CHLOROALKYL ETHERS

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

CRITERION DOCUMENT

CHLOROALKYL ETHERS

CRITERIA

Aquatic Life

For freshwater aquatic life, no criterion for any chloroalkyl ether can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

For saltwater aquatic life, no criterion for any chloroalkyl ether can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the protection of human health from the toxic properties of bis(2-chloroisopropyl) ether ingested through water and through contaminated aquatic organisms, the ambient water criterion is determined to be 175.8 µg/l. For the maximum protection of human health from the potential carcinogenic effects of exposure to bis-(2-chloroisopropyl) ether through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of bis(2-chloroisopropyl) ether estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 11.5 µg/l, 1.15 µg/l, and 0.115 µg/l, respectively. Further discussion of levels derived via carcinogenic properties versus toxic properties is presented in the Criterion Formulation section.

For the maximum protection of human health from the potential carcinogenic effects of exposure to bis(2-chloroethyl) ether through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of bis(2-chloroethyl) ether estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 0.42 µg/l, 0.042 µg/l, and 0.0042 µg/l, respectively.

For the maximum protection of human health from the potential carcinogenic effects of exposure to bis(chloromethyl) ether through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of bis-(chloromethyl) ether estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 0.02 ng/l, 0.002 ng/l, and 0.0002 ng/l, respectively.

Introduction

The chloroalkyl ethers have been widely used in laboratories and in industrial organic synthesis, textile treatment, preparation of ion exchange resins, and pesticide manufacture. They also have been used as solvents for polymerization reactions (Summers, 1955). Both bis-(chloromethyl)ether (BCME) and chloromethylmethyl ether (CMME) are listed as human carcinogens. Limited data are available on the effects of any of the chloroalkyl ethers on aquatic life. For this reason no water quality criterion can be established. However, because of the demonstrated carcinogenicity of BCME and CMME, human contact with these compounds should be avoided.

The chloroalkyl ethers are compounds with the general structure RClx-O-R' Clx, where x may be any positive integer, including zero, and R and R' are aliphatic groups. The chemical reactivity of these compounds varies widely, depending on the placement of chlorine atoms and the nature of the aliphatic groups involved. Chloromethylmethyl ether, bis-(chloromethyl) ether, 1-chloroethylethyl ether, and 1-chloroethylmethyl ether decompose in water (Hampel and Hawley, 1973). Tou and Kallo (1974) calculated a half-life of 14 seconds for bis(chloromethyl) ether in aqueous solution. chloromethylmethyl ether undergoes decomposition in water to form methanol, formaldehyde, and hydrochloric acid. Bis-(chloromethyl) ether will form spontaneously in the presence of hydrogen chloride and formaldehyde (Frankel, et al. 1974).

REFERENCES

Frankel, L.S., et al. 1974. Formation of bis-(chloromethyl) ether from formaldehyde and hydrogen chloride. Environ. Sci. Technol. 8: 356.

Hampel, C.A., and G.G. Hawley. 1973. Encyclopedia of chemistry. Van Nostrand Reinhold Co., New York.

Summers, L. 1955. The haloalkyl ethers. Chem. Rev. 55: 301.

Tou, J.C., and G.J. Kallos. 1974. Study of aqueous HCl and formaldehyde mixtures for formation of bis-(chloromethyl) ether. Jour. Am. Ind. Hyg. Assoc. 35: 419.

AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

The data base for freshwater organisms and chloroalkyl ethers is limited to a few toxicity tests with 2-chloroethyl vinyl ether and bis (2-chloroethyl) ether. No unadjusted LC50 or EC50 values were observed below 237,000 µg/l. Bioconcentration of bis (2-chloroethyl) ether by the bluegill was low.

Acute Toxicity

The adjusted 96-hour LC50 for the bluegill and 2-chloroethyl vinyl ether (U.S. EPA, 1978) is 194,000 µg/l and, after this concentration is divided by the species sensitivity factor (3.9), a Final Fish Acute Value of 50,000 µg/l is derived for that compound (Table 1). Since no data on an invertebrate species are available for 2-chloroethyl vinyl ether, the Final Acute Value is also 50,000 µg/l.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

No 96-hour LC50 value for the bluegill could be determined for bis (2-chloroethyl) ether in a test with exposure concentrations as high as 600,000 µg/l (Table 5). However, an unadjusted 48-hour EC50 value for Daphnia magna was determined to be 237,000 µg/l for bis (2-chloroethyl) ether (Table 2). This result provides a Final Invertebrate and Final Acute Value of 9,600 µg/l for that compound.

Chronic Toxicity

An embryo-larval test has been conducted with bis (2-chloroethyl) ether and the fathead minnow (U.S. EPA, 1978). No adverse effects were observed at test concentrations as high as 19,000 µg/l (Table 3). A Final Fish Chronic Value of greater than 1,400 µg/l is derived that also becomes the Final Chronic Value for bis (2-chloroethyl) ether, since no chronic data are available for any invertebrate species, there are no plant data, and no Residue Limited Toxicant Concentration is available.

Plant Effects

No data are available on the effects of any chloroalkyl ether on aquatic plants.

Residues

Using ^{14}C-bis (2-chloroethyl) ether and thin layer chromatography (U.S. EPA, 1978) a bioconcentration factor of 11 was determined during a 14-day exposure of bluegills (Table 4). The half-life was observed to be between 4 and 7 days.

Miscellaneous

The only datum in Table 5 was discussed earlier in this document.

CRITERION FORMULATION

Freshwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

2-chloroethyl vinyl ether

Final Fish Acute Value = 50,000 µg/l

Final Invertebrate Acute Value = not available

Final Acute Value = 50,000 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = not available

0.44 x Final Acute Value = 22,000 µg/l

bis (2-chloroethyl) ether

Final Fish Acute Value = not available

Final Invertebrate Acute Value = 9,600 µg/l

Final Acute Value = 9,600 µg/l

Final Fish Chronic Value = greater than 1,400 µg/l

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = greater than 1,400 µg/l

0.44 x Final Acute Value = 4,200 µg/l

No freshwater criterion can be derived for any chloroalkyl ether using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 1. Freshwater fish acute values for chloroalkyl ethers (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Bluegill, Lepomis macrochirus	S	U	2-chloroethyl vinyl ether	96	354,000	194,000

* S = static

** U = unmeasured

Geometric mean of adjusted values: 2-chloroethyl vinyl ether = 194,000 µg/l $\frac{194,000}{3.9}$ = 50,000 µg/l

Table 2. Freshwater invertebrate acute values for chloroalkyl ethers (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)
Cladoceran, *Daphnia magna*	S	U	Bis(2-chloro-ethyl) ether	48	237,000	201,000

* S = static

** U = unmeasured

Geometric mean of adjusted values: bis(2-chloroethyl) ether = 201,000 µg/l $\frac{201,000}{21}$ = 9,600 µg/l

Table 3. Freshwater fish chronic values for chloroalkyl ethers (U.S. EPA, 1978)

Organism	Test*	Limits (µg/l)	Chronic Value (µg/l)
Fathead minnow, *Pimephales promelas*	E-L	>19,000	>9,500**

* E-L = embryo-larva

Geometric mean of chronic values = >9,500 µg/l $\quad \frac{>9,500}{6.7}$ = >1,400 µg/l

Lowest chronic value = >9,500 µg/l

** Data for bis (2-chloroethyl) ether

Table 4. Freshwater residues for chloroalkyl ethers (U.S. EPA, 1978)

Organism	Bioconcentration Factor	Time (days)
	Bis(2-chloroethyl) ether	
Bluegill, *Lepomis macrochirus*	11	14

Table 5. Other freshwater data for chloroalkyl ethers

Organism	Test Duration	Effect	Result (ug/l)
Bluegill, Lepomis macrochirus	96 hrs	LC50	>600,000*

* Data for bis (2-chloroethyl) ether

SALTWATER ORGANISMS

Introduction

No appropriate data are available for saltwater organisms and any chloroalkyl ether.

CRITERION FORMULATION

Saltwater-Aquatic Life

No saltwater criterion can be derived for any chloroalkyl ether using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

REFERENCES

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency, Contract No. 68-01-4646.

Mammalian Toxicology and Human Health Effects

EXPOSURE

Introduction

The chloroalkyl ethers, a sub-class of haloethers, are widely used in industries and laboratories. Some of the members of this sub-class are potent carcinogens and some have been found in the aquatic environment. The chloroalkyl ethers discussed in this document are listed in Table 1a. Of these compounds, BCME (bis(chloromethyl)ether), CMME (chloromethyl methyl ether), BCEE (bis(2-chloroethyl)ether) and BCIE (bis(2-chloroisopropyl)-ether) have received the greatest attention because of their potential health hazards. Comprehensive reviews on the physical and chemical properties and biological effects of these chemicals have been published (Summers, 1955; Van Duuren, 1969; Int. Agency Res. Cancer, 1974, 1975; Durkin, et al. 1975; Nelson, 1976; NAS, 1977). The physical constants of the four environmentally most important chloroalkyl ethers are summarized in Table 1b.

Because of their high reactivity, BCME and CMME have found wide laboratory and industrial use as intermediates in organic synthesis, in the treatment of textiles, for the manufacture of polymers and insecticides, in the preparation of ion exchange resins, and in industrial polymerization reactions. Following recognition of the high potency of these chemicals as carcinogens by inhalation in animals, and various epidemiological evidence linking excessive human respiratory cancer incidence to exposure, BCME and CMME have been listed as two of the 14 carcinogens restricted

by Federal regulations, effective February 11, 1974 (39 FR 3756; Anonymous, 1974). Realization of the potential hazard of BCME grew dramatically when it was reported that at high concentrations, vapors of HCl and formaldehyde, two commonly used chemicals in many industries and laboratories, can combine spontaneously to form BCME.

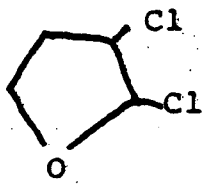
The concern over BCEE and BCIE arose mainly because of their presence in river water and the drinking water of several U.S. cities. These chemicals were found at high concentrations in waste water from chemical plants involved in the manufacturing of glycol products, rubber, and insecticides. As an end product, BCEE is an excellent solvent for fats, waxes and greases. It can be used as a scouring agent for textiles and has also been employed as an insecticide, ascaricide, and soil fumigant. The Environmental Protection Agency has included these two compounds in its National Organics Monitoring Survey of U.S. drinking water (U.S. EPA, 1977).

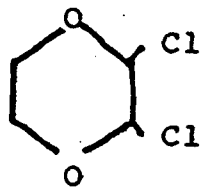
TABLE 1a

Chloroalkyl Ethers Covered in this Document

Names, Abbreviations and Synonyms	Formula
Chloromethyl methyl ether (CMME) other names: dimethylchloroether; methyl chloromethyl ether	$ClCH_2OCH_3$
Bis (chloromethyl)ether (BCME) other names: chloromethyl ether; Chloro(chloromethoxy) methane; dichloromethyl ether; dimethyl-1,1-dichloroether	$ClCH_2OCH_2Cl$
α,α-Dichloromethyl methyl ether other name: 1,1-dichloromethyl methyl ether	Cl_2CHOCH_3
Bis (α-chloroethyl)ether other name: bis (1-chloroethyl)ether	$CH_3\underset{Cl}{C}HO\underset{Cl}{C}HCH_3$
Bis (2-chloroethyl)ether (BCEE) other names: 1,1'-oxybis(2-chloro)ethane; bis(β-chloroethyl) ether; 1-chloro-2-(β-chloroethoxy)ethane; etc.	$ClCH_2CH_2OCH_2CH_2Cl$
Bis (2-chloroisopropyl)ether (BCIE) other name: bis(2-chloro-1-methylethyl)ether	$ClCH_2\underset{CH_3}{C}HO\underset{CH_3}{C}HCH_2Cl$
2-Chloroethyl vinyl ether	$ClCH_2CH_2OCH{=}CH_2$
Octachloro-di-n-propyl-ether	$Cl_3\underset{Cl}{C}CHCH_2OCH_2\underset{Cl}{C}HCCl_3$

Table 1a cont.

