationship between chloromethane exposure duration and neurotoxicity. Female C57BL/6 mice were exposed to chloromethane for 11 days, either continuously (22 hours/day) to 15, 50, 100, 150 or 200 ppm, or intermittently (5.5 hours/day) to 150, 400, 800, 1 600 or 2 400 ppm. The animal model was chosen because of its particular sensitivity to chloromethane neurotoxicity. The no-observable-effect levels for continuous and intermittent exposures were nearly proportionate to exposure concentration multiplied by duration, but the dose-effect curve was much steeper for continuously exposed mice. Cerebellar granular cell layer degeneration was observed in mice exposed continuously to 100 ppm and in mice exposed intermittently to 400 ppm chloromethane. This histopathological effect was observed at lower concentrations than a decrement in rotating rod running performance. No (histological or functional) effects of neurotoxicity were observed in mice exposed to 50 ppm continuously or to 150 ppm intermittently. Continuous exposure produced the cerebellar lesion with less effect on other tissues than did intermittent exposure. In mice exposed to 2 400 ppm intermittently, there were renal and hematopoietic effects, in addition to relatively slight cerebellar granular cell layer degeneration. The mice exposed to 2 400 ppm developed haemoglobinuria, apparently as a result of intravascular haemolysis. It was concluded by the authors that careful judgment is required in differentiating between effects of continuous vs. intermittent exposure situations. For intermittent daily exposure and based on cerebellar damage, the study is indicative of a NOAEC of 150 ppm and a LOAEC of 400 ppm chloromethane (US EPA 2001).

Further data on repeated dose neurotoxicity are discussed in conjunction with the chronic carcinogenicity bioassay (Section 7.7.2).

7.3.2.2. Oral exposure

Because of the gaseous nature of chloromethane, there are no oral studies.

7.3.2.3. Dermal exposure

Because of the gaseous nature of chloromethane, there are no dermal studies.

7.3.3. In vitro data

There are no relevant in vitro data with chloromethane being a gas.

7.4. Irritancy and corrosivity

7.4.1. Human data

There are no reports on irritancy or corrosivity in humans.

7.4.2. Animal data

7.4.2.1. Skin

There are no data available.

7.4.2.2. Eyes and respiratory tract

Grant (1986) reported that exposure of a rabbit's eye to pure chloromethane gas at room temperature for 90 seconds caused only slight conjunctival hyperaemia in two rabbits exposed for 5 days to concentrations from 250 to 465 ppm in air. There were no changes in the corneas, nor in pupillary reactions to light.

In an acute inhalation toxicity study in rats, no adverse effects were observed on the respiratory tract including no sign of respiratory irritation (Griffiths and Watson 2009).

7.4.3. In vitro data

There are no in vitro data on irritancy or corrosivity.

7.5. Sensitisation

There were no data regarding sensitisation caused by chloromethane. According to the joint submission REACH dossier, standard sensitisation testing is not applicable for a gas; from the case reports in the literature there are no indications of an elevated skin or respiratory sensitising potential.

7.6. Genotoxicity

The available results of short-term studies suggest that chloromethane (methyl chloride) has weak direct alkylating activity, which can be demonstrated in vitro. It is considerably weaker than that of methyl bromide or methyl iodide. In vivo, such effects are seen, if at all, only after extremely high and toxic doses of the substance (see also IARC 1986, Jäger et al 1988). This conclusion is supported by results of two DNA binding studies, which unequivocally demonstrate no alkylation of DNA bases by methyl chloride exposures in vivo. These results are in contrast with clear systemic DNA-methylating effects of methyl bromide (Gansewendt et al 1991a) and methyl iodide (Gansewendt et al 1991b) in vivo.

7.6.1. Human data

No data were available.

7.6.2. Animal data

In a test for dominant lethal mutations, groups of 40 male F344 rats were exposed to chloromethane concentrations of 1 000 or 3 000 ppm, 6 hours daily for 5 days and then mated with untreated females 2 weeks after the last exposure. Fertility was significantly reduced in the males of the 3 000 ppm group. In addition, pre-implantation and post-implantation losses were increased. The authors suggested that the high chloromethane concentration had produced dominant lethal mutations in the sperm in the vas deferens and epididymis and that these were responsible for the increase in post-implantation deaths. In the group exposed to 1 000 ppm, there were no findings which could be ascribed to the chloromethane exposure (Working et al 1985). In a subsequent publication, these effects were considered to be of non-genotoxic origin, an effect of failure of fertilisation (Working and Bus 1986b).

