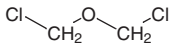
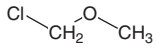
bis(Chloromethyl) Ether and Technical-Grade Chloromethyl Methyl Ether CAS Nos. 542-88-1 and 107-30-2

Known to be a human carcinogen
First Listed in the *First Annual Report on Carcinogens* (1980)



bis(Chloromethyl) ether



Chloromethyl methyl ether

Carcinogenicity

bis(Chloromethyl) ether (BCME) and technical-grade chloromethyl methyl ether (CMME) are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans. Numerous epidemiological studies and case reports from various geographical locations have demonstrated that occupational exposure to BCME or CMME causes lung cancer (predominantly small-cell type). The risk of lung cancer was shown to increase with increasing exposure (duration or cumulative). Among the most heavily exposed workers, the risk of lung cancer was increased at least 10-fold, and latency (the period between exposure and diagnosis of disease) was shorter. The studies were of workers exposed either to BCME or to CMME; however, because BCME is a contaminant of technical-grade CMME (at levels of 1% to 7%), CMME workers probably also were exposed to BCME. The International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence for the carcinogenicity of BCME and technical-grade CMME in humans (IARC 1974, 1987).

The findings in humans are supported by studies in experimental animals demonstrating that BCME and technical-grade CMME cause cancer in rats, mice, and hamsters. Exposure to BCME by inhalation caused lung tumors in both rats and mice and nasal-cavity tumors in rats. Subcutaneous (s.c.) injection of BCME caused lung tumors and fibrosarcomas (connective-tissue tumors) at the injection site in mice of both sexes and fibromas and fibrosarcomas in female rats. Both BCME and technical-grade CMME caused skin tumors in mice. BCME applied to the skin of female mice caused papillomas (benign tumors), most of which progressed to squamous-cell carcinomas (malignant tumors). Evaluation of technical-grade CMME is complicated by the presence of BCME as a contaminant. Exposure to technical-grade CMME by inhalation caused respiratory-tract tumors in rats and hamsters (at a low incidence), and s.c. administration caused injection-site sarcomas in mice. IARC (1987) concluded that there was sufficient evidence for the carcinogenicity of BCME and technical-grade CMME in experimental animals.

Additional Information Relevant to Carcinogencity

BCME caused mutations in bacteria. It also caused unscheduled DNA synthesis (a DNA repair response) in cultured human cells but did not cause chromosomal aberrations (changes in chromosome structure or number) in bone-marrow cells of rats exposed *in vivo*. CMME caused mutations in bacteria and enhanced virus-induced transformation of mammalian cells (a step in tumor formation). The incidence of chromosomal aberrations was increased slightly in white blood cells from workers exposed to BCME or CMME (IARC 1987).

Properties

BCME and CMME belong to a group of chemicals known as chloroalkyl ethers. The molecular weight of BCME is 115, and that of CMME is 80.5. They occur as flammable, volatile, colorless liquids with highly irritating odors and are miscible with ethanol and many other organic solvents. In water, they are rapidly hydrolyzed to form hydrochloric acid, methanol, and formaldehyde. When heated to decomposition, they emit toxic fumes of hydrochloric acid and other chlorinated compounds. Their vapors may form explosive mixtures with air (IARC 1974, HSDB 2003).

BCME melts at –41.5°C and boils at 106°C. It has a specific gravity of 1.32 (15°C/4°C), a vapor pressure of 29.4 mm Hg at 25°C, a vapor density of 4.0, and a log octanol-water partition coefficient of 1.04. CCME melts at –103.5°C and boils at 59.5°C. It has a specific gravity of 1.06 (20°C/4°C), a vapor pressure of 30 mm Hg at 22°C, and a vapor density of 0.52 (HSDB 2003).

Use

BCME and CMME are used primarily as chemical intermediates and alkylating agents. BCME is used as a laboratory reagent; to manufacture plastics, ion-exchange resins, and polymers; and as a monitoring indicator for chloromethyl ether (HSDB 2003). BCME formerly was used for crosslinking of cellulose, surface treatment of vulcanized rubber to increase adhesion, and in the manufacture of flame-retardant fabrics (ATSDR 1989). CMME is used as an alkylating agent and industrial solvent to manufacture dodecylbenzyl chloride, water repellants, ion-exchange resins, and polymers, and as a chloromethylation reagent (HSDB 2003).