2,3-Dichlorotetrahydrofuran 

2,3-trans-Dichloro-p-dioxane 

Bis-1,2-(chloromethoxy)ethane $ClCH_2-O-CH_2CH_2-O-CH_2Cl$

Bis-1,4-(chloromethoxy)butane $ClCH_2-O-CH_2CH_2CH_2CH_2-O-CH_2Cl$

Bis-1,6-(chloromethoxy)hexane $ClCH_2-O-CH_2CH_2CH_2CH_2CH_2CH_2-O-CH_2Cl$

Tris-1,2,3-(chloromethoxy)propane CH_2-O-CH_2Cl / $CH-O-CH_2Cl$ / CH_2-O-CH_2Cl

Bis-(2-chloroethoxy)methane (BCEXM) $ClCH_2CH_2-O-CH_2-O-CH_2CH_2Cl$

Bis-1,2-(2-chloroethoxy)ethane (BCEXE) $ClCH_2CH_2-O-CH_2-CH_2-O-CH_2CH_2Cl$

TABLE 1b

Physical Constants of Four Environmentally Most Significant Chloroalkyl Ethers

Compound	Mol. Wt.	Appearance at room temperature	m.p.	b.p. (760 mm Hg)	Density	n_D^{20}	Solubility
CMME	80.5	colorless liquid		59°C	d_4^{20}= 1.0605	1.3974[c]	Immediately hydrolyze in water; miscible with ethanol, ether and many other organic solvents.
BCME	115.0	colorless liquid		104°C	d_4^{15} =1.328	1.435	Immediately hydrolyze in water; miscible with ethanol, ether and many other organic solvents.
BCEE	143.01	colorless liquid	-24.5°C[a] -51.9°C[b]	176-178°C	d_4^{20} =1.213	1.457	Practically insoluble in water; miscible with most organic solvents (especially, benzene and chloroform)
BCIE	171.07	colorless liquid		187-188°C		1.4474	Practically insoluble in water; miscible with most organic solvents.

[a] IARC (1975)

[b] Schrenk, et al. (1933)

[c] n for refractive index

Ingestion from Water

Chloroalkyl ethers do not occur as such in nature; their occurrence is entirely anthropogenic. Discharges from industrial and manufacturing processes represent the major source of these organic pollutants in the aquatic environment. Chlorination of drinking water could also be a potential source.

The stability of chloroalkyl ethers in aqueous systems plays a crucial role in determining their persistence in the water. In general, α-chloroalkyl ethers have an extremely short lifetime in aqueous solutions and are therefore not expected to persist for any extended period of time in water. On the other hand, non-α-chloroalkyl ethers are quite stable and may persist in the aqueous environment. The rate of hydrolysis of a number of α-chloroalkyl-ethers in an aqueous system has been measured by Van Duuren, et al. (1972). In a solution of water-dimethylformamide (3:1) kept at $0^{\circ}C$, the four α-chloroalkyl ethers (BCME, CMME, bis (α-chloroethyl) ether, α,α-dichloromethylmethyl ether) tested, were found to have a rate constant greater than $0.35\ min^{-1}$ with a half-life of less than two minutes. Kinetic studies of BCME hydrolysis by Tou and coworkers confirmed the above finding. In neutral aqueous solution, the $t_{\frac{1}{2}}$ was 280, 38 and 7 seconds at $0^{\circ}C$, $20^{\circ}C$ and $40^{\circ}C$, respectively. The hydrolysis was faster in alkaline solution and slower in acidic solution (Tou, et al. 1974). A comparably fast rate of hydrolysis of BCME was observed in aqueous solutions containing hydrochloric acid and formaldehyde (Tou and Kallos, 1974a) or anion exchange resins (Tou, et al. 1975). CMME

is even more reactive than BCME. Its half-life in aqueous solution cannot be directly measured with accuracy. Jones and Thornton (1967) have measured the hydrolysis rate of CMME in aqueous isopropanol. Extrapolation of the data to pure water yielded a $t_{\frac{1}{2}}$ of less than one second (Tou and Kallos, 1974b). In aqueous methanol at 45°C, the hydrolysis rate of CMME was about 5,000 times faster than that of BCME (Nichols and Merritt, 1973).

In contrast to α-chloroalkyl ethers, the β-chloro compounds are much more stable. Van Duuren, et al. (1972) found that the half-life of BCEE was more than 23 hours in water-dimethylformamide (3:1) at 30°C. Bohme and Sell (1948) estimated the half-life of BCEE to be 12.8 days in a mixture of water-dioxane solution at 100°C. Kleopfer and Fairless (1972) observed that BCIE appeared to be quite persistent in contaminated river water; there was no sign of biodegradation.

The occurrence of chloroalkyl ethers in river water and finished drinking water has been reported by various investigators. Among the chloroalkyl ethers covered in this document, BCEE and BCIE have been consistently detected in some areas of the country and quantitatively determined in some cases. Shackelford and Keith (1976) have recently compiled information on the frequency of organic compounds identified in water from published literature and unpublished survey analyses from EPA laboratories. Occurrence of BCEE and BCIE in various types of water has been reported 10 and 19 times, respectively. Other chloroalkyl ethers oc-

casionally reported included BCEXM, BCEXE, vinyl 2-chloroethyl ether, 2-chloroethyl methyl ether, BCME, and chloromethyl ethyl ether. In view of the extremely short lifetime of α-chloroalkyl ethers in aqueous systems, reports of their presence in water are probably erroneous. Schulting and Wils (1977) have noted that even the sophisticated GC-MS selected ion monitoring (SIM) method may yield false results. Using SIM on a SE-30 column, the authors demonstrated that 1-chloro-2-propanol could be mistaken for BCME. Reports of occurrence of β-chloroalkyl ethers in water appear to be more reliable and in some cases quantified; the major findings of these reports are summarized in Table 2.

Rosen, et al. (1963) were the first to detect the presence of BCEE and BCIE in contaminated river water. Investigation of the cause of odor of the Kanawha River at Nitro, West Virginia, led to the qualitative identification of BCEE and BCIE as two of the pollutants. The threshold odor concentration for BCEE and BCIE was estimated to be 360 µg/l and 200 µg/l, respectively.

The presence of BCIE in river water and finished drinking water at Evansville, Indiana, was noted by Kleopfer and Fairless (1972). An industrial outfall located about 150 river miles upstream from the Evansville water intake was found to be the probable source of the pollutant. Samples from this outfall were analyzed using flame ionization and electron capture detection gas chromatography verified by IR and mass spectrometry on several occasions during the fall of 1971. In each case BCIE was found with concentra-

TABLE 2

Occurrence of Principal Chloroalkyl Ethers in Various Types of Water

Reference	Location and Source of Water	Type of water[a]	Compound identified[b]	Conc. (µg/l)[c]
Rosen, et al. (1963)	Nitro, W.Va.	RW	BCEE	n.q.
	Kanawha River	RW	BCIE	n.q.
Kleopfer and Fairless (1972)	Evansville, Ind.	WW	BCIE	500-35,000
	Ohio River	RW	BCIE	2.0(0.5-5.0)
		FDW	BCIE	0.8
Webb, et al. (1973)	Effluent from synthetic rubber plant	WW	BCEXM	140,000
		WW	BCEE	160
Webb, et al. (1973)	Glycol plant's thickening and sedimentation pond	WW	BCIE	n.q.
Keith, et al. (1976)	New Orleans, La. Mississippi River:			
	Carrollton station	FDW	BCEE	0.04
		FDW	BCIE	0.18
	Jefferson station #1	FDW	BCEE	0.16
		FDW	BCIE	0.08
	Jefferson station #2	FDW	BCEE	0.12
		FDW	BCIE	0.03
U.S. EPA (1975)	Unspecified	FDW	BCIE	1.58
U.S. EPA (1975)	Philadelphia, Pa.	FDW	BCEE	0.42-0.5
	Delaware River	FDW	BCEXE	0.03
Manwaring, et al. (1977)	Philadelphia, Pa.	WW	BCEE	0.23-41
	Delaware River	FDW	BCEE	0.04-0.6
Sheldon and Hites (1978)	Philadelphia, Pa.	RW	BCEE	n.d.-trace
	Delaware River	RW	BCEXE	15
Dressman, et al. (1977) and U.S. EPA (1977)--see Table 3				

[a] RW=river water; FDW=finished drinking water; WW=waste water or effluent from chemical plant.

[b] BCEE=bis(2-chloroethyl)ether; BCIE=bis(2-chloroisopropyl)ether; BCEXM=bis(2-chloroethoxy)methane; BCEXE=bis(2-chloroethoxy)ethane.

[c] n.q.=not quantified; n.d.=not detectable.

tions ranging from 0.5 to 35 mg/l; the estimated discharge was 68 kg/day. Concentrations of BCIE found in the Ohio River at Evansville ranged from 0.5 to 5.0 µg/l. The conventional drinking water treatment was capable of removing only 60 percent of BCIE from the raw river water. BCIE concentration of 0.8 µg/l was found in the finished drinking water.

The detection of BCEE and BCEXM in the treated effluent from synthetic rubber plants was reported by Webb, et al. (1973); the concentration was in the order of 0.16 mg/l and 140 mg/l, respectively. BCIE was also readily detected in a thickening and sedimentation pond of glycol plants.

The lower region of the Mississippi River is well known for being heavily contaminated with organic pollutants from industrial discharges. The drinking water of the New Orleans area has been closely monitored by EPA since 1969. Detection of various pollutants has been frequently reported. Keith, et al. (1976) have recently compiled detailed quantitative data from these studies. At the Carrollton station and two sites in Jefferson parish, the finished drinking water was found to contain BCEE at levels of 0.04, 0.16, and 0.12 µg/l, respectively. The corresponding values for BCIE were 0.18, 0.08, and 0.03 µg/l.

In a report to Congress, U.S. EPA (1975) summarized the findings of organics in U.S. drinking water. A number of chloroalkyl ethers were detected, the highest concentrations reported for BCEE, BCIE, and BCEXE were 0.42 µg/l, 1.58 µg/l, and 0.03 µg/l, respectively. In a ten-city study, the drinking water of Philadelphia was found to contain

0.5 µg/l BCEE and 0.03 µg/l BCEXE. The drinking water of the other nine cities did not contain these chloroalkyl ethers (U.S. EPA, 1975).

The discovery of BCEE in Philadelphia's drinking water initiated a flurry of activity to determine the source and find means of elimination (Manwaring, et al. 1977). A chemical manufacturing plant located near the city's water intake admitted that it had discharged approximately 61.4 kg/day of the compound into the river (Anonymous, 1975). The effluent from the chemical plant contained up to 41 µg/l BCEE. Samples of the river adjacent to the discharges showed the presence of up to 10 µg/l of the chemical. Between February and July of 1975, the city's finished drinking water contained BCEE ranging from 0.04 to 0.6 µg/l. The chemical company has since developed a BCEE destruction system for the treatment of its effluent and this system resulted in a greater than 99 percent reduction in the discharge of BCEE into the river (Manwaring, et al. 1977). In a more recent survey by Sheldon and Hites (1978), BCEE was barely detectable (0.01 µg/l) in the river water. However, a high concentration of another chloroalkyl ether (BCEXE (15 µg/l)) was detected in two out of the five samples examined.

A National Organics Monitoring Survey of the U.S. drinking water has recently been undertaken by U.S. EPA (1977). Three phases of the study were carried out in March-April 1976, May-July 1976, and November 1976-January 1977. The drinking water of up to 113 cities have been analyzed for organic pollutants including chloroalkyl ethers. In phase I, BCEE was not found in 112 cities at the minimum quanti-

fiable limit of 5 μg/l. In phases II and III, the limit was lowered to 0.01 μg/l. In phase II, the drinking water of 13 of the 113 cities was found to contain BCEE with a mean concentration of 0.10 μg/l. BCIE was also found in 8 of the 113 cities. The quantitative data of the phase II study have been published by Dressman, et al. (1977) and are summarized in Table 3. In phase III,8/110 (7.27 percent) cities had BCEE with a mean of 0.024 μg/l. For BCIE, 7/110 (6.36 percent) cities gave positive results with a mean of 0.11 μg/l (U.S. EPA, 1977).

BCME can be chemically produced by saturating a solution of paraformaldehyde in cold sulfuric acid with HCl. Van Duuren, et al. (1969) studied the reaction of BCME with deuterium oxide in dioxane. Rapid disappearance of BCME was observed with 70 percent of the compound hydrolyzed within two minutes. However, after 18 hours, about 20 percent of BCME still appeared to be present. This suggested a possible equilibrium between BCME and its hydrolysis products, HCl and formaldehyde, and further raised the question of whether BCME could be formed spontaneously from HCl and formaldehyde. This question received great attention when the Rohm and Haas Company disclosed that BCME could be detected in humid air or aqueous or nonaqueous liquid-phase systems containing high concentrations of HCl and formaldehyde (Anonymous, 1972). However, more recent studies by Tou and Kallos (1974a, 1976) have indicated that, at least for aqueous systems, there was no evidence of BCME formation from HCl and formaldehyde at a detection limit of an order of magnitude of parts per trillion.

TABLE 3

The Levels of BCEE and BCIE Detected in the Finished Water of 113 Cities in the Phase II Study of National Organics Monitoring Survey.[a]

City number	BCEE (µg/l)	BCIE (µg/l)
17	0.19	——
18	0.14	0.03
32	0.02	——
40	——	0.03
56	0.01	——
60	0.17	——
65	0.13	——
67	——	0.14
75	0.01	——
77	0.30	0.17
80	0.06	0.09
88	0.06	0.09
102	0.36	0.55
109	——	0.02
121	0.02	——
122	0.01	——
Mean conc. of positives	0.10	0.17
Percent incidence among cities surveyed	11.5%	7.1%

[a]Summarized from Dressman, et al. (1977)

Ingestion from Foods

There is no information on the possible human exposure to chloroalkyl ethers via ingestion of food. The levels of chloroalkyl ethers in food have not been monitored nor has there been any attempt to study the bioaccumulation of chloroalkyl ethers. However, in view of their relative stability and low water solubility, β-chloroalkyl ethers may have a high tendency to be bioaccumulated.