Inhalation of a chloromethane concentration of 3 000–3 500 ppm, 6 hours daily for 5 days, did not result in DNA repair in hepatocytes, spermatocytes or tracheal epithelial cells in male F344 rats. In vivo exposure of rats to 15 000 ppm for 3 hours caused a slight increase in UDS in hepatocytes but not in spermatocytes or tracheal epithelial cells (Working et al 1986).

A DNA binding study carried out in male Fischer 344 rats which inhaled 14C-chloromethane demonstrated that radioactivity was incorporated into bases of the RNA and DNA, but that methylated bases could not be detected in any of the tissues examined (liver, lung, kidneys, testes, brain, muscle, intestines) (Kornbrust et al 1982). Another DNA binding study (Peter et al 1985b) in which Fischer 344 rats and B6C3F1 mice were exposed to 14C-chloromethane also showed that no methylation of guanine at the positions O6 or N7 was detectable in liver or kidneys of the exposed animals. The association of radioactivity with the DNA, probably because of its incorporation into normal DNA bases, was most marked in the kidneys of B6C3F1 mice.

The time-course of DNA lesions (DNA-protein cross-links, single-strand breaks) induced by high concentrations of chloromethane (1 000 ppm) was measured in renal tissue of male mice by means of the alkaline elution assay in order to gain an insight into repair processes. DNA-protein cross-links were removed at a fast rate, whereas single-strand breaks appeared to accumulate, even during repair of DNA-protein cross-links. However, 48 hours after exposure to chloromethane, neither of these lesions were detectable in mouse kidney. Both types of DNA damage were ascribed to the action of formaldehyde as a local intermediate in chloromethane metabolism (Ristau et al 1990).

7.6.3. In vitro

Chloromethane is a direct mutagen in the Ames test (Andrews et al 1976, Fostel et al 1985, Simmon et al 1977). This is to be expected because of its alkylating activity, which is, however, relatively weak and markedly weaker than that of methyl bromide or methyl iodide (order of activity: methyl iodide > methyl bromide > methyl chloride). In plants (Tradescantia sp.), chloromethane produced chromosomal aberrations (Smith and Lotfy 1954).

Chloromethane caused transformation of cultured Chinese hamster embryo cells (Hatch et al 1983).

Very high concentrations of chloromethane, 1–10 % in a closed container, caused unscheduled DNA synthesis (UDS) in rat hepatocytes and spermatocytes incubated for 18 and 3 hours, respectively, but not in primary cultures of rat tracheal epithelial cells (Working et al 1986).

In cultures of human lymphocytes, chloromethane (in concentrations up to 5 % in the gas phase) induced sister chromatid exchange and mutations but no DNA strand breaks (Fostel et al 1985).

7.7. Carcinogenicity

Based on "inadequate evidence" for carcinogenicity to humans as well as in experimental animals, chloromethane has been evaluated by IARC (1999) as "not classifiable as to its carcinogenicity to humans (Group 3)."

7.7.1. Human data

There was no conclusive evidence for an effect of acute, severe exposure to chloromethane on mortality from all cancers or from lung cancer in a small cohort (ship crew) accidentally exposed to chloromethane from a leaking refrigeration unit (Rafnsson and Gudmundsson 1997). A follow-up through record linkage of personal identifiers with

the nation-wide mortality registry was published by Rafnsson and Kristbjornsdottir (2014). Hazard ratios (HR) and 95 % confidence intervals (CI) were estimated in Cox proportional hazards model. The intoxicated crew was composed of 20 deckhands and 7 officers; the reference group counted 100 deckhands and 35 officers. At follow-up at the end of 2010, 14 of the exposed deckhands and 6 of the officers had died, versus 49 deckhands and 26 officers among the reference group. For all cardiovascular events, the HR was 2.06 (95 % CI 1.02–4.15), for acute coronary heart disease, the HR was 3.12 (95 % CI 1.11–8.78), for cerebrovascular diseases, the HR was 5.35 (1.18–24.35), and for suicide, the HR was 13.76 (1.18–160.07). Detailed information on risk factors for chronic diseases was lacking in this study.

