IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

UNEP

Environmental Health Criteria 201

Selected Chloroalkyl Ethers

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among UNEP, ILO, FAO, WHO, UNIDO, UNITAR and OECD

WORLD HEALTH ORGANIZATION

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Environmental Health Criteria 201

SELECTED CHLOROALKYL ETHERS

First draft prepared by Dr R. Liteplo and Ms R. Gomes, Health Canada, Canada

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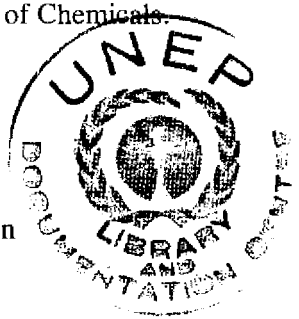
World Health Organization
Geneva, 1998



The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer-review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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CONTENTS

ENVIRONMENTAL HEALTH CRITERIA FOR SELECTED CHLOROALKYL ETHERS

NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (telephone no. + 41 22 - 9799111, fax no. + 41 22 - 7973460, E-mail irptc@unep.ch).

* * *

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Environmental Health Criteria

P R E A M B L E

Objectives

In 1973 the WHO Environmental Health Criteria Programme was initiated with the following objectives:

(i) to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits;

(ii) to identify new or potential pollutants;

(iii) to identify gaps in knowledge concerning the health effects of pollutants;

(iv) to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.

The first Environmental Health Criteria (EHC) monograph, on mercury, was published in 1976 and since that time an ever-increasing number of assessments of chemicals and of physical effects have been produced. In addition, many EHC monographs have been devoted to evaluating toxicological methodology, e.g., for genetic, neurotoxic, teratogenic and nephrotoxic effects. Other publications have been concerned with epidemiological guidelines, evaluation of short-term tests for carcinogens, biomarkers, effects on the elderly and so forth.

Since its inauguration the EHC Programme has widened its scope, and the importance of environmental effects, in addition to health effects, has been increasingly emphasized in the total evaluation of chemicals.

The original impetus for the Programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. Subsequently the work became an integral part of the International Programme on Chemical Safety (IPCS), a cooperative programme of UNEP, ILO and WHO. In this manner, with the strong support of the new partners, the

importance of occupational health and environmental effects was fully recognized. The EHC monographs have become widely established, used and recognized throughout the world.

The recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety with the priorities for action in the six programme areas of Chapter 19, Agenda 21, all lend further weight to the need for EHC assessments of the risks of chemicals.

Scope

The criteria monographs are intended to provide critical reviews on the effect on human health and the environment of chemicals and of combinations of chemicals and physical and biological agents. As such, they include and review studies that are of direct relevance for the evaluation. However, they do not describe *every* study carried out. Worldwide data are used and are quoted from original studies, not from abstracts or reviews. Both published and unpublished reports are considered and it is incumbent on the authors to assess all the articles cited in the references. Preference is always given to published data. Unpublished data are only used when relevant published data are absent or when they are pivotal to the risk assessment. A detailed policy statement is available that describes the procedures used for unpublished proprietary data so that this information can be used in the evaluation without compromising its confidential nature (WHO (1990) Revised Guidelines for the Preparation of Environmental Health Criteria Monographs. PCS/90.69, Geneva, World Health Organization).

In the evaluation of human health risks, sound human data, whenever available, are preferred to animal data. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies. It is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration.

The EHC monographs are intended to assist national and international authorities in making risk assessments and subsequent risk management decisions. They represent a thorough evaluation of risks and are not, in any sense, recommendations for regulation or standard setting. These latter are the exclusive purview of national and regional governments.

Content

The layout of EHC monographs for chemicals is outlined below.