Neely, et al. (1974) have noted a linear correlation between the octanol-water coefficients ($P_{octanol}$) and bioconcentration factors of chemicals in trout muscle. The relationship can be expressed by the equation:

$$\log (\text{bio-concentration factor}) = 0.542 \log (P_{octanol}) + 0.124.$$

The $P_{octanol}$ for chloroalkyl ethers is not available. However, Suffet and Radziul (1976) have published partition coefficients of BCEE in a number of other organic solvents. Ether was the most extensively used solvent; the average P_{ether} calculated from their data was 8.35. Using the solvent regression equation of Leo, et al. (1971), P_{ether} may be converted to $P_{octanol}$ by employing the formula:

$$\log(P_{ether}) = 1.142 \log (P_{octanol}) - 1.070$$

From these data, it can be calculated that the bioconcentration factor of BCEE in trout muscle should be around 11.7.

The $P_{octanol}$ of chloroalkyl ethers may also be calculated based on their solubility in water according to the method outlined by Chiou and Freed (1977). Using the above method, the information on water solubility of chloroalkyl ethers (Durkin, et al. 1975), and the linear regression model of

Neely, et al. (1974), the extrapolated bioconcentration factors for BCEE, BCIE and 2-chloroethyl vinyl ether are 12.6, 56.2, and 34.2, respectively.

Another approach to calculating bioconcentration factors has been recommended by the EPA's ecological laboratory in Duluth. This approach states that a bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but that BCF's are not available for the edible portion of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

2.3 for consumed fish and shellfish.

A measured steady-state bioconcentration factor of 11 was obtained for bis (2-chloroethyl) ether using bluegills containing about one percent lipids (U.S. EPA, 1978). An adjustment factor of 2.3/1.0 = 2.3 can be used to adjust the measured BCF from the 1.0 percent lipids of the bluegill to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for bis (2-chloroethyl) ether and the edible portion of all aquatic organisms consumed by Americans is calculated to be 11 x 2.3 = 25.

No measured steady-state bioconcentration factor (BCF) is available for bis (chloromethyl) ether or bis (2-chloroisopropyl) ether. A weighted average BCF of 25 is available for bis (2-chloroethyl) ether and the calculated octanol-water partition coefficients for the three compounds are 11.5, 5.8, and 8.7, respectively. The proportionality (Veith, et al. Manuscript) BCF/BCF = antilog (0.76 log (P/P)) can be used to calculate weighted average bioconcentration factors of 31 and 106 for bis (chloromethyl) ether and bis (2-chloroisopropyl) ether, respectively, for the edible portion of all aquatic organisms consumed by Americans.

The use of aquatic organisms as a typical exposure factor requires the quantification of pollutant residues in the edible portion of the ingested species. For this reason, the EPA recommended calculations, based upon the percent lipids of aquatic organisms, were used in the formulation of the criterion.

Inhalation

There is no evidence of occurrence of chloroalkyl ethers in the atmosphere. Human exposure to compounds via inhalation appears to be confined to occupational settings. It is important to note that, in contrast to its instability in aqueous solution, BCME is considerably more stable in humid air. Frankel, et al. (1974) found that BCME introduced into a Saran bag containing moist air was stable for at least 18 hours. Tou and Kallos (1974b) have studied the stability of BCME and CMME in humid air. At an ambient temperature with a relative humidity of 81 percent, the $t_{\frac{1}{2}}$ of BCME in the gaseous phase could be as long as 25 hours. The rate of hydrolysis was dependent on the surface of the container. In a ferric oxide-coated Saran reactor, the $t_{\frac{1}{2}}$ of BCME was in the order of seven to nine hours. A similar surface effect on the hydrolysis of CMME in the gaseous phase was also observed. The $t_{\frac{1}{2}}$ of CMME in the gaseous phase ranged from 2.3 minutes to 6.5 hours.

The extreme potency of BCME and/or CMME as inhalation carcinogens has prompted industrial hygienists and researchers to closely monitor the atmospheric level of these compounds in the work place. Various such methods have been developed (e.g., Collier, 1972; Solomon and Kallos, 1975; Sawicki, et al. 1976; Parkes, et al. 1976; Kallos, et al. 1977; Bruner, et al. 1978). The finding of spontaneous formation of BCME from HCl and formaldehyde vapor has expanded the potential site of BCME exposure to any place where high atmospheric levels of these two reactants may co-exist. Rohm and Haas Company first disclosed information on the

spontaneous formation of BCME from HCl and formaldehyde. (Anonymous, 1972). At room temperature of about 71°F and with a 40 percent relative humidity, a steady state level of BCME could be reached within one minute. In general, ppm levels of the reactants yielded ppb levels of BCME. This important finding has since been confirmed; however, the yield in such a reaction is much lower than was previously anticipated. Frankel, et al. (1974) reported that at 25°C and 40 percent relative humidity, fewer than 0.5 ppb of BCME was formed from 20 ppm each of HCl and formaldehyde. At 100 ppm or 300 ppm of each reactant, the average yield was 2.7 or 23 ppb BCME, respectively. The factors that affect the yield included the reactant concentration, the surface of the reactor, the reaction time, the humidity and temperature. A substantially lower yield was observed by Kallos and Solomon (1973). At 100 ppm of each of the reactants, only 0.1 ppb BCME was detected. Nevertheless, with high concentrations of the reactants, substantial amounts of BCME could be detected. The National Institute of Occupational Safety and Health is currently investigating the possible formation of BCME in various work places where HCl and formaldehyde may be used simultaneously (Lemen, et al. 1976).

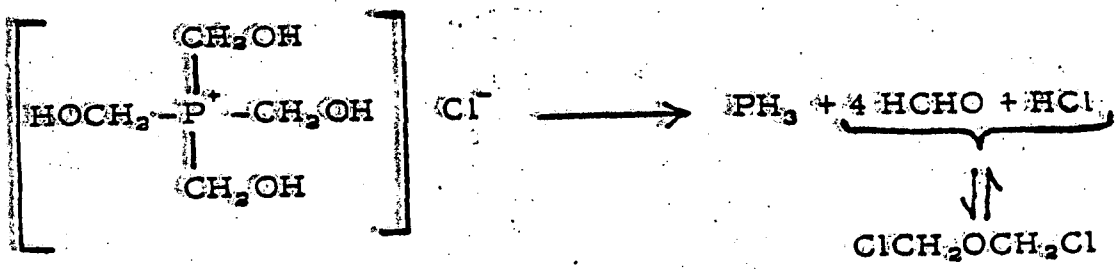
In addition to HCl and formaldehyde, a number of other chemicals are potential reactants for forming of BCME. Gamble (1977) reported that BCME could be detected in an animal room that had been washed with a 15 percent hypochlorite solution followed by routine gassing with formaldehyde.

Duplicate air samples were taken from both high levels (3 m) and low levels (1 m). No BCME was detected in the high-level sample whereas 0.2 ppb of BCME was found in the low-level sample. The author recommended that chlorine-containing disinfectants should not be used when animal rooms are gassed with formaldehyde. Another possible source of BCME in the work place was suspected to be from the reaction of dimethyl ether and chlorine in air. Kallos and Tou (1977) have investigated this possibility. The reaction was found to be photochemical in nature. In ambient air BCME was barely detectable; the highest amount detected was 2 ppb from 100 ppm each of chlorine and dimethylether. However, it is interesting to note that as much as 1.5 ppm BCME was found to be generated during the reaction of 100 ppm of each of the reactants in dry nitrogen.

Dermal

There is no information available on the dermal exposure of humans to chloroalkyl ethers; no evaluations can be made regarding the relative importance of dermal exposure. One potential source of dermal exposure has, however, been investigated by Loewengart and Van Duuren(1977). Tetrabis(hydroxymethyl)phosphonium chloride (THPC), a widely used flame retardant in children's sleepwear, is synthesized from phosphine, hydrochloric acid and formaldehyde and may decompose thermally or chemically to these chemicals. Thus, THPC is also a potential source of BCME reactants under the right conditions. Because of the high add-on(up to 35 percent of the final fabric weight) of the flame retardant, it seems likely

that a fraction of THPC may be loosely bound and that common solutions such as sweat, urine, and saliva may be able to extract some free THPC. A sample of commercial THPC was found to contain 4 to 14 percent (w/w) free formaldehyde. Gas chromatographic analysis of aqueous commercial THPC did not reveal any peak characteristic of BCME; however, the limit of detection of the study was only 0.1 ppm. THPC is also marginally active as a skin carcinogen and active as a tumor promotor, (Loewengart and Van Duuren, 1977).



PHARMACOKINETICS

No information is available on the pharmacokinetics of chloroalkyl ethers in humans; animal data are also rather scanty. The α-chloroalkyl ethers, by virtue of their high reactivity and short lifetime in aqueous systems, are not expected to persist in the body. Nonetheless, Gargus, et al. (1969) observed a significant increase in the incidence of lung tumors after s.c. injection of BCME to newborn mice. This finding may indirectly indicate that BCME may be absorbed from the subcutaneous tissue and induce tumors at a site remote from the site of injection.

Smith, et al. (1977) have recently published detailed pharmacokinetic data on BCIE, believed originally to be

labeled with ^{14}C at the β-position, in female rats and monkeys. However, subsequently it was ascertained that labeling actually occurred in the α-position (Lingg, personal communication). After single oral doses, BCIE appeared to be readily absorbed by both species. In the monkey, the blood radioactivity level reached a high peak within two hours and then declined in a biphasic manner with a $t_{\frac{1}{2}}$ of about five hours and greater than two days for the first and second phase, respectively. In the rat, the blood radioactivity level reached a maximum between two and four hours after dosing and then slowly declined with a $t_{\frac{1}{2}}$ of two days. There was a substantial difference in the tissue distribution and excretion pattern seven days after a single parenteral dose of 30 mg/kg of ^{14}C-BCIE. The monkey retained substantially higher amounts of radioactivity in the liver (equivalent to 28.8 µg/g BCIE) than did the rat (3.2 µg/g). Higher quantities were also found in the muscle and brain of the monkey. On the other hand, with respect to the percentage of administered dose recovered in the tissues and excreta, higher amounts of radioactivity were found in the fat (1.98 percent), urine (63.36 percent), feces (5.87 percent), and expired air (15.96 percent) of the rat. The corre-sponding figures in the monkey were 0.78 percent, 28.61 percent, 1.19 percent, and 0 percent. Metabolites of BCIE in the rat included 1-chloro-2 propanol, propylene oxide, 2-(1-methyl-2-chloroethoxy)-propionic acid and carbon dioxide. Initial attempts to analyze the urinary metabolites of BCIE in the monkey have been inconclusive because of the presence of interfering substances.

The fate of BCEE in rats after acute oral administration has been studied by Lingg, et al. (1978). Bis((1-^{14}C) chloroethyl)ether (40 mg/kg) was administered to male Sprague-Dawley rats by intubation. Preliminary results showed that virtually all of the BCEE was excreted as urinary metabolites with more than 60 percent of the compound excreted within 24 hours. One major metabolite was thiodiglycolic acid. A lesser metabolite was identified as 2-chloroethanol-β-D-glucuronide. The presence of these two metabolites suggests that cleavage of the ether linkage is a major step in the biotransformation of BCEE. The products of this cleavage then conjugate with nonprotein free sulfhydryl groups or with glucuronic acid with the former as the major route of conjugation in the rat.

The metabolic fate of other chloroalkyl ethers is not known. However, it is interesting to note that cleavage of the ether linkage also appears to be a route of metabolism for diethyl ether in mice (Geddes, 1971). For p-dioxane, a cyclic ether, ring hydroxylation has been postulated as the first step of metabolism in the rat (Woo, et al. 1977). The major urinary metabolite has been identified as 2-hydroxyethoxyacetic acid (Braun and Young, 1977) or p-dioxane-2-one (Woo, et al. 1977) which are readily interconvertible depending on the pH of the system.

EFFECTS

Acute, Sub-acute and Chronic Toxicity

Animal Studies: The acute toxicity of a variety of chloroalkyl ethers has been studied in different animal

species. Tables 4 and 5 summarize the acute toxicity data. It is apparent from Table 4 that the route of exposure may play a determining factor in the acute toxicity of chloroalkyl ethers. In the rat, the inhalational toxicity follows the order, BCME $\gg$ CMME $>$ BCEE $\geq$ BCIE; by oral administration, however, the order is changed to BCEE $>$ BCIE $\geq$ BCME $>$ CMME. Apparently, the extremely short lifetime of BCME and CMME in aqueous solution significantly reduces their toxic potential by oral administration. It is also of interest to note the dramatic enhancement of toxicity of p-dioxane after chlorination. The acute LD_{50} of p-dioxane has been reported as 5.3 gm/kg (Woo, et al. 1978). Chlorination of p-dioxane increases the toxicity by 10 to 1000 fold. The stereochemistry of the compound also plays a significant role; the 2r,3t, 5t,6c-tetrachloro isomer was found to be 80 times more toxic than its 2r,3c,5t,6t-stereoisomer (Woo, et al. 1979).