Other occupational studies involved exposure to multiple chemicals in addition to chloromethane, making it difficult to attribute any effects specifically to chloromethane (US EPA 2001).

An extensive population-based case-control study to determine which industries may be related to an increased risk of pancreatic cancer was conducted by Kernan et al (1999). Death certificates of 63 097 persons who had died from pancreatic cancers in 24 US states from 1984–1993 were obtained and the occupations were determined. In addition, potential exposure to specific solvents, including chloromethane, was assessed. No association with exposure to chloromethane was found.

7.7.2. Animal data

The results of a 2-year inhalation study with rats (Fischer 344) and mice (B6C3F1), which was carried out for CIIT, have raised the question of a potential carcinogenic activity of chloromethane (Battelle Columbus 1981). The evaluation of IARC (1986) was only based on an abstract of this study. On this basis, it was stated by IARC (1986 and 1999) that, although an excess of kidney tumours was reported in male mice exposed to the highest dose, incomplete reporting precluded an evaluation of this finding. Later, this study was evaluated by US EPA (2001) as follows:

Groups of F-344 rats and B6C3F1 mice (117–120/sex/species/concentration) were exposed 6 hours/day, 5 days/week for up to 24 months to concentrations of 0, 50, 225 or 1 000 ppm (0, 103, 465 or 2 065 mg/m^3) of 99.97 % pure chloromethane. Duration-adjusted exposure levels were 0, 8.9, 40.2 or 178.6 ppm (18.4, 83.0 or 368.8 mg/m^3). Mouse: Mouse mortality was significantly increased in females (beginning at 10 months) at 1 000 ppm compared to controls, but was unaffected at 50 and 225 ppm. Signs suggestive of central nervous system toxicity (e.g. tremor, paralysis) were noted only in 1 000-ppm mice. Neurofunctional impairment (clutch response) was found in nearly all 1 000-ppm mice of either sex after 18–22 months of exposure. This finding was supported by the histopathological observation of cerebellar lesions (degeneration and atrophy of the granular layer) that first appeared in 1 000-ppm male and female mice at the 18-month sacrifice. It did not occur in the 0, 50 or 225-ppm groups. At the 24-month end-of-study sacrifice, there was no difference in incidence of spinal cord axonal swelling and degeneration between exposed and control mice. Hepatocellular lesions (vacuolisation, karyomegaly, cytomegaly, multinucleation, degeneration), first noted at 6 months in 1 000-ppm male mice, were found with increasing frequency at 12 and 18 months and were seen in the majority of males suffering unscheduled deaths. Renal tubule-epithelial hyperplasia and karyomegaly were first apparent in 1 000-ppm male mice at 12 months, subsequently increasing in incidence and severity until the last males in this group were sacrificed at 21 months. Seminiferous tubule atrophy and degeneration were also statistically significant and considered exposure-related in 1 000-ppm males. Finally, 1 000-ppm mice developed splenic atrophy and lymphoid depletion during months 6–22 that was considered related to chloromethane exposure. In mice, 1 000 ppm was identified as a fatal exposure level (FEL) on the basis of high mortality. Rat: There was no treatment-related mortality in the rat. The testes were the only target organs examined that were considered to have significant gross or histopathological lesions (bilateral, diffuse degeneration and atrophy of the seminiferous tubules) related to

chloromethane exposure (1 000 ppm). At the end of the 18-month period, age-related interstitial hyperplasia and/or adenomas were present in controls and the 225-ppm group; these lesions exhibited an increasing incidence with level of exposure. The testicular results in rats were found consistent with a LOAEC of 1 000 ppm, based on early signs of seminiferous tubule degeneration and atrophy in the absence of age-related degeneration. According to US EPA (2001), a NOAEC of 225 ppm appeared reasonable, because tubule degeneration and atrophy at this exposure level occurred upon onset of age-related hyperplasia and compressive adenomas.

A shortcoming of this study was addressed, related to some incorrect sexing (periodic pregnancies were observed in the mouse population) and misplacement of specific mice. The investigators considered this problem serious but not one that threatened the validity of interpretation of the experimental results. US EPA (2001) concluded that this argumentation appeared reasonable, considering that the types of effects and the levels at which they occurred were confirmed in several shorter-term studies.

