Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for 1,1'-dichlorodimethyl ether

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8-hour TWA:	not assigned
STEL (15 min):	not assigned
Notation:	not assigned
BLV:	not assigned
SCOEL carcinogen group:	A (genotoxic carcinogen, no threshold)
Recommendation:	Any occupational contact must be avoided

Substance identification: dichlorodimethyl ether

Synonyms: bis(chloromethyl) ether, chloro(chloromethoxy)methane, symmetrical dichlorodimethyl ether

Structural formula: $Cl\text{-}CH_2\text{-}O\text{-}CH_2\text{-}Cl$

CAS No.: 542-88-1

Molecular formula: $C_2H_4OCl_2$

Molecular weight: 115.0
Melting point: -41.5 °C
Boiling point: 104-106°C

EC Classification:

Flam. Liq. 2	H225	Highly flammable liquid and vapour
Carc. 1A	H350	May cause cancer
Acute Tox. 2 *	H330	Fatal if inhaled
Acute Tox. 3 *	H311	Toxic in contact with skin
Acute Tox. 4 *	H302	Harmful if swallowed

Conversion factor: 1 ppm = 4.778 mg/m^3; 1 mg/m^3 = 0.209 ppm

1 Occurrence/use and occupational exposure

The two chloromethyl ethers, dichlorodimethyl ether and monochlorodimethyl ether, have been used primarily as chemical intermediates and alkylating agents. Dichlorodimethyl ether, in particular, has been extensively used as a chemical intermediate in organic synthesis, namely as a crosslinking agent in the manufacture of ion-exchange resins and in the textile industry; two textile mills using formaldehyde resins, magnesium chloride and zinc nitrate catalysts in the permanent press process detected a maximum dichlorodimethyl ether of 2.7 ppb (Durkin PR et al. 1975).

Because of their carcinogenic potency, the industrial production of chloromethyl ethers ended in most countries in the early 1980s. For instance, in the U.S.A. dichloromethyl ether was no longer produced in 1982. Small quantities may eventually be further produced or repackaged as laboratory chemical and it is a contaminant of technical grade chloromethylmethylether (1 to 8%).
The generation of bis-chloromethyl-ether seems also possible with the mixture of formaldehyde and chlorhydric acid; that is mainly the case in the laboratories of anatomo-pathology (Carson FL, 1978).
The primary routes of potential human exposure to chlorodimethyl ethers have been inhalation and dermal contact (Bernucci et al., 1997; U.S. NTP, 2008).

2 Health significance

2.1 Toxicokinetics

No data on toxicokinetics have been reported.

2.2 Acute toxicity

2.2.1 Human data

A fatal accident with dichlorodimethyl ether has been reported by Thiess et al. (1973). A reaction mixture containing the substance was poured over the entire body of a chemical worker. There was severe local irritation of skin and eyes, with caustic burns of 2nd and 3rd degree. Later, atrophy of the optical nerves and pneumonia occurred, with subsequent lung fibrosis that was also the cause of death.

2.2.2 Animal data

Upon 6 h inhalation, an LC_{50} in mice has been reported of 5.3 ppm (Leong et al., 1971).

2.3 Irritation and corrosivity

As evidenced by experience in humans, dichlorodimethyl ether is irritating and corrosive to the skin (see 2.2.1). This also applies to the related compound, monochlorodimethyl ether (data compiled by DFG, 1973).

2.4 Sensitisation

No data have been reported.

2.5 Repeated dose toxicity

Repeated doses of dichlorodimethyl ether have caused malignant tumours, both in industrial workers and in experimental animals (see 2.8). There are no specific reports on repeated dose toxicity other than cancer.

2.6 Genotoxicity

Dichlorodimethyl ether is directly mutagenic. It causes mutations in bacteria. It also has caused unscheduled DNA synthesis (DNA repair response) in cultured human cells, but did not cause chromosomal aberrations in bone-marrow cells of rats exposed in vivo [presumably due to a very short biological half-life]. The incidence of chromosomal aberrations was increased slightly in white blood cells from workers exposed to mono- or di-chlorodimethyl ether (U.S. NTP, 2008).