The acute physiological response of the guinea pig to air containing toxic concentrations of BCEE has been studied by Schrenk, et al. (1933). The primary action was the irritation of the respiratory passages and the lungs. In the order of their appearance, the symptoms produced were nasal irritation, eye irritation, lacrimation, disturbances in respiration, dyspnea, gasping and death. The principal gross pathology findings were congestion, emphysema, edema and hemorrhage of the lungs.

Gage (1970) exposed rats to eight, 5-hour exposures of 350 ppm BCIE in air; the toxic sign observed included respiratory difficulty, lethargy and retarded weight gain.

TABLE 4

Acute Toxicity of Chloroalkyl Ethers

Compound	Test Species	Route	Lethal Dose or Concentration	Reference
Chloromethylmethyl ether, CMME	Rat	Oral	LD_{50}=817 mg/kg	*NIOSH* (1974)
		Inhalation	LC_{50}=55 ppm for 7 hr	Drew, et al. (1975)
	Hamster	Inhalation	LC_{50}=65 ppm for 7 hr	Drew, et al. (1975)
Bis(chloromethyl)ether, BCME	Rat	Oral	LD_{50}=0.21 ml/kg*	Smyth, et al. (1969)
		Inhalation	LC_{50}=7 ppm for 7 hr	Drew, et al. (1975)
	Mouse	Inhalation	LC_{50}=25 mg/m^3 for 6 hr***	Leong, et al. (1971)
	Rabbit	Skin	LD_{50}=0.28 ml/kg**	Smyth, et al. (1969)
	Hamster	Inhalation	LC_{50}=7 ppm for 7 hr	Drew, et al. (1975)
Bis(2-chloroethyl)ether, BCEE	Rat	Oral	LD_{50}=75 mg/kg	Smyth and Carpenter (1948)
		Inhalation	LCLo=1000 ppm for 45 min or 250 ppm for 4 hr	Smyth and Carpenter (1948) Carpenter, et al. (1949)
	Guinea Pig	Skin	LD_{50}=300 mg/kg	Smyth and Carpenter (1948)
		Inhalation	LCLo=105 ppm for 250 min	Schrenk, et al. (1933)
Bis(2-chloroisopropyl)ether, BCIE	Rat	Oral	LD_{50}=240 mg/kg	Smyth, et al. (1951)
		Inhalation	LCLo=700 ppm for 5 hr	Gage (1970)
	Rabbit	Skin	LD_{50}=3000 mg/kg	Smyth, et al. (1951)
2-Chloroethylvinyl ether	Rat	Oral	LD_{50}=250 mg/kg	Smyth, et al. (1949)
		Inhalation	LCLo=250 ppm for 4 hr	Carpenter, et al. (1949)
	Rabbit	Skin	LD_{50}=3200 mg/kg	Smyth, et al. (1949)

LD_{50}=lethal dose for 50% kill

LC_{50}=lethal concentration for 50% kill

LCLo=lowest lethal concentration published

*equivalent to 278 mg/kg; **equivalent to 370 mg/kg; ***equivalent to 5.3 ppm

TABLE 5

Acute Toxicity of Chloro-cycloalkyl Ethers

Compound	Test Species	Route	Lethal Dose	Reference
2-Chloromethyltetrahydro-furan	Mouse	i.p.	LDLo=250 mg/kg	NIOSH (1974)
Trans-2,3-dichloro-p-dioxane	Rat	oral	LD_{50}=1.41 ml/kg	Smyth, et al. (1969)
		i.p.	LD_{50}=435 mg/kg	Woo, et al. (1979)
	Rabbit	skin	LD_{50}=0.44 ml/kg	Smyth, et al (1969)
2,3,5-Trichloro-p-dioxane (isomer I*)(m.p. 41°)	Rat	i.p.	LD_{50}=83.2 mg/kg	Woo, et al, (1979)
2,3,5-Trichloro-p-dioxane (isomer II*)(m.p. 71°)	Rat	i.p.	LD_{50}=146 mg/kg	Woo, et al. (1979)
2r,3t,5t,6c-Tetrachloro-p-dioxane (m.p. 99°)	Rat	i.p.	LD_{50}=5.3 mg/kg	Woo, et al. (1979)
2r,3c,5t,6t-Tetrachloro-p-dioxane (m.p. 141°)	Rat	i.p.	LD_{50}=424 mg/kg	Woo, et al. (1979)

LD_{50}=lethal dose for 50% kill

LDLo=lowest lethal dose published

*the exact stereochemistry of the isomers has not been determined

Histological examination of liver and kidneys revealed signs of congestion. Lethargy and retarded weight gain were also observed in a group exposed 20 times, six hours each, to 70 ppm of BCIE in air. The highest concentration with no toxic signs was 20 ppm.

The National Cancer Institute (unpublished results) has recently completed a chronic toxicity study of BCIE. The observations of non-tumor pathology are summarized in Table 6. The most significant change in the mouse appeared to be an increased incidence of centrilobular necrosis of the liver. However, the effect was inexplicably higher in the low-dose group than in the high-dose group. In the rat, the major effect of BCIE was on the lungs, causing congestion, pneumonia, and aspiration.

A detailed study of the inhalational toxicity of BCME and CMME has recently been carried out by Drew, et al. (1975) with Sprague-Dawley rats and Syrian golden hamsters as the test species. The most characteristic acute toxic effect of both compounds was the irritation of the respiratory tract manifested by congestion, edema, and hemorrhage (mainly of the lungs) and acute necrotizing bronchitis. The lung-to-body weight ratios, which were used as an objective criterion for the evaluation of lung damage, in animals exposed to CMME were elevated in a dose-related fashion. Multiple exposures of animals to sub-acutely toxic concentrations of BCME or CMME resulted in severe shortening of lifespan and a variety of regenerative, hyperplastic and metaplastic alterations of trachea and bronchi, which were often histopathologically atypical (such as nuclear abnormality).

TABLE 6

Summary of Non-Tumor Pathology in Mice and Rats After Repeated Oral Doses of BCIE (NCI, unpublished results).*

Organism	Pathology	Incidence (%)			
		Untreated Control	Vehicle Control	Low Dose 100 mg/kg/day (rats) 10 mg/kg/day (mice)	High Dose 200 mg/kg/day (rats) 25 mg/kg/day (mice)
Rats, male	Lungs, congestion	2	2	0	14
	pneumonia, aspiration	0	4	14	24
	Liver, centrilobular necrosis	8	10	4	22
	Esophagus, hyperkeratosis	0	18	20	82
Rats, female	Lungs, congestion	0	0	2	15
	pneumonia, aspiration	0	2	33	46
	Liver, centrilobular necrosis	0	2	2	15
	Esophagus, hyperkeratosis	0	26	20	65
	Adrenal cortex, angiectasis	10	4	1	27
Mice, male	Lung, hemorrhage	0	6	2	14
	Liver, centrilobular necrosis	0	2	27	0
	Esophagus, inflammation	0	0	2	5
Mice, female	Liver, centrilobular necrosis	0	0	19	6

*Animals dosed 5 days/week for total of 728 days.

Incidences of mucosal changes were generally increased in a dose-related manner in both species. Similar changes were observed in studies of the long term effects of single exposure to BCME or CMME. For animals surviving beyond the median life span, pathological alterations of respiratory epithelium, abnormality of alveolar lining cells and bronchoalveolar squamous metaplasia were also occasionally noted.

Human Studies: The effect of brief exposures of man to BCEE vapor was studied by Schrenk, et al. (1933). Concentrations of greater than 260 ppm were found to be very irritating to the nasal passages and eyes with profuse lacrimation. Deep inhalations were nauseating in effect. The highest concentration with no noticeable sign of irritation was 35 ppm. For comparison, BCME was reported (Flury and Zernik, 1931, cited in Schrenk, et al. 1933) to be distinctly irritating at a concentration of 3 ppm. A concentration of 100 ppm would incapacitate a person under chemical warfare conditions in a few seconds, and an exposure of one to two minutes might produce a fatal lung injury. A fatal case of accidental, acute poisoning of a research chemist by BCME has been reported (Schierwater, 1971, cited in Thiess, et al. 1973).

The respiratory effects of chronic exposures of industrial workers to CMME (contaminated with BCME) have been extensively investigated by Weiss and coworkers. Symptoms of chronic bronchitis were noted more often among exposed men, and a dose-response relationship was apparent with

smoking as a cofactor. There was no demonstrable chemical effect on the ventilatory function, as measured by the forced vital capacity (FVC) and the one-second forced expiratory volume (FEV_1), suggesting the absence of abnormality in the large airways (Weiss and Boucot, 1975). The small airways were, however, noticeably affected by the chemical exposure. The end-expiratory flow rate (EEFR) was below 60 percent of the predicted value in one-third of the exposed men compared to only three percent of the unexposed men. There was a dose-response relationship between chemical exposure and the frequency of low EEFR (Weiss, 1977).

Synergism and/or Antagonism

There is very little information available on the synergistic or antagonistic interaction of chloroalkyl ethers with other types of chemical carcinogens in experimental animals. Promotion of tumorigenesis after initiation by chloroalkyl ethers has, however, been extensively studied. In two-stage mouse skin carcinogenesis studies, the following compounds have been considered as "incomplete" carcinogens (i.e., active only as "initiators"): CMME, octachlorodi-n-propyl ether, and α,α-dichloromethyl ether (Van Duuren, et al. 1969, 1972). Induction of papillomas was also observed after promotion of the initiation by BCEE, bis(α-chloroethyl)ether, or 2,3-dichlorotetrahydrofuran; whether these compounds are "complete" carcinogens or not is not known (Van Duuren, et al. 1972). Chloroalkyl ethers capable of inducing papillomas or carcinomas on mouse skin without promotion include BCME (Van Duuren, et al. 1969) and 2,3-

trans-dichloro p-dioxane (Van Duuren, et al. 1974); the carcinogenic activity of these compounds can be substantially enhanced by promotors (Van Duuren, 1969; Van Duuren, et al. 1969, 1974; Slaga, et al. 1973). The details of these carcinogenicity data will be presented in the Carcinogenicity section. The promotors used included croton oil, croton resin or the pure phorbol myristate acetate. The tumor-promoting activity of several chloroalkyl ethers has been tested using benzo(a)pyrene as the initiator. BCME was found to decrease the latent period for induction of benign and malignant tumors but did not affect the tumor yield (Van Duuren, et al. 1968, 1969). CMME and octachlorodi-n-propyl ether were marginally active as promotors (Van Duuren, et al. 1969).

The ability of chloro derivatives of p-dioxane to modify microsomal drug-metabolizing enzyme activity has been studied by Woo, et al. (1979). Of the compounds tested (listed in Table 5), only 2r,3c,5t,6t-tetrachloro-p-dioxane was found to have a significant effect. The activities of microsomal aryl hydrocarbon hydroxylase and dimethylnitrosamine-demethylase were decreased by 44 percent and 61 percent, respectively.

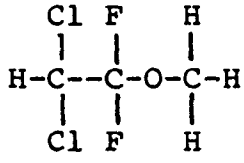
Cigarette smoking has been found to act synergistically with CMME to produce chronic bronchitis and small airway disorders among exposed industrial workers (Weiss and Boucot, 1975; Weiss, 1976,1977). In sharp contrast, however, there was an unexpected inverse relationship between smoking and the induction of lung cancer by CMME (Weiss and Boucot, 1975; Weiss, 1976). The reason for this apparent antagonism

is not known. Self-selection by the workers has been suggested as a possible factor. Heavy cigarette smokers might have tended to avoid heavy chemical exposure because chronic cough was directly related to both CMME exposure and cigarette smoking, and simultaneous exposure might produce a greater effect than either one alone. However, no data on smoking habit changes were available to verify the self-selection hypothesis. Another possible factor was the protective action of bronchorrhea associated with chronic bronchitis. The excessive discharge from bronchial mucous membrane may protect against the carcinogenic effect of CMME or its contaminant BCME by reducing the residence time of these chemicals because of their instability in aqueous systems. Finally, it is conceivable that some component of cigarette smoke may neutralize the carcinogenicity of CMME. It is not known whether the apparent antagonism observed by Weiss may be a general phenomenon. In reviewing the case reports of four different groups of workers, Lemen, et al. (1976) expressed the view that smoking may provide a promotional or synergistic effect on the induction of lung cancer by BCME.