7.8. Reproductive toxicity

7.8.1. Human data

No data were reported in humans concerning reproductive toxicity of chloromethane.

7.8.2. Animal data

7.7.2.1. Fertility

Male F344 rats were exposed to a chloromethane concentration of 3 500 ppm, 6 hours daily for 5 days and then, after a 3-day pause, were exposed again for another 4 days. The exposure resulted in damage to the seminiferous epithelium, formation of inflammatory granulomas in the cauda epididymidis and marked reduction in plasma testosterone levels. Glutathione depletion was found in the tissues but was not correlated with the severity of the lesions (Chapin et al 1984). A follow-up study (Working and Bus 1986b) with male Fischer 344 rats which inhaled chloromethane in concentrations of 1 000 or 3 000 ppm, 6 hours daily for 5 days before mating revealed that the fertility of the higher dose group animals was markedly reduced (see Section 7.6.2). After carrying out comparative studies with triethylenemelamine, the authors concluded that the effects of chloromethane resulted from non-genotoxic processes.

Groups of 40 male and 80 female F344 rats were exposed to chloromethane concentrations of 150, 475 or 1 500 ppm, 6 hours daily for 10 weeks before mating, 7 hours daily during the mating interval and for the females also until day 18 of gestation and 6 hours daily from day 4 to day 28 post partum (Hamm et al 1985). Ten males from each group were killed on day 28 post partum and subjected to gross pathological examination. Regression of the lesions at various times after the end of exposure was studied with the remaining 30 males per group. The progeny were treated in the same way as the animals of the parent generation. The results demonstrated delays in body weight gain in the males and females of the 475-ppm and 1 500-ppm groups. All males exposed to 1 500 ppm were infertile. The pathological examination of the gonads revealed testis atrophy in all 1 500-ppm group males and granulomas in the epididymis in about 30 % of the animals. In the 475-ppm group, fertility disorders were detected in 57 % of the males. The fertility of the male animals in the 150-ppm group was not different from that of the controls. Ten weeks after the end of exposure, the fertility disorder had regressed in 25 % of the males in the 1 500-ppm group. In the males of the 475-ppm group 10 weeks after the end of exposure, fertility was no longer different from that of the controls. The progeny of fertile males from the 150-ppm and 475-ppm groups were exposed in the same way as their parents from birth until 10 weeks after weaning and were then mated. In the 475-ppm group, the fertility of the F1 males was slightly

impaired and the postnatal development of the F2 generation was delayed. The authors considered 150 ppm to be the no-effect level.

7.7.2.2. Developmental toxicity

Groups of 25 female F344 rats were exposed to chloromethane concentrations of 100, 500 or 1 500 ppm for 6 hours daily from day 7 to day 19 of gestation. In the groups exposed to 1 500 ppm, body weight development of dams and foetuses was delayed as was ossification in the foetuses. In the groups exposed to 100 or 500 chloromethane, no evidence of maternal or embryonal toxic effects was seen. Teratogenic effects were not observed in any of the dose groups (Wolkowsky-Tyl et al 1983a).

Groups of 33 C57BL/6 mice were exposed to chloromethane concentrations of 100, 500 or 1 500 ppm, 6 hours daily from day 6 to day 17 of gestation. In the dams, which inhaled 1 500 ppm, marked signs of toxicity (vaginal bleeding, haematuria, neurotoxicity) developed after 6–9 days of treatment; these dams were therefore killed prematurely. Autopsy revealed selective necrosis of the neurones in the inner granular layer of the cerebellum in all animals. In the 500-ppm group, there were no signs of maternal toxicity. There were no externally visible effects on the foetuses. Visceral examination, however, revealed heart defects (reduced or absent atrioventricular and bicuspid valves) in 16.7 % of the foetuses. In the 100-ppm group, neither maternal nor embryonal toxic effects nor teratogenic effects were seen (Wolkowsky-Tyl et al 1983a).

In an additional study, groups of 62–67 pregnant mice were exposed according to the same schedule to chloromethane concentrations of 250, 500 or 750 ppm (Wolkowsky-Tyl et al 1983b). Ataxia, tremor, convulsions, delayed body weight gain and deaths were observed from day 7 of exposure in the animals of the 750-ppm group. Heart defects (absent or abnormal tricuspid valve, reduced number of papillary muscles and/or chordae tendineae on the right side of the heart, right ventricle reduced in size, spherical heart, white spots on the wall of the left ventricle) were significantly increased in the foetuses of the 500- and 750-ppm groups. No toxic effects were detected in either dams or progeny in the 250-ppm group.