2.7 Carcinogenicity

2.7.1 Human data

Thiess et al. (1973) reported a retrospective investigation of a small group of dichlorodimethyl ether workers exposed to the compound between 1956 and 1962. They observed 6 cases of lung cancer amongst 18 men employed in an industrial testing laboratory. Five of the 6 men were moderate smokers, 1 was non-smoker. Two further cases of lung cancer were found amongst a group of 50 production workers. Five of the total 8 reported cases were stated to be oat-cell carcinomas. The exposure period ranged from 6 to 9 years, and the latent period from first exposure to diagnosis was from 8 to 16 years (Thiess et al., 1973).

Dichlorodimethyl ether had been an impurity (1-7%) in the related (mono) chloromethyl methyl ether. A cohort of 125 chemical workers was established in 1963 to investigate an epidemic of lung cancer caused by industrial exposure to both chloromethyl ethers. Exposure occurred in one chemical plant, and 14 cases of lung cancer, mainly oat cell carcinomas, were detailed (Figueroa et al., 1973). Three of the 14 individuals were non-smokers, and 1 additional subject smoked pipe only.

After over 30 years of observation of this cohort, Weiss and Nash (1997) published an update. Ninety-three of the men had been exposed to dichlorodimethyl ether, and approximate estimates of exposure were made. Standardized mortality ratios (SMRs) were calculated for lung cancer, based on Philadelphia city rates. Within over 30 years of observation, 25 of 67 deaths were due to lung cancer, with a dose-response relationship. SMRs were elevated among 59 moderately and heavily exposed workers, peaked at 23.1 in the first decade, and then declined to 7.4 and 7.9 in later decades. The mean latency period from onset of exposure to death was 21 to 25 years and was inversely related to cumulative exposure. Three of 12 heavily exposed cases occurred in non-smokers. Small cell (oat-cell) carcinoma accounted for 80% of the moderately and heavily exposed cases.

2.7.2 Animal data (according to IARC, 1974)

Van Duuren et al. (1972) described dichlorodimethyl ether as a powerful cutaneous carcinogen. Complete carcinogenic activity was revealed in a test in which 2 mg

dichlorodimethyl ether dissolved in 0.1 ml benzene were applied to the skin of female ICR/Ha Swiss mice 3 times per week for a total of 325 days. Papillomas developed in 13/20 mice, 12 of which progressed to squamous cell carcinomas by 325 days. The first papilloma was seen at 161 days, the first carcinoma at 231 days. In an initiation-promotion experiment, application to the skin of a single dose of 1 mg dichlorodimethyl ether dissolved in 0.1 ml benzene, followed by thrice-weekly applications of an acetone solution of 0.025 mg in 0.1 ml mixed phorbol esters from croton oil 14 days after initiation treatment, yielded papillomas in 5/20 female mice, the first papilloma being noted at 76 days. Two mice had squamous cell carcinomas, one with metastases to the lung. The median survival time was 474 days. No tumours were seen in a control group which received dichlorodimethyl ether as initiator and no promoting treatment. In mice receiving the mixed phorbol esters alone, papillomas developed in 2/20 mice, the first appearing at 322 days. In a test involving pre-treatment with 0.15 mg benzo(a)pyrene in 0.1 ml benzene solution, followed 2 weeks later by thrice-weekly applications of dichlorodimethyl ether (2 mg in 0.1 ml phorbol esters), as in the complete carcinogenicity experiment, papillomas developed in 13/20 mice, 12 of which progressed to carcinomas. The latent period of the first papilloma was 98 days, shorter than in the test without benzo(a)pyrene pre-treatment. However, the median survival time of 315 days was almost identical (Van Duuren et al., 1968, 1969, 1972).