Teratogenicity

The teratogenicity of the chloroalkyl ethers covered in this document has not been studied. It is relevant to note, however, that there is some epidemiological evidence that anesthetic gases (including methoxyflurane) may lead to congenital abnormalities. Although the evidence has been considered less than unequivocal, there is little doubt

that these gases are teratogenic in experimental animals when administered in relatively high doses (rev., Smith, 1974; Corbett, 1976; Ferstandig, 1978). A detailed discussion of this subject is beyond the scope of this document. However, in view of the fact that methoxyflurane can actually be classified as a chloroalkyl ether, the teratogenicity of other chloroalkyl ethers (especially the environmentally important and stable BCEE and BCIE) should be critically studied.



methoxyflurane

Mutagenicity

The mutagenicity of chloroalkyl ethers has been investigated in bacterial, eukaryotic, and mammalian systems. Table 7 compares the carcinogenicity data to the mutagenicity data in microbial systems for a variety of chloroalkyl ethers. With a few exceptions, there is a relatively good correlation between mutagenicity and carcinogenicity. For most of these studies, E. coli and S. typhimurium were used as the test organisms and the test was designed for direct-acting mutagens that do not require metabolic activation.

There are some disagreements regarding the mutagenicity of BCEE. Shirasu, et al. (1975) have found BCEE to be a direct-acting, base-change mutagen using different tester strains of E. coli, S. typhimurium, and B. subtilis. Also Simmon, et al. (1977; cited in Fishbein, 1977) reported that BCEE, when tested in a desiccator containing the vapor,

TABLE 7

Comparison of Carcinogenic and Mutagenic (in Microbial System) Activity of Chloroalkyl Ethers

Compound	Mutagenicity[a]	Carcinogenicity
CMME	+	+
BCME	+	+
BCIE	+[b]	-
, -Dichloromethylmethyl ether	+	+
Bis(-chloroethyl)ether	+	+
BCEE	-,+[b]	+,-
Octachloro-di-n-propyl ether	not tested	+
2,3-Dichlorotetrahydrofuran	-	+
2,3-trans-Dichloro-p-dioxane	not tested	+

[a]The mutagenicity data were mainly from Mukai and Hawryluk (1973), Mukai, et al. (cited in Nelson, 1976)

[b]Positive mutagenic activity of BCEE was observed by Shirasu, et al. (1975) and the mutagenicity of BCEE and BCIE were observed by Simmon, et al. (1977; cited in Fishbein,1977).

was mutagenic to S. typhimurium strains TA 1535 and TA 100 and weakly mutagenic to strains TA 1538, TA 98, and E. coli WP2. In suspension assays, BCEE also proved to be mutagenic toward strain TA 1535. BCEE was not mutagenic in host-mediated assays when given as a single oral dose or when administered for two weeks prior to the injection of S. typhimurium into the peritoneal cavity.

In eukaryotic and non-mammalian systems, BCEE was reported to be mutagenic to Saccharomyces cerevisiae D3 in suspension assay (Simmon, et al. 1977; cited in Fishbein, 1977). BCEE has been quoted as mutagenic to Drosophila melanogaster (Fishbein, 1976, 1977); however, a careful examination of the original publication of Auerbach, et al. (1947) failed to confirm the quotation. It was bis(2-chloroethylmercaptoethyl)ether (not BCEE) that was mutagenic.

The mutagenic potential of BCEE and BCIE in mice has been studied by Jorgenson, et al. (1977) using the heritable translocation test. Adult male mice were treated by gavage daily for three weeks with three dose levels of BCEE or BCIE. They were then mated to virgin females to produce an F_1 generation. The F_1 males were bred twice and examined cytogenetically. Preliminary evaluation of the breeding and cytogenetic data suggests that BCEE and BCIE were not mutagenic; no heritable translocations were observed.

The genetic risks of occupational exposures to CMME and BCME have been evaluated by Zudova and Landa (1977). Cytogenetic analysis of peripheral lymphocytes was performed. Scoring 200 cells per person, the authors detected 6.7 percent of aberrant cells in exposed workers while the corres-

ponding value in the controls reached only two percent. The frequency of aberrant cells in exposed workers decreased toward the control value after the removal of exposure. It was proposed that cytogenetic analysis of peripheral lymphocytes should become a part of a routine medical check-up of workers at risk.

Carcinogenicity

Animal Studies: Van Duuren, et al. (1968) were the first to demonstrate the carcinogenicity of chloroalkyl ethers. Application of 2 mg BCME three times a week, for 325 days led to the induction of papillomas in 13/20 mice, 12 of which developed to squamous cell carcinomas. A comparison with a number of other carcinogenic alkylating agents (Table 8) indicated that BCME was, for the mouse skin, more potent than the β-lactones and epoxides listed, in terms of tumor yield, dose, and latency. In contrast, CMME was found to be inactive as a complete carcinogen by skin application.

In an effort to delineate the structure-activity relationships of chloroalkyl ethers, Van Duuren and coworkers have extended their cutaneous carcinogenicity studies to a variety of compounds. The test procedures used included s.c. injection in mice, repeated direct application to mouse skin, and tests in mice by the initiation-promotion procedure involving a single application of the test compound followed by repeated applications of phorbol myristate acetate. Table 9 summarizes the results of this extensive series of studies. By skin application, BCME, trans-2,3-dichloro-p-dioxane, bis-1,2-(chloromethoxy)ethane, and tris-1,2,3-

TABLE 8

Comparison of Carcinogenic Potency[a] of Alkylating Agents on Mouse Skin

Compound	Dose[b] (mg)	Days to 1st tumor	Mice with carcinoma/no. of mice tested	Median survival time (days)
BCME	2.0	161	12/20[c]	313
β-Butyrolactone	10	252	15/30[c]	438
β-Propiolactone	2.5	—	9/30[d]	200
Glycidaldehyde	3.0	212	8/30[c]	496
D,L-1,2:3,4-Di-epoxybutane	3.0	326	6/30[c]	475

[a]From Van Duuren, et al. (1968)

[b]Administered 3 times/week in 0.1 ml solvent; the solvents used were benzene for the first 4 compounds and acetone for diepoxybutane.

[c]Female Swiss ICR/Ha mice

[d]Male Swiss mice

TABLE 9

Carcinogenicity of Chloroalkyl Ethers by Skin Application or s.c. Injection*

Compound	Carcinogenicity on Mouse Skin (mice with papillomas/group size[a])		s.c. Injection in Mice: (sarcomas at injection site/group size)	s.c. Injection in Rats: (sarcomas at injection site/group size)
	as "complete" carcinogen	as "initiator"		
CMME	0/40 (0)	12/40 (5)	10/30	1/20[b]
BCME	13/20 (12)	5/20 (2)	21/50	7/20
α,α-Dichloromethylmethyl ether	0/20 (0)	3/20 (1)	—	—
Bis (α-chloroethyl ether	—	7/20 (0)	4/30	—
BCEE	—	3/20 (0)	2/30	—
Octachlorodi-n-propyl ether	0/20 (0)	3/20 (1)	—	—
2,3-Dichlorotetrahydrofuran	—	5/20 (1)	1/30	—
2,3-trans-Dichloro-p-dioxane	2/50 (0)	8/30 (2)	14/30[c]	—
Bis-1,2-(chloromethoxy)ethane	4/50 (4)	—	9/50	—
Bis-1,4-(chloromethoxy)butane	1/50 (1)	—	0/50	—
Bis-1,6-(chloromethoxy)hexane	0/50 (0)	—	1/50	—
Tris-1,2,3-(chloromethoxy)propane	6/50 (3)	—	10/50[d]	—

*Summarized from Van Duuren, et al. (1968, 1969, 1971, 1972, 1974, 1975)

[a]Number of mice with carcinomas given in parentheses.

[b]Considered inactive.

[c]Two additional animals had squamous cell carcinomas and one had adenocarcinoma.

[d]Two additional animals had carcinomas.

(chloromethoxy)propane were found to be active as complete carcinogens. Most of the other compounds tested were active as initiators. From these studies, three salient features of structure-activity relationships were observed. (1) The bifunctional α-chloroalkyl ethers (e.g., BCME) are more active than their monofunctional analogs(e.g., CMME). (2) The carcinogenic activity of chloroalkyl ether decreases as chlorine moves further away from the ether oxygen. Thus, β-chloroalkyl ethers (e.g., BCEE) are substantially less active than their α-chloro isomers or analogs(e.g., bis (α-chloroethyl)ether). (3) The carcinogenic activity decreases as the alkyl chain length increases. For example, if one considers BCME, bis-1,2-(chloromethoxy)ethane, bis-1,4-(chloromethoxy)butane, and bis-1,6-(chloromethoxy)hexane as a homologous series of di-α-chloro ethers of increasing length, it is clear that in general the longer the chain length the lower is the carcinogenicity.

The carcinogenicity of BCME and CMME in newborn ICR Swiss random bred mice has been tested by Gargus, et al. (1969) by s.c. injection. A single dose of 12.5 μl BCME/kg body weight was found to increase the pulmonary tumor incidence after six months. In 50 males and 50 females injected with BCME, pulmonary tumors developed in 45 percent of the animals, with a multiplicity of 0.64 tumors per mouse. In addition, one mouse developed an injection site papilloma and another a fibrosarcoma; such tumors were not seen in control animals. In the vehicle (peanut oil) controls, the pulmonary tumor incidence was 14 percent with a multipli-

city of 0.14. Mice receiving CMME (125 µl/kg) had an incidence of 17 percent with a multiplicity of 0.21; these values were slightly higher but not significantly different from the controls. It is of particular interest to point out the high carcinogenic potency of BCME in this study. A single, very small dose of 12.5 µl (equivalent to 0.017 mg/kg) was sufficient to induce pulmonary adenomas within six months. Furthermore, this study indicated that, despite its short lifetime in an aqueous system, the biological effects of BCME were not confined to the site of injection. On the other hand, using rats, s.c. injection of BCME produced no increase in the incidence of tumors remote from the injection site (Van Duuren, et al. 1969).

The tumor initiating ability of BCME and CMME has also been studied by Slaga, et al. (1973) using female Charles River CD 1 mice. A single dose of 9 moles (1.03 mg) BCME was sufficient to induce papillomas within 15 weeks after promotion by croton oil. CMME, up to a dose of 25 moles (2.0 mg), was found to be a very weak or inactive initiating agent.

The high vapor pressure of CMME (b.p. 59°C) and BCME (b.p. 104°C) at ambient temperatures and their extensive industrial uses have prompted investigators to examine the inhalational carcinogenicity of these compounds. Leong, et al. (1971) were the first to test the inhalational carcinogenicity of BCME and CMME in mice. Strain A/Heston male mice, which are known to be highly responsive to pulmonary tumor induction with a spontaneous incidence of about 40 percent were used in this study. The animals were exposed

six hours/day, five days/week to filtered room air (negative control), aerosols of urethane (positive control), or vapors of BCME or CMME for up to a maximum of six months. The CMME used contained 0.3 to 2.6 percent BCME as an impurity. The animals were sacrificed at the end of the six-month period (Table 10 summarizes the results). Mice in the BCME exposed group had a 34 percent increase in the incidence of lung tumors and a 3.3-fold enhancement in the average number of tumors/animal/treatment group. The corresponding figures in the CMME exposed group were 21 percent and 1.75-fold. It was concluded that BCME was a potent inhalational carcinogen. CMME was also, for practical purposes, carcinogenic although it was not certain whether the effect was exerted by CMME itself or its contaminant, BCME.

An extensive series of inhalational carcinogenicity studies of BCME and CMME in rat and hamster has been carried out by Laskin, et al. (1971,1975), Drew, et al. (1975), and Kuschner, et al. (1975). Table 11 summarizes the results of their findings. BCME was found to be an extremely potent respiratory carcinogen in the rat. Limited exposures (no more than 100 daily exposures of six hours each) of 200 rats to 0.1 ppm BCME led to the induction of respiratory cancers in 40 animals. The type of tumors induced and the time required for the induction are summarized in Table 12. Twenty-six rats had tumors of the nose with esthesioneuroepithelioma as the major histological type. Fourteen rats had tumors of the lung, 13 of them squamous cell carcinomas. The carcinogenic effect of BCME was clearly dependent on the number of exposures (see Table 13) showing an excel-

TABLE 10

Pulmonary Tumors in Strain A/Heston Mice Following Inhalation Exposures to BCME, CMME and Urethane[a]

Compound	Conc. (ppm)	Exposure duration (days)	Incidence of lung tumor (no. tumor-bearing animals/no. examined)	Average number of tumors/animal/treatment group
Control	-	130	20/49 (41%)	0.87
Urethane	138	130	46/49 (94%)	54.20
BCME	1	82	26/47 (55%)	2.89
CMME	2	101	25/50 (50%)	1.53

[a]Summarized from Leong, et al. (1971)

TABLE 11

Inhalational Carcinogenicity of BCME and CMME in Rats and Hamsters

Compound	Species & strain	Conc. (ppm)	Exposure duration[a]	No. of animals	No. of animal with tumors, type	Mean latent period (days)	Reference
BCME	Sprague-Dawley male rats	0.1	10 to 100 exposures	200	26 nasal tumors[b]	253-852	Kuschner, et al. (1975)
					14 lung tumors	215-877	
		1.0	3 exposures	50	1 squamous cell carcinoma of skin	570	Drew, et al. (1975)
	Syrian golden male hamsters	0.1	lifetime exposure	100	1 undifferentiated carcinoma of lung	501	Kuschner, et al. (1975)
		1.0	1 exposure	50	1 undifferentiated malignant tumor of the nose	1000	Drew, et al. (1975)
		1.0	3 exposures	50	1 esthesioneuro-epithelioma of nose	756	Drew, et al. (1975)
CMME	Sprague-Dawley male rats	1.0	lifetime exposure	74	1 squamous cell carcinoma of lung	700	Laskin, et al. (1975)
					1 esthesioneuroepi-thelioma of olfactory epithelium	790	
	Syrian golden male hamsters	1.0	lifetime exposure	90	1 adenocarcinoma of lung	134	Laskin, et al. (1975)
					1 squamous papilloma of trachea	683	

[a] Animals were exposed 6 hr/day, 5 days/week for the number of exposures indicated; they were then kept for lifetime.
[b] See Table 12 for detail.

