Chloroalkyl Ethers

Chloroalkyl ethers have been widely used in a variety of applications as solvents, textile treatments, and pesticides, and as alkylating agents and chemical intermediates in the manufacture of dyes, polymers, ion exchange resins, pharmaceuticals, and other chemicals. Chloroalkyl ethers may also be formed as by-products of chemical manufacture and drinking water disinfection. Discharges from industrial and manufacturing processes represent the major sources of chloroalkyl ether water contamination. Occupational exposure may occur during manufacture and use of chloroalkyl ethers. Exposure of the general population may occur as a result of ingestion of contaminated water.

Four chloroalkyl ethers – bis(chloro-methyl) ether [BCME]; chloromethyl methyl ether [CMME], technical grade; bis(chloroethyl) ether [BCEE]; and bis(2-chloro-1-methylethyl) ether [BCMEE], technical grade – are already listed as carcinogens under Proposition 65.

Several other individual chloroalkyl ethers and the chemical group as a whole passed the human and animal data screens, underwent a preliminary toxicological evaluation, and are being brought to the Carcinogen Identification Committee (CIC) for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data

There is sufficient evidence from numerous occupational epidemiology studies that workers exposed to the Proposition 65 carcinogens BCME and CMME have an increased risk of lung cancer (U.S. EPA, 1989; 1991).

No cancer epidemiology studies on other chloroalkyl ethers were identified.

Animal carcinogenicity data

Tables 1 and 2 present animal carcinogenicity data for several chloroalkyl ethers.

Table 1. Animal tumor findings of several chloroakyl ethers

Chemical (CAS Number)	Structure	Animal data
Tris-1,2,3-(chloromethoxy) propane (38571-73-2)	CH_2OCH_2Cl | CH_2OCH_2Cl | CH_2OCH_2Cl	Female ICR/Ha Swiss mice (U.S. EPA, 1987, Tables 6-7, 6-9 & 6-10) - 502-day dermal study: Increase in skin papillomas (by pairwise comparison); - 569-day *s.c.* injection study: Increase in injection-site sarcomas and carcinomas (combined) (by pairwise comparison); - 532-day *i.p.* injection study: Increase in injection-site sarcoma (by pairwise comparison)
Bis-1,2-(chloromethoxy) ethane (13483-18-6)	$ClCH_2$-O-CH2CH_2-O-CH_2Cl	Female ICR/Ha Swiss mice (U.S. EPA, 1987, Tables 6-7, 6-9 & 6-10) - 502-day dermal study: Increases in skin papilloma and skin carcinoma (by pairwise comparison); - 569-day *s.c.* injection study: Increase in injection-site sarcoma (by pairwise comparison); - 546-day *i.p.* injection study: Increase in injection-site sarcoma and undifferentiated malignant tumors (combined) (by pairwise comparison)
Bis (α-chloroethyl) ether (6986-48-7)	$CH_3CHOCHCH_3$ | | Cl Cl	Female ICR/Ha Swiss mice (U.S. EPA, 1987, Tables 6-8 & 6-9) - Life-long *s.c.* injection study: Increase in injection-site sarcoma ($p = 0.056$ by pairwise comparison) - 590-day skin tumor-initiating study with phorbol 12-myristate 13-acetate: Increase in skin papilloma (by pairwise comparison)
Bis-1,6-(chloromethoxy) hexane (56894-92-9)	$ClCH_2$-O-$(CH_2)_6$-O-CH_2Cl	Female ICR/Ha Swiss mice (U.S. EPA, 1987, Tables 6-7, 6-9, 6-10) - 503-day dermal study: No treatment-related findings - 569-day *s.c.* injection study: No treatment-related findings - 567-day *i.p.* injection study: No treatment-related findings
Bis-1,4-(chloromethoxy) butane (13483-19-7)	$ClCH_2$-O-$(CH_2)_4$-O-CH_2Cl	Female ICR/Ha Swiss mice (U.S. EPA, 1987, Tables 6-7, 6-9 & 6-10) - 503-day dermal study: No treatment-related findings - 569-day *s.c.* injection study: No treatment-related findings - 567-day *i.p.* injection study: No treatment-related findings
α,α-Dichloromethyl methyl ether (4885-02-3)	Cl_2CH-O-CH_3	Female Swiss-Millerton mice (U.S. EPA, 1987, Tables 6-7 & 6-8) - 450-day dermal study: No treatment-related findings - 450-day skin tumor-initiating study with phorbol ester: No treatment-related skin tumor initiating activity
Octachlorodi-*n*-propyl ether (127-90-2)	Cl_3CCHCH_2-O-CH_2CHCCl_3 | | Cl Cl	Female Swiss-Millerton mice (U.S. EPA, 1987, Tables 6-7 & 6-8) - 450-day dermal study: No treatment-related findings - 450-day skin tumor-initiating study with phorbol ester: No treatment-related tumor initiating activity