7.9. Mode of action and adverse outcome pathway considerations

The 2-year inhalation study with rats (Fischer 344) and mice (B6C3F1, which was carried out for CIIT (Batelle Columbus 1982), is described in 7.7.2. In this study, groups of 120 rats or mice per sex and concentration were exposed to methyl chloride concentrations of 0, 50, 225 or 1000 ppm, 6 hours daily on 5 days per week. In the male mice of the highest exposure group and only in that group, the incidence of kidney tumours (cystadenomas, adenomas of the renal cortex and papillary cystadenomas) was increased significantly. In female mice or in rats of either sex, these lesions did not develop and no tumours were observed. These results had raised concern regarding carcinogenicity of chloromethane and were the reason for H351 classification.

At the same time, there were intensive scientific efforts to elucidate the mode of action of the tumour formation in male mice. The following discussion of this study produced arguments against the applicability of these results to man; drawbacks of the study were pointed out. In particular, mortality was unusually high in all groups of male mice and highest in the group exposed to ppm chloromethane. In the study protocol, this is ascribed to the fact that the animals were kept in groups so that fighting for dominance between the male mice was common, especially during the first 6 months. Bite wounds predominated in the genital area and led to frequent retrograde urinary tract infections (Greim 1996). A discussion of this study by the MAK Commission provided arguments against the applicability of these results to man. In particular, the following issues were put forward (Greim 1996):

- Kidney tumours developed only in male mice exposed to the highest chloromethane concentration of 1 000 ppm. No tumours were seen in the lower concentration groups, in female mice or in rats of either sex.
- The exposure concentration of 1 000 ppm is close to the level that produced a marked increase in replication rate in the kidney tissue of mice exposed repeatedly (1 500 ppm).
- This exposure concentration (1 000 ppm) caused glutathione depletion in the kidney and liver of the mouse, reducing the concentration to less than 5 % of the initial value and so impairing the glutathione-dependent metabolism of chloromethane. The enzyme activity required for the alternative oxidative pathway, which converts chloromethane to formaldehyde, is present in the kidneys of the male B6C3F1 mouse at higher levels than in those of females.
- Glutathione depletion reduces the activity of formaldehyde dehydrogenase, which converts formaldehyde to formic acid using glutathione as cofactor.
- DNA-protein cross-links, lesions typically produced by formaldehyde, were found in the kidneys of male mice (but not in females) exposed once for 8 hours to a chloromethane concentration of 1 000 ppm. DNA single strand breaks were also observed. The latter kind of lesion could also be produced by reactive oxygen species, a proposal which is supported by the observation that lipid peroxidation occurred.
- In addition to these effects, secondary effects were also observed in the long-term study: retrograde urinary tract infections (inflammatory processes associated with the production of reactive oxygen species and increased cell replication).
- Unlike the structurally analogous compounds, methyl bromide and methyl iodide, chloromethane (methyl chloride) is not able to methylate DNA directly *in vivo*. This conclusion is supported by two negative DNA binding studies.

It was concluded that, in the long-term study, the formation of renal tumours in the male mouse occurred only under such conditions, which do not permit any extrapolation of the results to human workplace situations (Greim 1996).

Backed by this argumentation, SCOEL concludes that the tumours reported in the study of Battelle Columbus (1981) in male mice have no relevance for humans at the workplace.

7.10. Lack of specific scientific information

The toxicity of chloromethane has been well investigated. There are no major data gaps.

8. GROUPS AT EXTRA RISK

In the metabolism of chloromethane the human polymorphic glutathione transferase GSTT1-1 is involved, which is deficient in about 20% of the European population (see 7.1.1.). As the neurotoxicity of chloromethane might be mediated via this glutathione-dependent pathway (see 7.1.2.) it could mean that this part of the population would be more resistant to chloromethane neurotoxicity than the majority of persons. At this point, firm conclusions regarding population groups at extra risk cannot be drawn. Nevertheless, some uncertainty remains, which is considered in the derivation of an OEL (see Recommendation Executive Summary).

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