TABLE 12
Cancers and Induction Times Seen in 200 Rats Following Limited Exposures to 0.1 ppm BCME[a]

Origin and type of cancer	Total no. of cancers	Mean latent period (days)	Range, days
Nose			
Esthesioneuroepithelioma	17	447	266-853
Malignant olfactory tumor (unclassified)	1	405	405
Ganglioneuroepithelioma	1	334	334
Squamous cell carcinoma involving turbinates and gingiva	1	594	594
Poorly differentiated epithelial tumors	4	462	253-676
Adenocarcinoma (nasal cavity)	2	696	652-739
Lung			
Squamous cell carcinoma	13	411	215-578
Adenocarcinoma	1	877	877

[a]From Kuschner, et al. (1975)

TABLE 13

Incidence of Tumors of Respiratory Tract in Rats Following Limited Exposures to 0.1 ppm BCME[a]

No. of exposures	Cancer incidence (no. of tumor-bearing animals/no. of animals observed[b])
100	12/20 (60.0%)
80	15/34 (44.1%)
60	4/18 (22.2%)
40	4/18 (22.2%)
20	3/46 (6.5%)
10	1/41 (2.4%)

[a]Summarized from Kuschner, et al. (1975)

[b]Animals surviving beyond 210 days.

lent dose-response. The exposure-response curve (probit vs. log dose) showed a sigmoid type of relationship, and a linear relationship was obtained by plotting log probit vs. log dose. The number of exposures at 0.1 ppm required to induce tumors in 50 percent of the rats was calculated to be 88. In experiments designed for sub-acute toxicity study, exposure of rats to 1 ppm BCME for three days (six hours/day) led to the induction of squamous cell carcinoma of skin in 1 of the 50 animals. Syrian golden hamsters appeared to be very resistant to carcinogenesis by BCME. Lifetime exposure of hamsters to 0.1 ppm BCME resulted in only one undifferentiated carcinoma of the lung in one of the 100 animals, whereas limited exposures(one or three exposures) brought about one tumor of the nose in one of each of the two groups of 50 animals.

The inhalational carcinogenicity of commercial grade CMME, which is usually contaminated with one to seven percent BCME, has also been tested in rats and hamsters. Lifetime exposure to 1 ppm CMME led to the induction of one pulmonary and one nasal tumor in 74 exposed rats or two respiratory tumors in 90 exposed hamsters. Thus, in practical terms, commercial grade CMME must be considered as a respiratory carcinogen, although of a lower order of activity than BCME.

The carcinogenicity of BCEE by oral administration has been evaluated by Innes, et al. (1969); more recently, in view of its frequent occurrence in finished drinking water, further evaluations have been undertaken by Theiss, et al. (1977) and in the National Cancer Institute (Ulland, et al. 1973; Weisburger, personal communication). The major

findings of these studies are summarized in Table 14. Two strains of mice of both sexes were used by Innes, et al. (1969). They received 100 mg/kg/day of BCEE for 80 weeks, first by intubation for three weeks followed by ingestion of food containing 300 ppm BCEE (estimated to be equivalent to daily intake of 100 mg/kg). The most significant finding was a substantially increased incidence of hepatoma, especially in male mice. The incidence of hepatomas in male and female controls of the strains were 8/79 and 0/87 in (C57BL/6X C3H/Anf)F_1 mice and 5/90 and 1/82 in (C57BL/6XAKR)F_1 mice. The incidence of hepatomas in male treated mice was significantly different from that in controls at the p=0.01 level. In contrast to the above study, Theiss, et al. (1977), using strain A mice (which have a high spontaneous pulmonary tumor incidence), were unable to detect any enhancement of pulmonary tumor incidence after repeated i.p. injections of BCEE. The average number of lung tumors/mouse was actually smaller in the treated group (0.11 to 0.15) than that in the tricaprylin vehicle controls (0.39). In the study by the National Cancer Institute on the oral carcinogenicity of BCEE, Charles River CD rats of both sexes were used. Although, detailed statistical analyses have not yet been completed, preliminary analyses suggest that BCEE did not cause any significant increase in the tumor incidence in the rat (Ulland, et al. 1973; Weisburger, personal communication).

The oral carcinogenicity of BCIE, another compound detected in the finished drinking water, has also been recently evaluated by the National Cancer Institute (unpublished).

TABLE 14

Carcinogenicity of BCEE in Mice and Rats by Oral or i.p. Administration

Species & strain	Treatment	Carcinogenic response[a]	Reference
7-day-old (C57BL/6XC3H/Anf)F_1 mice	oral, 100 mg/kg/day for 80 weeks (BCEE given by intubation for the first 21 days followed by 300 ppm in diet), mice sacrificed at the end of treatment	Male: 14/16 hepatoma(p 0.01) 2/16 Lymphoma Female: 4/18 hepatoma	Innes, et al. (1969)
7-day-old (C57BL/6XAKR)F_1 mice	oral, 100 mg/kg/day for 80 weeks (BCEE given by intubation for the first 21 days followed by 300 ppm in diet), mice sacrificed at the end of treatment	Male: 9/17 hepatoma(p 0.01) 2/17 pulmonary tumor Female: 1/17 lymphoma	Innes, et al. (1969)
6-8 weeks old, male Strain A/St mice	*i.p., 3x/week to a maximum of* 24 injections; 3 dose levels: 4 x 40 mg/kg, 24 x 20 mg/kg, 24 x 8 mg/kg; mice sacrificed 24 weeks after the first injection	*Pulmonary tumor response* not significantly different from that of the control animals	*Theiss, et al. (1977)*
Charles River CD rats	oral, 50 mg/kg/day or 25 mg/kg/day, 5 days/week for two years	Preliminary analyses suggest no significant increase in the development of tumors	Ulland, et al. (1973) Weisburger (personal communication)

[a]No. of tumor-bearing animals/no. of animals observed at the end of experiment.

Mice of both sexes were intubated with BCIE at doses of 10 mg or 25 mg/kg/day, five days a week, for two years. Rats were similarly treated at doses of 100 or 200 mg/kg/day. The results of this study are summarized in Tables 15a & b. Although these data have not yet been fully analyzed, they suggest that no marked increase in tumor incidence is induced by BCIE exposure.

The carcinogenicity of BCME and a number of other chloroalkyl ethers in mice by i.p. administration has been studied by Van Duuren, et al. (1974, 1975). The results are summarized in Table 16. In general, these compounds led to the induction of local tumors. However, papillary tumors of the lung were observed in 12 of the 30 animals treated with 2,3-trans-dichloro-p-dioxane.

Human Data: There is now sufficient epidemiological evidence to indicate unequivocally that BCME and, for practical purposes, CMME are human respiratory carcinogens. Including as yet unreported cases, a total of at least 47 cases of respiratory cancer deaths in association with occupational exposure to these compounds has been observed (Nelson, 1976). A German report (Bettendorf, 1976) has placed the total figure at a minimum of 60 cases. Table 17 summarizes the published case reports of respiratory cancer deaths among exposed workers. These cases were observed in the United States, Germany, and Japan among exposed workers in the chemical manufacturing plants and laboratories. It is important to point out the relatively short latency for the induction of respiratory cancers by these chemicals. The latency period may be as short as eight years. Short durations

TABLE 15a

Summary of Total Tumor Incidence in Rats After Repeated Oral Doses of BCIE (NCI, unpublished)

	Untreated Control	Vehicle Control	Low Dose 100 mg/kg/day	High Dose 200 mg/kg/day
RATS, MALE:				
Animals Initially in Study	50	50	50	50
Animals Necropsied	50	50	50	50
Animals Examined Histopathologically	50	50	50	50
Tumor Summary				
Total animals with primary tumors*	50	45	47	34
Total primary tumors	102	84	82	48
Total animals with benign tumors	47	43	46	30
Total benign tumors	67	56	63	38
Total animals with malignant tumors	29	22	17	8
Total malignant tumors	35	27	18	8
Total animals with secondary tumors+	1		4	1
Total secondary tumors	1		6	1
Total animals with tumors uncertain-benign or malignant		1	1	2
Total uncertain tumors		1	1	2
RATS, FEMALE:				
Animals Initially in Study	50	50	50	50
Animals Necropsied	50	50	49	48
Animals Examined Histopathologically	49	50	49	48
Tumor Summary				
Total animals with primary tumors*	36	39	32	15
Total primary tumors	59	62	51	22
Total animals with benign tumors	29	31	28	11
Total benign tumors	43	47	39	15
Total animals with malignant tumors	14	13	12	7
Total malignant tumors	16	15	12	7
Total animals with secondary tumors+	3	1	1	1
Total secondary tumors	4	1	1	1

*Primary Tumors: All tumors except secondary tumors.
+Secondary Tumors: Metastatic tumors or tumors invading into an adjacent organ.

TABLE 15b

Summary of Total Tumor Incidence in Mice After Repeated Oral Doses of BCIE (NCI, unpublished)

	Untreated Control	Vehicle Control	Low Dose 10 mg/kg/day	High Dose 25 mg/kg/day
MICE, MALE:				
Animals Initially in Study	50	50	50	50
Animals Missing				1
Animals Necropsied	50	50	50	49
Animals Examined Histopathologically	50	50	50	49
Tumor Summary				
Total animals with primary tumors*	13	11	10	12
Total primary tumors	13	11	10	12
Total animals with benign tumors	3	4	2	3
Total benign tumors	3	4	2	3
Total animals with malignant tumors	10	7	8	9
Total malignant tumors	10	7	8	9
Total animals with secondary tumors+		1		
Total secondary tumors		1		
MICE, FEMALE:				
Animals Initially in Study	50	50	50	50
Animals Missing		1		
Animals Necropsied	50	49	49	50
Animals Examined Histopathologically	50	49	48	50
Tumor Summary				
Total animals with primary tumors*	6	5	4	4
Total primary tumors	6	5	4	4
Total animals with benign tumors	1	2	1	2
Total benign tumors	1	2	1	2
Total animals with malignant tumors	5	3	3	2
Total malignant tumors	5	3	3	2

*Primary Tumors: All tumors except secondary tumors.
+Secondary Tumors: Metastatic tumors or tumors invading into an adjacent organ.

TABLE 16

Carcinogenicity of Chloroalkyl Ethers in Mice by i.p. Administration[a]

Compound	Dose regime and duration	Carcinogenic response[b]	Median survival time (days)
BCME	0.02 mg, once/week for 424 days	4/30 local sarcoma	287
2,3-trans-Dichloro-p-dioxane	0.5 mg, once/week for 450 days	12/30 papillary tumor of lung 1/30 local undifferentiated malignant tumor	——
1,2-Bis-(chloromethoxy)ethane	0.3 mg, once/week for 546 days	2/30 local sarcoma 2/30 undifferentiated malignant tumor at injection site	481
1,4-Bis-(chloromethoxy)butane	0.1 mg, once/week for 567 days	no tumor response	478
1,6-Bis(chloromethoxy)hexane	0.3 mg, once/week for 567 days	no tumor response	472
1,2,3-Tris-(chloromethoxy)propane	0.3 mg, once/week for 532 days	5/30 local sarcoma	428

[a]Summarized from Van Duuren, et al. (1974, 1975). The mice were 6-8 weeks old ICR/Ha Swiss female mice.

[b]No. of tumor-bearing animals/no. of animals tested.