- Summary - a review of the salient facts and the risk evaluation of the chemical
- Identity - physical and chemical properties, analytical methods
- Sources of exposure
- Environmental transport, distribution and transformation
- Environmental levels and human exposure
- Kinetics and metabolism in laboratory animals and humans
- Effects on laboratory mammals and *in vitro* test systems
- Effects on humans
- Effects on other organisms in the laboratory and field
- Evaluation of human health risks and effects on the environment
- Conclusions and recommendations for protection of human health and the environment
- Further research
- Previous evaluations by international bodies, e.g., IARC, JECFA, JMPR

Selection of chemicals

Since the inception of the EHC Programme, the IPCS has organized meetings of scientists to establish lists of priority chemicals for subsequent evaluation. Such meetings have been held in: Ispra, Italy, 1980; Oxford, United Kingdom, 1984; Berlin, Germany, 1987; and North Carolina, USA, 1995. The selection of chemicals has been

based on the following criteria: the existence of scientific evidence that the substance presents a hazard to human health and/or the environment; the possible use, persistence, accumulation or degradation of the substance shows that there may be significant human or environmental exposure; the size and nature of populations at risk (both human and other species) and risks for environment; international concern, i.e. the substance is of major interest to several countries; adequate data on the hazards are available.

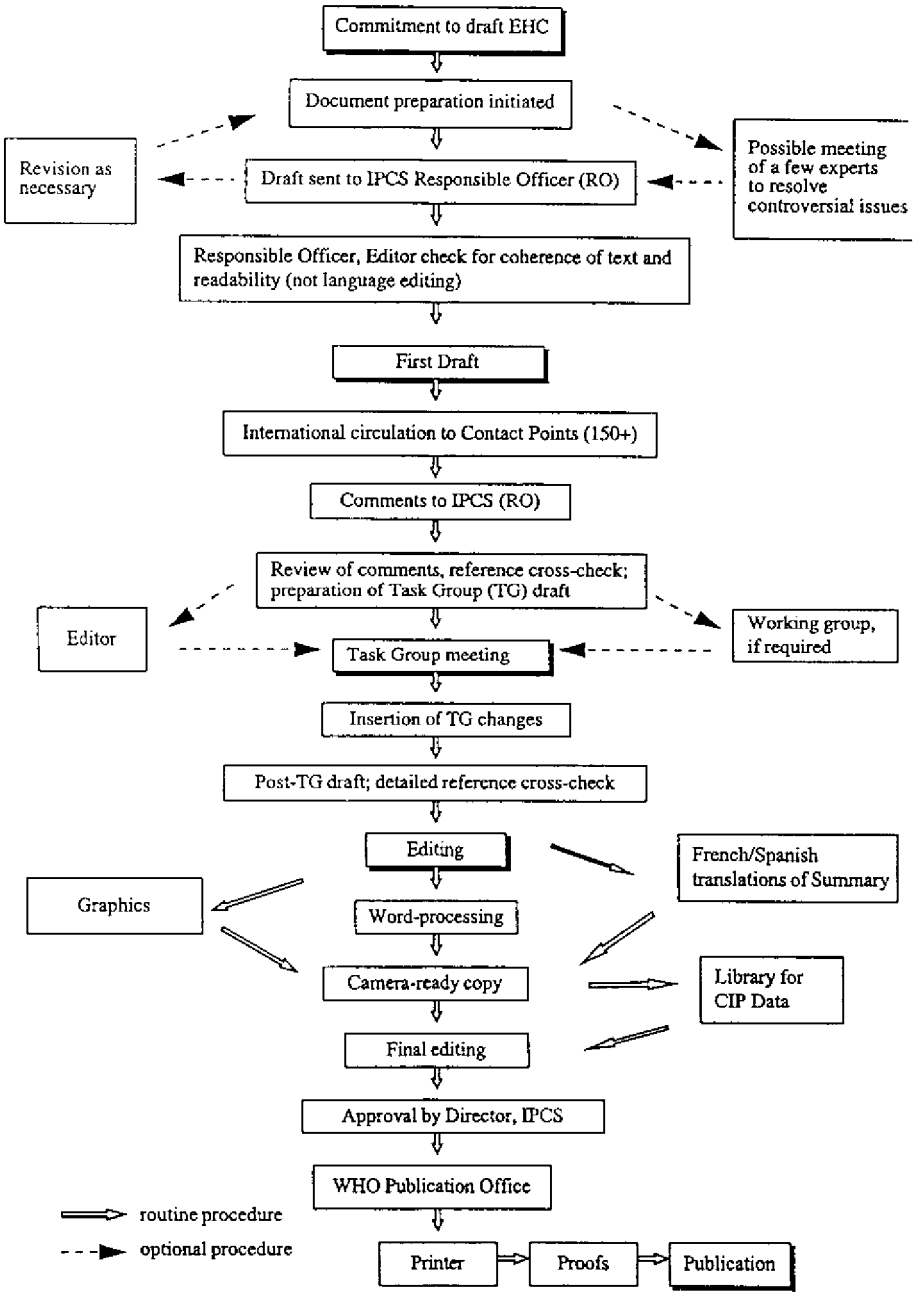
If an EHC monograph is proposed for a chemical not on the priority list, the IPCS Secretariat consults with the Cooperating Organizations and all the Participating Institutions before embarking on the preparation of the monograph.