Production

BCME and CMME previously were manufactured in the United States, but use of these chemicals had been widely curtailed by 1976 (HSDB 2003). In 1977, U.S. production of BCME was about 45,400 kg (100,000 lb), and that of CMME was 4.6 million kilograms (10 million pounds). In 1982, BCME was no longer produced, and only 2,270 kg (5,000 lb) of CMME was produced. There were three U.S. manufacturers of CMME in 1969, one in 1973, and none in 2003 (IARC 1974, HSDB 2003, SRI 2003). Although BCME is no longer produced as a commercial product in the United States, small quantities may be produced or repackaged as a chemical intermediate or laboratory chemical (ATSDR 1989, HSDB 2003). In 2003, five U.S. suppliers of BCME and ten suppliers of CMME were identified (ChemSources 2003). No data on imports or exports of these compounds were found.

Exposure

The primary routes of potential human exposure to BCME and technical-grade CMME are inhalation and dermal contact. Because BCME is little used in the United States and because it is rapidly degraded in the environment, the probability of human exposure is very low. BCME has not been detected in ambient air or water (ATSDR 1989). According to the U.S. Environmental Protection Agency's Toxics Release Inventory (TRI), almost all environmental releases of BCME and CMME have been to the air. Reported annual releases of BCME to air ranged from 255 to 574 lb (116 to 261 kg) in the early 1990s, but since 1995, annual releases to air have not exceeded 7 lb (3 kg), and no releases to air were reported in 1995, 1996, 1998, 2000, or 2001. Releases of CMME to the air since 1988 (the earliest year for which reports were available) have fluctuated between 1,000 lb (455 kg) in 1988 and 4,155 lb (1,889 kg) in 1997. In 2001, three facilities reported releases of 2,101 lb (953 kg) of CMME, of which 1,841 lb (837 kg) was released to air and 260 lb (118 kg) was transferred for off-site disposal (landfill or surface impoundment) (TRI01 2003).

The primary route of occupational exposure to BCME or CMME is inhalation of vapors; however, the potential for exposure is low, because these chemicals are no longer produced or sold in large quantities, and most industrial operations involving them take place in closed process vessels. The most likely means of exposure to BCME is

during the production or use of chemicals in which it may occur as a contaminant or may be formed inadvertently. The potential for occupational exposure to BCME or CMME is greatest for chemical plant workers, ion-exchange resin makers, laboratory workers, and polymer makers (ATSDR 1989). The National Occupational Exposure Survey (1981–1983) estimated that 14 workers (all laboratory workers, including 5 women) were potentially exposed to BCME. No estimate of potential CMME exposure was reported (NIOSH 1984).

Regulations

EPA

Clean Air Act

NESHAP: Both are listed as a Hazardous Air Pollutants (HAPs)

Prevention of Accidental Release: Threshold Quantity (TQ) = 1,000 lb for BCME and 5,000 lb for CMME

Clean Water Act

Water Quality Criteria: Based on fish/shellfish and water consumption = 0.00010 µg/L (BCME); based on fish/shellfish consumption only = 0.00029 µg/L (BCME)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable Quantity (RQ) = 10 lb (for both BCME and CMME)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Both are listed substances subject to reporting requirements

Threshold Planning Quantity (TPQ) = 100 lb (for each)

Reportable Quantity (RQ) = 10 lb (for each)

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes in which listing is based wholly or partly on substance - P016 and U046 for BCME and CCME respectively

Both are listed as a Hazardous Constituents of Waste

OSHA

Both listed as potential occupational carcinogens: Engineering controls, work practices, and personal protective equipment required

Guidelines

ACGIH

Threshold Limit Value - Time-Weighted Average Limit (TLV-TWA) = 0.001 ppm (BCME)

NIOSH

Both are listed as potential occupational carcinogens

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