TABLE 17

Case Reports of Respiratory Cancers Among Workers Exposed to BCME and/or CMME

Reference	No. of cases	Age at cancer	Years of possible exposure	Induction -latency period (yr)	Working activity	Smoking habit	Histologic type of cancer
Sakabe (1973)	5	37-47	4-9	9-14	Dyestuff factory (Japan)	All moderate to heavy smokers	1 oat cell 1 adenocarcinoma 3 unspecified
Thiess, et al. (1973)	8	31-65	6-9	8-16	Chemical plant (Germany)	6 moderate to heavy smokers 2 unknown	5 small cell-undifferentiated 3 unspecified
Figueroa, et al. (1973)	14	33-55	1-14	—	Chemical plant (Philadelphia)	3 nonsmokers 1 pipe smoker 10 smokers	12 small cell-undifferentiated or oat cell 1 epidermal 1 unknown
Weiss and Figueroa (1976)	11	36-55	2.2-16.6	10-24	Chemical plant (Philadelphia)	3 nonsmokers 1 cigar smoker 2 ex-smokers 5 smokers	10 small cell-undifferentiated 1 oat cell
DeFonso and Kelton (1976)	20	33-66	0.1-16.5	8.3-25.2	Chemical plant (Philadelphia	—	—
Lemen, et al. (1976)	5	35-61	8-13	8-26	Anion-exchange resin plant (California)	4 smokers 1 unknown	4 small cell-undifferentiated 1 large cell-undifferentiated
Bettendorf (1976)	1	42	6	—	Research chemist (Germany)	—	adenocarcinoma
Reznik, et al. (1977)	1	45	2	12-13	Research chemist (Germany)	nonsmoker	adenocarcinoma

of exposures may be sufficient to initiate carcinogenesis. Respiratory cancers occurred among cigarette smokers, cigar or pipe smokers, ex-smokers as well as non-smokers. The average age of cancer death was around 42. The predominant histologic type of cancer was small-cell-undifferentiated carcimona. The calculated increased risk factors of cancer due to chemical exposure are summarized in Table 18.

The five cases of lung cancer reported in Japan (Sakabe, 1973) occurred among 32 employees exposed to BCME and many other noxious chemicals in a dyestuff factory. Four of the workers exposed were involved in the synthesis of dyestuffs; the fifth case was exposed only in the laboratory. This represents a very high increased lung cancer risk.

Thiess, et al. (1973) reported eight cases of respiratory cancer deaths in a chemical plant in Germany. Six of the cases occurred among 18 experimental technical department workers, a group known to experience very high exposures. In contrast, among the manufacturing workers, only two cases were observed among 50. Heavy exposures to BCME and CMME have been attributed as the cause of induction of lung adenocarcinomas in two research chemists in Germany (Bettendorf, 1976; Reznik, et al. 1977). One of the chemists was exposed for only two years; this individual was not involved with other known pulmonary carcinogens, although his contact with unspecified agents cannot be excluded (Reznik, et al. 1977).

In the United States, two of the most well known groups of cases occurred in an anion-exchange resin plant in California and a chemical manufacturing plant in Philadelphia.

TABLE 18

Increased Risk of Respiratory Cancers After Exposure to BCME and/or CMME

Reference	No. of cases	Population at risk	Cancer incidence in risk group (X)	Cancer incidence in control group (Y)	Increased risk (X/Y)	p-value
Sakabe (1973)	5	32	5/32/16 yrs.	0.024/32/16 yrs	208	< 0.001
Figueroa, et al. (1973) prospective study	4	88	4.54/100/5 yrs	0.57/100/5 yrs.	7.96	< 0.0017
Lemen, et al. (1976)	5	136	5/136/18 yrs	0.54/136/18 yrs.	9.24	< 0.01
Albert, et al. (1975)* total of 6 U.S. firms	22	1800	1.48/1000/yr	0.59/1000/yr.	2.53	—
heavy exposure for more than 5 yrs.	3	12	23/1000/yr.	0.97/1000/yr.	23.7	—
heavy exposure for 1-5 yrs.	12	91	8.7/1000/yr.	0.97/1000/yr.	8.97	—
heavy exposure for less than 1 yr.	4	188	1.5/1000/yr.	0.97/1000/yr.	1.56	—
DeFonso and Kelton (1976)	19	699	—	—	3.8	< 0.01

*age-adjusted rate

In the anion-exchange resin plant, five cases occurred among 136 manufacturing employees. Only 0.54 cases were expected among them if they were not exposed; thus, a 9.24 fold increase in the respiratory cancer risk was observed. The average age of cancer death was 47 and the mean induction time was 15 years (Lemen, et al. 1976). Heavy exposures to CMME, contaminated with BCME, occurred among workers in the Philadelphia chemical plant. In 1962, the management became aware that an excessive number of workers who were suspected of having lung cancers were reported in one area of the plant where CMME was used. Extensive prospective and retrospective studies have since been carried out independently by several groups of investigators (Figueroa, et al. 1973; Weiss and Figueroa, 1976; Weiss and Boucot, 1975; Weiss, 1976; DeFonso and Kelton, 1976). The latest figure shows that a total of 20 cases of respiratory cancer deaths had occurred (DeFonso and Kelton, 1976). In one of the prospective studies including 88 exposed workers, an increased risk of 7.96 was observed (Figueroa, et al. 1973). A more recent analysis on an age-specific basis revealed an increased risk of lung cancer 3.8 times higher in 669 exposed compared to 1616 unexposed workers (DeFonso and Kelton, 1976).

An extensive retrospective cohort mortality study of the respiratory cancer death among employees of six of the seven major users and producers of CMME in the U.S. has been carried out by Albert, et al. (1975) and Pasternack, et al. (1977). The cohort chosen included 1827 exposed workers and 8870 controls. The age-adjusted respiratory

cancer death rate for the exposed group as a whole was found to be 2.53 times that in the control group, whereas death rates due to other causes were comparable. Most of the CMME-related deaths were associated with one of the six industrial firms in which heavy exposures occurred. Among workers who were reported to be heavily exposed for more than five years, a 23.7-fold increase in the respiratory cancer risk was observed (Albert, et al. 1975). The increased risk was clearly dependent on the duration and intensity of exposure. Based on job description, personnel records, and information supplied by the supervisory personnel, Pasternack, et al. (1977) estimated the duration (years) and cumulative weighted exposure index (duration of exposure X intensity) of workers and compared with their relative respiratory cancer risk. As shown in Table 19, there was a clear dose-response relationship. The linear trend χ^2 tests gave a highly significant p-value of less than 0.00001. Similar dose-response relationships were reported by DeFonso and Kelton (1976), and Weiss and Figueroa (1976). Thus, there is no doubt that BCME and CMME are potent human respiratory carcinogens.

TABLE 19

Relationship of Respiratory Cancer Mortality to Duration and Intensity of Exposure to BCME and/or CMME[a]

Duration of Exposure (years)	Observed Deaths	Expected Deaths	Relative Risk	Man-year-at-risk
10-19	3	0.2	26.6	97
5-9.9	7	1.9	6.0	1,024
2-4.9	10	2.8	5.7	1,981
0.1-1.9	3	6.7	0.7	5,591
Control	18	29.4	1.0	21,909

Cumulative Weighted Exposure Index[b]	Observed Deaths	Expected Deaths	Relative Risk	Man-year-at-risk
20-50	8	0.9	14.5	482
10-19.9	8	2.4	5.4	1,398
5-9.9	4	1.6	4.2	1,176
0.1-4.9	3	0.7	0.7	5,637
Control	18	29.4	1.0	21,909

[a]Adapted from Pasternack, et al. (1977)

[b]CWEI = Σ Duration of Exposure X Intensity (varing across exposure periods)

CRITERION FORMULATION

Existing Guidelines and Standards

Both BCME and CMME have been recognized as human carcinogens; all contact with them should be avoided. In 1973, these two chloroalkyl ethers were listed as 2 of the 14 carcinogens restricted by Federal regulation. Emergency temporary standards were established for limiting occupational exposure. These regulations applied to all preparations containing 1 percent (w/w) or more of the chloroalkyl ethers. The use, storage, or handling of these chemicals must be limited to a "controlled area" in which elaborate precautions were specified to minimize worker exposure. Decontamination, waste disposal, monitoring and medical surveillance programs were also required (38 FR 10929). More detailed regulations have recently been established; they apply to all preparations containing 0.1 percent of the chloroalkyl ethers by volume or weight (39 FR 3756; Anonymous, 1974). Based on the known carcinogenicity of BCME in animal inhibition studies, the American Conference of Governmental and Industrial Hygienists (1978) has recommended a Threshold Limit Value (TLV) of 1 ppb (4.71 $\mu g/m^3$) for BCME. This value is for the time-weighted average (TWA) concentration for a normal eight-hour workday or 40-hour work-week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

The Federal standard for BCEE is 15 ppm (90 mg/m^3) (Tabershaw, et al. 1977). The ACGIH has recommended a time-weighted-average threshold limit value (TLV-TWA) of 5 ppm

(30 mg/m^3) for BCEE. For a short-term exposure limit, the tentative value (TLV-STEL) suggested is 10 ppm (60 mg/m^3). These values are based on the irritant properties of the chemical to the eye and the respiratory tract. It is also recommended that appropriate measures should be taken for the prevention of cutaneous absorption (Am. Conf. Gov. Ind. Hyg., 1978). The guideline level adopted by the Philadelphia regional office of EPA for BCEE level permitted in Philadelphia's drinking water is 0.02 µg/l. This value is based on an evaluation of the available toxicological data for BCEE by the National Environmental Research Center; a safety factor of 500,000 has been applied in the calculation (Manwaring, et al. 1977).

The TLV's for the other chloroalkyl ethers are not available. The provisional operational limit suggested for BCIE was 15 ppm (Gage, 1970). The value was based on the irritant properties of the compound to the eye and respiratory tract.

Current Levels of Exposure

There is no information available on the levels of chloroalkyl ethers in food or in the atmosphere; hence, no estimates can be made of the extent of human exposures to these compounds via these two routes. Information on the dermal exposure is also virtually nonexistent. Only incomplete data are available for the calculation of exposure via ingestion of drinking water; therefore, only rough estimates can be made. The highest concentration of BCEE, BCIE, and BCEXE in drinking water reported by U.S. EPA (1975) was 0.5, 1.58 and 0.03 µg/l, respectively. Assuming that

(i) these values are representative of yearly averages, (ii) the average daily intake of water is 2 liters and (iii) the average body weight is 70 kg, then the maximum possible daily exposure from water to BCEE, BCIE and BCEXE would be 14.3, 45.1 and 0.86 ng/kg. These values are of course the upper limits and are based on the dubious assumption that the highest value is representative of the yearly average and that they only apply to specific contaminated areas. For national averages, the data of Dressman, et al. (1977) and U.S. EPA (1977) may be used. The national average concentration of BCEE or BCIE in drinking water is calculated as the mean concentration multiplied by the percent incidence of occurrence. Thus, the average concentration in drinking water of BCEE and BCIE was respectively 11.5 ng/l (0.1 µg/lx11.5 percent), and 12.1 ng/l (0.17 µg/lx7.1 percent) in phase II and 1.7 ng/l (0.024 µg/lx7.27 percent) and 7.0 ng/l (0.11 µg/lx6.36 percent) in phase III. Using the same three assumptions mentioned above, the estimated daily exposure to BCEE and BCIE would be, respectively, 0.33 ng/kg and 0.35 ng/kg in phase II and 0.05 ng/kg and 0.20 ng/kg in phase III.

Special Groups at Risk

Exposure to BCME and CMME appears to be confined to occupational settings. A partial list of occupations in which exposure may occur includes: ion-exchange resin makers, specific organic chemical plant workers, laboratory workers, and polymer makers (Tabershaw, et al. 1977). Of these groups, workers in small non-commercial laboratories should probably be particularly cautious because of the lack of monitoring

and surveillance and because of the fact that this group is more likely to be relatively more heavily exposed. Potential exposure to BCME may also occur in workplaces where vapors of hydrochloric acid and formaldehyde may co-exist. The National Institute of Occupational Safety and Health (NIOSH) has already found trace levels of BCME in the textile industry. Other such places include biological, medical and chemical laboratories, and particle-board and paper manufacturing plants (Lemen, et al. 1976).

Exposure to β-chloroalkyl ethers may occur in residents in areas where the source of drinking water is from the contaminated river water and the treatment of drinking water is inadequate to remove the contaminants. Individuals consuming the water in these areas may be at a greater risk than the general population. Occupational exposure to BCEE may also occur. A partial list of occupations in which exposure may occur includes: cellulose ester plant workers, degreasers, dry cleaners, textile scourers, varnish workers, and processors or makers of ethyl cellulose, fat, gum, lacquer, oil, paint, soap and tar (Tabershaw, et al. 1977).

