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Employment, Social Affairs and Inclusion DG

Employment and Social Legislation, Social Dialogue
Health, Safety and Hygiene at Work

Luxembourg,
EMPL B3/JJ/zp ARES (2014)

SCOEL Contact Points

Subject: **Activities of the Scientific Committee on Occupational Exposure Limits (SCOEL)**

Dear Sir or Madam,

In the context of cooperation and transparency concerning the Commission's activities in the establishment of OELs, I send you the provisional SCOEL recommendation on the substance:

SCOEL/SUM/191 - Chloromethane CAS: 74-87-3

SCOEL has developed and published a methodology for evaluating the health effects of chemicals. The purpose of sending this document is to allow interested parties to submit additional information, if necessary, or to contribute to the scientific discussion. There are three main areas where SCOEL welcomes scientific comments, namely:

- Are there any important or critical published papers that have not been taken into consideration?
- Has any of the scientific data been misinterpreted?
- Are you aware of any other relevant information?

Employment, Social Affairs and Inclusion DG
Health, Safety and Hygiene at Work
European Commission
Ms. Zofia Podolan
Euroforum Building - Room EUFO 2186
L-2920 LUXEMBOURG

I would therefore be grateful to receive any scientific comments or data that you may have on these substances by the 15th September 2014 at the latest.

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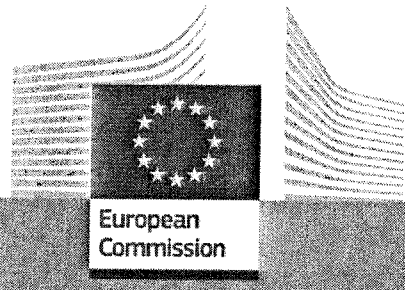
Yours faithfully,

Maria-Teresa Moitinho de Almeida
Head of Unit

C.c.: SCOEL Members, Members of AC Working Party on Chemicals



Recommendation from the Scientific Committee on Occupational Exposure Limits for Chloromethane

SCOEL/SUM/191
March 2014

Draft for 6-month consultation
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Employment, Social Affairs and Inclusion

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Recommendation from the Scientific Committee on Occupational Exposure Limits for Chloromethane

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

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

1. Substance identification, physico-chemical properties

Name:	Chloromethane
Synonyms:	Monochloromethane, methyl chloride, chloromethyl
Molecular formula:	CH_3Cl
EC No.:	200-817-4
CAS No.:	74-87-3
Molecular weight:	50.49 g/mol
Boiling point:	-24.0 °C
Melting point:	-97.7 °C
Conversion factors:	1 ppm = 2.09 mg/m^3
(20 °C, 101.3kPa)	1 mg/m^3 = 0.477 ppm
Log P_{OW}	0.91

Chloromethane is a colourless gas with an ethereal odour and sweet taste (IARC 1999).

EU harmonised classification:

Press. Gas		
Flam. Gas 1	H220	Extremely flammable gas
Carc. 2	H351	Suspected of causing cancer
STOT RE 2	H373	May cause damage to organs through prolonged or repeated exposure

2. Occurrence/use and occupational exposure

Low levels of chloromethane occur naturally in the environment. It is formed in the oceans by natural processes (e.g. marine phytoplankton) and from biomass burning in grasslands and forested areas (e.g. forest fires); it has been detected at low levels in air all over the world. Higher levels may occur at chemical plants where it is made or used. In the chemical industry, the compound serves as an intermediate methylating compound. It is used mainly in the production of silicones where it is used to make methylate silicon. It is also used in the production of agricultural chemicals, methyl cellulose, quaternary amines, and butyl rubber and for miscellaneous uses including manufacture of tetramethyl lead (in the past). Chloromethane has also widely been

used in refrigerators, but generally this use has been taken over by other chemicals (US EPA 2000).

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 chromatography. 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).

According to WHO (2000), chloromethane can be analysed by Method 1001 of the US National Institute for Occupational Safety and Health (NIOSH 1994). Analysis is performed by gas chromatography (GC), and the sample detection limit is 3.1 $\mu g/m^3$ (1.5 ppb). Using the method of Oliver *et al* (1996), the detection limit is 1.1 $\mu g/m^3$ (0.53 ppb). Hence, no analytical problems should be encountered.

3. Health significance

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).

3.1. Toxicokinetics

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 to 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.