Procedures

The order of procedures that result in the publication of an EHC monograph is shown in the flow chart. A designated staff member of IPCS, responsible for the scientific quality of the document, serves as Responsible Officer (RO). The IPCS Editor is responsible for layout and language. The first draft, prepared by consultants or, more usually, staff from an IPCS Participating Institution, is based initially on data provided from the International Register of Potentially Toxic Chemicals, and reference data bases such as Medline and Toxline.

The draft document, when received by the RO, may require an initial review by a small panel of experts to determine its scientific quality and objectivity. Once the RO finds the document acceptable as a first draft, it is distributed, in its unedited form, to well over 150 EHC contact points throughout the world who are asked to comment on its completeness and accuracy and, where necessary, provide additional material. The contact points, usually designated by governments, may be Participating Institutions, IPCS Focal Points, or individual scientists known for their particular expertise. Generally some four months are allowed before the comments are considered by the RO and author(s). A second draft incorporating comments received and approved by the Director, IPCS, is then distributed to

EHC PREPARATION FLOW CHART



Task Group members, who carry out the peer review, at least six weeks before their meeting.

The Task Group members serve as individual scientists, not as representatives of any organization, government or industry. Their function is to evaluate the accuracy, significance and relevance of the information in the document and to assess the health and environmental risks from exposure to the chemical. A summary and recommendations for further research and improved safety aspects are also required. The composition of the Task Group is dictated by the range of expertise required for the subject of the meeting and by the need for a balanced geographical distribution.

The three cooperating organizations of the IPCS recognize the important role played by nongovernmental organizations. Representatives from relevant national and international associations may be invited to join the Task Group as observers. While observers may provide a valuable contribution to the process, they can only speak at the invitation of the Chairperson. Observers do not participate in the final evaluation of the chemical; this is the sole responsibility of the Task Group members. When the Task Group considers it to be appropriate, it may meet *in camera*.

All individuals who as authors, consultants or advisers participate in the preparation of the EHC monograph must, in addition to serving in their personal capacity as scientists, inform the RO if at any time a conflict of interest, whether actual or potential, could be perceived in their work. They are required to sign a conflict of interest statement. Such a procedure ensures the transparency and probity of the process.

When the Task Group has completed its review and the RO is satisfied as to the scientific correctness and completeness of the document, it then goes for language editing, reference checking, and preparation of camera-ready copy. After approval by the Director, IPCS, the monograph is submitted to the WHO Office of Publications for printing. At this time a copy of the final draft is sent to the Chairperson and Rapporteur of the Task Group to check for any errors.

It is accepted that the following criteria should initiate the updating of an EHC monograph: new data are available that would

substantially change the evaluation; there is public concern for health or environmental effects of the agent because of greater exposure; an appreciable time period has elapsed since the last evaluation.

All Participating Institutions are informed, through the EHC progress report, of the authors and institutions proposed for the drafting of the documents. A comprehensive file of all comments received on drafts of each EHC monograph is maintained and is available on request. The Chairpersons of Task Groups are briefed before each meeting on their role and responsibility in ensuring that these rules are followed.

WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR SELECTED CHLOROALKYL ETHERS

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IPCS TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR SELECTED CHLOROALKYL ETHERS

A WHO Task Group on Environmental Health Criteria for Selected Chloroalkyl Ethers met at the British Industrial Biological Research Association (BIBRA) Toxicology International, Carshalton, Surrey, United Kingdom, from 18 to 23 March 1996. Dr D. Anderson opened the meeting and welcomed the participants on behalf of the host institute. Dr G.C. Becking, IPCS, welcomed the participants on behalf of Dr M. Mercier, Director of the IPCS and the three cooperating organizations (UNEP/ILO/WHO). The Task Group reviewed and revised the draft criteria monograph and made an evaluation of the risks to human health and the environment from exposure to selected chloroalkyl ethers.