Basis and Derivation of Criterion

There is no empirical evidence that BCIE is carcinogenic; however, some chronic toxic effects of the compound have been noted (see table 6). One approach to estimating a safe level of BCIE in drinking water utilizes the following general equation:

$$NOAEL \times SF \times BW = W \times Z + R \times F \times Z + A\ D-(R \times F \times Z)$$

where NOAEL = no apparent adverse effect level in mammals

SF = safety factor

BW = body weight of average human (assume 70 kg)

W = daily consumption of water (assume 2 liters)

Z = safe level for water

R = bioconcentration factor (in l/kg)

F = daily consumption of fish (assume 0.0187 kg)

A = daily amount absorbed from air

D = daily amount from total diet (including fish)

Since valid estimates on current exposure from air and total diet cannot be made, the equation can be simplified to NOAEL x SF x BW=(W + R x F) x Z. Referring to Table 6, the lowest dose tested which caused minimum adverse effects was 10 mg/kg/day for the mice. However, even at this dose, there was an increased incidence of centrilobular necrosis of the liver which was not seen in the high-dose group. To be conservative, a safety factor of 1/1,000 will be applied. Assuming an average human body weight of 70 kg, acceptable daily intake calculated is 700 µg/day. Using the estimated bioconcentration factor of 106 for BCIE and assuming daily consumption of 0.0187 kg fish and 2 liters of water, the safe level calculated from these data is 175.8 µg/l. Since this safe level is calculated on the basis of several assumptions that cannot be defended, it should be regarded as a very crude estimate.

Another approach to deriving a criterion has been suggested by the Carcinogens Assessment Group, EPA (see Appendix I). As previously stated, BCIE has not been empirically proven to be a carcinogen; nevertheless, it is mutagenic and is in a class of compounds that are known carcinogens. Based on these facts, credence can be lent to deriving a suggested criterion based upon NCI preliminary data (1978) as applied to the linear, non-treshold model described in

Appendix I. Therefore, a lower bound water concentration of 11.5 µg/l has been calculated such that there is a 95 percent confidence that this level is lower than the actual level which would produce a 10^{-5} lifetime cancer risk due to exposure to BCIE.

Although both approaches to calculating a criterion are somewhat tenuous, the weight of evidence for the carcinogenic potential of BCIE is sufficient to be "qualitatively suggestive" and must not be ignored from a public health point of view. Until further conclusive data become available, the Agency feels it is prudent to consider BCIE as a potential carcinogen.

The estimated safe level of BCEE in drinking water may be calculated using the same linear, non-threshold model as applied to BCIE. The data of Innes, et al. (1969) on the carcinogenicity of this compound by oral administration to male mice are used in the calculation. The bio-accumulation factor used is 25. Based on this approach, the calculated water quality criterion for BCEE is .42 µg/l. Compliance to this level should limit human lifetime risk of carcinogenesis from BCEE in drinking water to not more than 10^{-5} (one case in 100,000 persons at risk), assuming water to be the only source of exposure. It should also very adequately protect against noncarcinogenic toxicity since the daily dose of contaminant that would be absorbed from water containing the criterion limit is many times less than the minimal daily oral dose required to produce a detectable toxic response in animals.

The setting of drinking water standards for BCME and CMME is of academic interest only, since these α-chloroalkyl ethers may not, under ordinary conditions, exist in water for periods of time longer than a few hours. Carcinogenicity data generated by oral administration of these compounds are not available.

In the case of CMME, no criterion was calculated due to its extremely short half-life in aqueous solution. Jones and Thornton (1967) have measured the hydrolysis rate of CMME in aqueous isopropanol. Extrapolation of the data to pure water yielded a $t_{\frac{1}{2}}$ of less than one second. BCME has a slightly longer half-life. Therefore, as a guideline, the safe level of BCME in drinking water may be calculated using the tumor incidence data from chronic rat inhalation studies (Kuschner, et al. 1975). In this study, Sprague-Dawley rats were exposed to 0.1 ppm BCME six hours per day, five days per week throughout their lifetime. Additional groups of rats were given 10, 20, 40, 60, 80 and 100 exposures to 0.1 ppm BCME. The validity of the incidence rates for humans was established by evaluating the cancer incidence in workers after accounting for their exposure (Pasternack, et al. 1977).

Therefore, using the linear, non-threshold model (Appendix I) and a bioconcentration factor of 31, the recommended maximum permissible concentration of BCME for the ingested water is .02 ng/l. Compliance to this level should limit human lifetime risk of carcinogenesis from BCME in drinking water to not more than 10^{-5}, assuming water to be the only source of exposure.

Under the Consent Decree in NRDC vs. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." BCIE, BCEE, and BCME are suspected of being human carcinogens. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of these chloroalkyl ethers in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of BCIE, BCEE, and BCME corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the following table.

Exposure Assumptions	Risk Levels and Corresponding Criteria[1]			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams of fish and shellfish (2)		(µg/l)	(µg/l)	µg/l)
Bis(2-chloroisopropyl)ether	0	0.115	1.15	11.5
Bis(2-chloroethyl)ether	0	0.0042	0.042	0.42
Bis(chloromethyl)ether	0	0.02×10^{-5}	0.02×10^{-4}	0.02×10^{-3}
Consumption of fish and shellfish only				
Bis(2-chloroisopropyl)ether	0	0.231	2.31	23.1
Bis(2-chloroethyl)ether	0	0.0219	0.219	2.19
Bis(chloromethyl)ether	0	0.09×10^{-5}	0.09×10^{-4}	0.09×10^{-3}

(1) Calculated by applying a modified "one hit" extrapolation model described in the FR 15926, 1979. Appropriate bioassay data used in the calculation of the model are presented in Appendix 1. Since the extrapolation model is linear to low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Fifty percent of BCIE exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 106 fold. The remaining 50 percent of BCIE exposure results from drinking water.

Nineteen percent of BCEE exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 25 fold. The remaining 81 percent of BCEE exposure results from drinking water.

Twenty-two percent of BCME exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 31 fold. The remaining 78 percent of BCME exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of BCIE, BCEE, and BCME, (1) occurring from the consumption of both drinking water and aquatic life grown in water containing the corresponding chloroalkyl ether concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding chloroalkyl ether concentrations.

Although total exposure information for these chloroalkyl ethers is discussed and an estimate of the contributions from other sources of exposure can be made, this data will not be factored into the ambient water quality criteria formulation because of the tenuous estimates. The criteria presented, therefore, assume an incremental risk from ambient water exposure only.

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APPENDIX I

Summary and Conclusions Regarding the Carcinogenicity of Chloroalkyl Ethers*

Chloroalkyl ethers have a wide variety of industrial and laboratory uses in organic synthesis, treatment of textiles, manufacture of polymers and insecticides, and as degreasing agents. Bis(chloromethyl) ether (BCME) and chloromethylmethyl ether (CMME) have been included in OSHA's list of restricted chemicals (1974) based on animal studies and human epidemiological evidence indicating that these compounds are carcinogenic by inhalation. An additional occupational hazard is the spontaneous combination at high concentrations of vapors of HCL and formaldehyde to form BCME. Bis(2-chloroethyl) ether (BCEE) is present in rivers and drinking water in several cities, and is found in high concentrations in waste water from chemical plants.

Several of the chloroalkyl ethers including BCME, CMME, BCEE, and BCIE were mutagenic in bacterial systems without metabolic activation, indicating that they are direct-acting mutagens. Data for BCME, CMME, and BCEE indicate that these compounds are both mutagenic and carcinogenic.

BCME has been shown to be carcinogenic in animals following inhalation or dermal exposure. In an inhalation study by Kuschner, et al. (1975), BCME induced malignant tumors of

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the respiratory tract in male Sprague-Dawley rats. Application of BCME to mouse skin induced skin tumors (van Duuren, et al. 1968), while s.c. injection of BCME to newborn ICR Swiss random-bred mice induced pulmonary tumors (Gargus, et al. 1969). There were no studies reported using oral administration of BCME.

The carcinogenicity of BCEE by oral administration was investigated by Innes, et al. (1969) in two strains of mice. There was a statistically significant increase of hepatomas in the male mice of both strains (C57BL/6 x C3H/Anf)F_1 and C57BL/6 x AKR)F_1, respectively) and in the female mice of one strain (C57BL/6 x C3H/Anf)F_1).

Epidemiological studies of workers in the United States, Germany, and Japan who were occupationally exposed to BCME and/or CMME (choromethylmethyl ether) have indicated that these compounds are human respiratory carcinogens.

The water quality criterion for BCEE is based on the results of the Innes study in which hepatomas were induced in mice given a daily oral dose of 300 ppm (i.e., 39 mg/kg/day). The concentration of BCEE in drinking water calculated to limit human lifetime cancer risk from BCEE to less than 10^{-5} is 0.42 microgram per liter.

There is no carcinogenicity data from oral exposure to BCME. The rapid hydrolysis rate of BCME in water precludes a realistic exposure. However, a criterion is calculated in the event that levels are monitored in the water. Since BCME is a locally acting carcinogen and it is expected that the stomach would be the target organ from oral exposure,

the lung tumor data from the inhalation study was accepted for estimating human risk, and 100 percent absorption of BCME was assumed. The water quality criterion was calculated using data from the Kuschner, et al. inhalation study, where rats given 100 exposures of 0.1 ppm BCME for six hours per day, five days per week, developed malignant respiratory tract tumors. The concentration of BCME calculated to maintain lifetime cancer risk below 10^{-5} is 0.02 nanograms per liter.

The only oncogenicity study available for BCIE (Bis(2-chloroisopropyl)ether) is an NCI rat study which showed no carcinogenic response. However, BCIE is probably a direct-acting alkylating agent as suggested by its mutagenicity without activation and its structural similarity to BCME. Thus, although the NCI study was negative, based on the other ancillary information, it was decided to take a conservative approach by calculating a water quality criterion. Using the data from the NCI study, a lower bound water concentration of 11.5 micrograms per liter is calculated such that there is a 95 percent confidence that this level is lower than the actual level which would produce a 10^{-5} lifetime cancer risk due to exposure to BCIE.

Summary of Pertinent Data

Bis (2-Chloroisopropyl) Ether

A 95 percent lower bound estimate of the water concentration of BCIE producing 10^{-5} cancer risk is calculated from the preliminary data of the NCI study in Osborne-Mendel rats. Since there is no statistically significant tumor incidence in any treated group compared with controls, the incidence of total malignant tumors in the male rats of the low dose group is compared with that of the respective vehicle control male group. The low dose group was given 100 mg/kg/day of BCIE by intubation five days per week for two years, so that the average lifetime exposure was 71.4 mg/kg/day. The lower bound water concentration is calculated from the values and the equation shown below. To obtain an upper 95 percent confidence bound on the slope, the following estimate was used

$$B_a u = \ln\left[\frac{1 - P_c(1)}{1 - P_t(u)}\right]$$

where $P_c(1)$ is the lower 2.5 percent confidence limit on the control malignant tumor rate and $P_t(u)$ is the upper 97.5 percent confidence bound on the malignant tumor rate in the treated group.

n_t = 17 d = 71.4 mg/kg/day
N_t = 50 w = .550 kg
n_c = 22 F = .0187 kg
N_c = 50 R = 106
Le = 104 wk
lc = 104 wk
L = 104 wk

Based on these parameters, the upper 95 percent confidence limit on the one-hit slope ($B_H u$) is 1.53×10^{-2} $(mg/kg/day)^{-1}$. Therefore, the 95 percent lower bound estimate of the water concentration of BCIE producing 10^{-5} lifetime cancer risk is 11.5 micrograms per liter.

Bis (2-Chloroethyl) ether

The water quality criterion for BCEE is based on the induction of hepatomas in male mice (strain C57BL/6 x C3H/Anf)F_1) given a daily oral dose of 300 ppm for 80 weeks (Innes, et al. 1969). The tumor incidence was 14/16 in the treated group compared with 8/79 in the control group. The criterion was calculated from the following parameters.

n_t = 14 d = 300 ppm X 0.13 = 39 mg/kg/day

N_t = 16 w = .030 kg

n_c = 8 F = .0187 kg

N_c = 79 R = 25

Le = 80 wk

le = 80 wk

L = 80 wk

Based on these parameters, the one-hit slope (B_H) is 6.8510×10^{-1} $(mg/kg/day)^{-1}$. The resulting water concentration of BCEE calculated to keep the individual lifetime cancer risk below 10^{-5} is 0.42 micrograms per liter.

Bis (Chloromethyl) Ether

The water quality criterion for BCME is based on the induction of malignant respiratory tract tumors in male Sprague-Dawley rats given 100 exposures of 0.1 ppm by inhalation six hours per day, five days per week (Kuschner, et al. 1975). The average lifetime exposure was calculated to be 3.510×10^{-4} mg/kg/day. The tumor incidence was 12/20 in the treated group and 0/240 in the control rats. The criterion was calculated from the following parameters.

$n_t = 12$ $\quad$ $d = 3.510 \times 10^{-4}$ mg/kg/day

$N_t = 20$ $\quad$ $w = .500$ kg

$n_c = 0$ $\quad$ $F = .0187$ kg

$N_c = 240$ $\quad$ $R = 31$

$Le = 104$ wk

$le = 104$ wk

$L = 104$ wk

Based on these parameters, the one-hit slope (B_H) is 1.3603×10^4 $(mg/kg/day)^{-1}$. The resulting water concentration of BCME calculated to maintain the individual lifetime cancer risk below 10^{-5} is 0.02 nanograms per liter.