3.1.1. 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 3.1.3) 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 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 plateaued. 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.

3.1.2. 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 ^{14}C-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 ^{14}C-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*-(methylthioacetyl)glycine have been identified as metabolites of ^{14}C-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 (Kornbrust and Bus 1984, Bolt *et al* 1988). 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).

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.

3.1.3. 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 3.1.1). 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.

3.2. Acute toxicity

3.2.1. 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 (DFG 1996).

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 (DFG 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, cited in Browning 1965) 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.

The odour threshold is given as 10 ppm (Leonardos *et al* 1969).

3.2.2. Animal data

It appears that the mechanism of acute toxic action of chloromethane differs between animal species. In rats e.g., *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 LC_{50} 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 LC_{50} by a factor of 14 even with the low casein diet (Smith and von Oettingen 1947a).

3.3. Irritancy and corrosivity

There were no data regarding irritation or corrosion effects due to chloromethane.

3.4. Sensitisation

There were no data regarding sensitisation caused by chloromethane.

3.5. Repeated dose toxicity

3.5.1. 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, cited in ACGIH 1986).

3.5.2. Animal data

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 DFG 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 postvaccinal 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) study, 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).

Oral and dermal

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

3.6. Genotoxicity

3.6.1. 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).

3.6.2. In vivo – human data

No data were available.

3.6.3. In vivo – animal data

In a test for dominant lethal mutations, groups of 40 male Fischer 344 (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 F344 rats which inhaled ^{14}C- 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 F344 rats and B6C3F1 mice were exposed to ^{14}C-chloromethane also showed that no methylation of guanine at the positions *O*6 or *N*7 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.

3.6.4. Interpretation of genotoxicity data

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. 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*.

3.7. 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)."

3.7.1. 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 accidentally exposed to chloromethane from a leaking refrigeration unit (Rafnsson and Gudmundsson 1997). 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.

3.7.2. Animal data

The results of a 2-year inhalation study with rats (F344) 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, 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 F344 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 CNS 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.

3.7.3 Discussion of the mode of action

In essence, in male mice of the highest exposure group (1 000 ppm) 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. A discussion of this study by DFG provided arguments against the applicability of these results to man. In particular, the following issues were put forward (DFG 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.*

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 (DFG 1996).

3.8. Reproductive toxicity

3.8.1. Human data

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

3.8.2. Animal data

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 F344 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 3.6.3). 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 F_1 males was slightly impaired and the postnatal development of the F_2 generation was delayed. The authors considered 150 ppm to be the no-effect level.

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 ppm 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, heart spherical, 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.

4. Recommendation

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 3.5.2). These NOAEC/LOAEC figures were based on both functional and morphological (cerebellar granular cell layer degeneration) effects. For these experiments, the animal model (C57BL/6 mouse) had been chosen because of its particular 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 F344 rats and B6C3F1 mice, were all higher than 150 ppm. Therefore, the NOAEC of 150 ppm can serve as point of departure for the derivation of a recommended OEL based on experimental neurotoxicity, without the need of an adjustment to longer study durations. In the available experimental studies on reproductive toxicity (see above), the NOAEC was either 150 ppm (Hamm *et al* 1985) or higher.

Chloromethane is weakly mutagenic in *in vitro* tests; *in vivo*, however, genotoxicity effects are noticed only at very high and already toxic doses. 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 F344 rats and B6C3F1 mice revealed renal tumours (cystadenomas and adenomas), but only in male mice of the highest exposed group (1 000 ppm). Based on a number of arguments (for details, see Section 3.7.2) 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. Based on these data in

total, SCOEL concludes that an experimentally derived NOAEC of 150 ppm chloromethane is a valid point of departure, and that there is no indication of a genotoxic or carcinogenic effect at this level or below. A SCOEL carcinogenicity group is not assigned.

Starting from the experimentally established 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. The 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.

Some observations in occupationally exposed humans, described under Section 3.5.1, provide a high degree of confidence that this recommended OEL is indeed safe for human workforce. A recommended OEL of 20 ppm is also consistent with the notion of Löf *et al* (2000) that no irritation or CNS 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.

As explained in Section 3.1.3, there is presently no proven strategy for a biological monitoring.

At the recommended OEL, no measurement difficulties are foreseen.

The present Recommendation was adopted by SCOEL on Date Month Year.

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