Male and female ICR Swiss random bred mice were given a single s.c. injection of a pre-determined maximum tolerated dose of 12.5 µl dichlorodimethyl ether /kg bw in peanut oil solution. All mice were killed and examined for lung tumours after 6 months. Control mice received a single s.c. dose of peanut oil, and a positive control group received a single s.c. dose of 1500 mg/kg bw urethane. In 50 males and 50 females injected with dichlorodimethyl ether, pulmonary tumours developed in 45% of the animals, with a multiplicity of 0.64 tumours per mouse. In addition, 1 mouse developed an injection site papilloma and a fibrosarcoma; such tumours were not seen in control animals. In the vehicle controls, 7/50 mice had lung tumours, with a multiplicity of 0.14 tumours per mouse; and in the urethane group, 100% of the mice, had lung tumours, with a multiplicity of 17 tumours per mouse (Gargus et al., 1969).

A group of 20 female Sprague-Dawley rats received once weekly s.c. injections of 3 mg dichlorodimethyl ether in 0.1 ml nujol (a refined pharmaceutical mineral oil with a low polycyclic aromatic hydrocarbon content). After 100 days, the dose was reduced to 1 mg per week because of local irritation at the initial dose level. Later (time not specified), the number of injections was reduced to 3 times per month, and was discontinued altogether after 300 days from the start of treatment. After a median survival time of 325 days, 2 local fibromas and 5 fibrosarcomas were seen. The first tumour was noted at 58 days. No increase in the incidence of remote tumours was seen. Control animals without treatment or injected repeatedly with 0.1 ml nujol vehicle exhibited no local tumours (Van Duuren et al., 1969).

Nominal concentrations of 1 ppm dichlorodimethyl ether were introduced into a chamber containing 50 strain A/HE mice for 6 hours per day on 5 days per week, for a total of 82 exposure days in 27 weeks. Twenty-six of the surviving 47 animals exhibited lung tumours, with an average of 2.9 tumours per mouse. In untreated controls held under the same conditions for 130 days in a chamber and maintained for a total of 28 weeks 20/49 animals had lung tumours (Leong et al., 1974).

Laskin et al. (1971) exposed Sprague-Dawley rats to several dose levels of dichlorodimethyl ether in inhalation chambers for 6 hours per day on 5 days per week. A preliminary report details findings at a low exposure level (0.1 ppm, or 0.5 mg/m^3) for a total of 101 exposures. After 659 days, all 30 animals at risk were dead. Of 19 animals in which pathological examination was completed at the time of reporting, 5 died between 332 and 463 days after the beginning of the test with squamous cell carcinomas of the lung. In 5 others, dying between 346 and 488 days after the beginning of the test, tumours of the nasal cavity (diagnosed as aesthesioneuro-

epitheliomas invading the sinuses, cranial vault and brain) were noted. In the same report, mention was made of the occurrence of multiple tumours in the lung and nasal cavity in rats exposed for shorter periods.

2.8 Reproductive toxicity

No data have been reported.

Recommendation

1,1'-Dichlorodimethyl ether (also called *bis*-chloromethyl ether; BCME) is a reactive bifunctional alkylating agent. The compound has been used industrially to a larger extent until the early 1980s. It is directly mutagenic and strongly carcinogenic. In occupationally exposed persons, it has caused lung cancer, mainly oat cell carcinoma. These findings are in line with studies in experimental animals demonstrating that dichlorodimethyl ether causes cancer in all species tested, *i.e.* rats, mice and hamsters. Upon inhalation, lung tumours occurred in rats and mice (see 2.8).

There are no recent studies into the mode of the carcinogenic action of dichlorodimethyl ether. However, its high chemical reactivity and mutagenicity, along with knowledge on similarly acting compounds, make it almost certain that direct DNA reactivity is the principal mode of action (Bernucci et al. 1997). Hence, the compound is categorised into the SCOEL carcinogen group A (Bolt and Huici-Montagud, 2008), as a genotoxic carcinogen without threshold. Consequently, a health-based OEL or BLV cannot be recommended.

Experimentally, long-term inhalation exposures of rats to concentrations as low as 0.1 ppm dichlorodimethyl ether were clearly carcinogenic (2.8.2). ***In view of this extremely high carcinogenic potency, any occupational contact to dichlorodimethyl ether must strictly be avoided.***

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Criteria documents used: This summary rests mainly on the documentation of IARC (1974). This was supplemented using data compiled by DFG (1973), by Bernucci et al. (1997), by the U.S. NTP (2008) and by a recent literature search conducted by SCOEL.