Table 2. Animal tumors induced by chloroalkyl ethers listed as carcinogens under Proposition 65

Chemical (CAS Number)	Chemical Structure	Animal tumor findings	Year listed under Proposition 65
BCME[1] (542-88-1)	$ClCH_2OCH_2Cl$	Male & female mice: respiratory tract tumors, skin tumors; Male rats: respiratory tract tumors	1987
CMME, technical grade[2]	$ClCH_2OCH_3$	Male mice: lung adenomas Female mice: injection site sarcomas Male rats: respiratory tract tumors Female rats: injection site sarcomas Male Syrian hamsters: respiratory tract carcinomas	1987
BCEE[3] (111-44-4)	$ClCH_2CH_2OCH_2CH_2Cl$	Male mice: liver tumors in two strains, and Female mice: liver tumors, injection site sarcomas	1988
BCMEE, technical grade[4]	$ClCH_2CHOCHCH_2Cl$ CH_3 CH_3	Male mice: liver adenomas and carcinomas, and lung adenomas Female mice: lung adenomas and carcinomas	1999

References: [1] U.S. EPA (1991); [2] U.S. EPA (1989); [3] U.S. EPA (1994); [4] OEHHA (1999)

Other relevant data

- Genotoxicity

Several chloroalkyl ethers are direct-acting mutagens (*e.g*., U.S. EPA 1989; 1991; 1994). In addition, some metabolites of chloroalkyl ethers have been reported as mutagens. Table 3 presents the genotoxicity findings for seven chloroalkyl ethers.

Table 3. Genotoxicity findings for several chloroalkyl ethers

Chemical	Gene mutation		Chromosome aberration (SCE)	DNA effects		Others
	Salmonella	Other		UDS	Other	
α,α-Dichloromethyl methyl ether (Nelson, 1976; Mukai and Hawryluk, 1973)	+	+ *E. coli*	*NA*	*NA*	*NA*	*NA*
Bis (α-chloroethyl) ether (Nelson, 1976; Mukai and Hawryluk, 1973)	+	+ *E. coli*	*NA*	*NA*	*NA*	*NA*
Bis(2-chloro-*n*-propyl) ether (HSDB, 2010)	+	*NA*	*NA*	*NA*	*NA*	*NA*
Proposition 65 carcinogens[1]						
BCME	+	+ *E. coli*	-	+ human skin fibroblasts	+ Direct DNA binding (G,A sites)	+ transformed cells; RNA damage
CMME	+	+ *E. coli*	*NA*	+ human lymphocytes	*NA*	*NA*
BCEE	+	+ *D. melanogaster, E. coli, B.subtilis, S. cerevisiae*	*NA*	*NA*	*NA*	+ Covalently binds to proteins (rats),
BCMEE	+	+ mouse lymphoma, *E. coli* ± *S. cerevisiae*	+ CHO cells; SCE	-	+ S-phase DNA synthesis (male mouse hepatocytes); DNA damage in *E. Coli*	*NA*

[1]References: U.S. EPA, 1987; 1989; 1991; 1995; OEHHA, 1999
NA = not available

- Structure activity considerations: Van Duuren *et al.* (1975); Nelson (1976)
  - The bifunctional α-chloroalkyl ethers (*e.g.*, BCME) are more carcinogenic than their monofunctional analogs (*e.g.*, CMME).

- The carcinogenic activity of the chloroalkyl ethers increases the closer the chlorine moiety is to the ether oxygen.
- The carcinogenic activity of the chloroalkyl ethers increases as the alkyl chain length decreases.

References[1]

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[1] Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.