Financial support for this Task Group was provided by the United Kingdom Department of Health as part of its contribution to the IPCS.

The first and second drafts of this monograph were prepared by Dr R. Liteplo and Ms R. Gomes, Health Canada, Ottawa. The second draft incorporated the comments received following circulation of the first draft to the IPCS contact points for environmental health criteria monographs.

Dr G.C. Becking (IPCS Central Unit, Interregional Research Unit) and Dr P.G. Jenkins (IPCS Central Unit, Geneva) were responsible for the overall scientific content and technical editing, respectively.

The efforts of all who helped in the preparation of the document are gratefully acknowledged.

ABBREVIATIONS

BCEE	bis(2-chloroethyl) ether
BCME	bis(chloromethyl) ether
CMME	chloromethyl methyl ether
MTD	maximum tolerated dose
PMA	phorbol myristate acetate
TDGA	thiodiglycolic acid

1. SUMMARY AND CONCLUSIONS

1.1 Identity, physical and chemical properties, analytical methods

Bis(2-chloroethyl) ether (BCEE), bis(chloromethyl) ether (BCME) and chloromethyl methyl ether (CMME) are chemicals from a large class known as chloroalkyl ethers. The three ethers are colourless volatile liquids at room temperature having characteristic odours. The vapour pressure of these three compounds is high. The solubility of BCEE is 1.7% in water and its octanol/water partition coefficient is 1.46. The α-chloroalkyl ethers BCME and CMME are reactive compounds, hydrolysing rapidly in aqueous media (with half-lives of approximately 38 seconds and <0.007 seconds, respectively); hydrolysis of the more stable β-chloroether BCEE is slower (with a half-life in water of about 20 years).

Sampling and analytical methods have been described for BCEE in water and for BCME and CMME in air. Typically, determination is by gas chromatography (GC-electron capture) or GC mass spectrometry.

1.2 Sources of human exposure

Natural sources of BCEE, BCME or CMME in the environment have not been identified. The recent production data available are limited and confined to the USA and Canada. Approximately 10^4 tonnes of BCEE were produced in the USA in 1986 for use as a solvent and in the production of polymers and several industrial processes. Industrial uses of BCME are currently restricted in the USA to specific intermediate chemical reactions. BCME has also been produced for use in the production of ion exchange resins, manufacture of other polymers, and as a solvent in polymerization reactions. In China, some 200 tonnes of BCME are produced annually as an intermediate in the manufacture of the insecticide synergist, octachlorodipropyl ether. Technical grade CMME contains from 1 to 8% BCME.

1.3 Environmental transport, distribution and transformation

The mobility and distribution of the selected chloroalkyl ethers is influenced by the high reactivity of BCME and CMME and the water solubility and stability of BCEE. The α-chloroalkyl ethers BCME and CMME are hydrolysed rapidly in aqueous media and degraded quickly by photolysis. In aqueous media, the hydrolytic products of BCME and CMME are formaldehyde and hydrochloric acid, and methanol, formaldehyde and hydrochloric acid, respectively. The decomposition products of BCME and CMME in air include hydrogen chloride, formaldehyde and chloromethylformate, and chloromethyl and methyl formate, respectively. BCEE is soluble in water; rainfall removes it from the atmosphere and it tends to remain in water with very slow hydrolysis. BCEE evaporates from surface water within a week and is degraded in a little more than a day in the atmosphere by abiotic processes.

Owing to the highly reactive nature of the α-chloroalkyl ethers in water and air, CMME and BCME are not expected to be present in the environment; however BCEE may be persistent due to the relative stability of β-chloroalkyl ethers.

1.4 Environmental levels and human exposure

Only limited data on levels of BCEE in environmental media are available. It has been identified in air but not quantified; levels up to 0.42 μg/litre have been found in drinking-water in the USA. Reported levels of BCEE in groundwater have ranged from 0.001 μg/litre at an industrial gypsum waste disposal site in Belgium to 840 μg/litre near a waste disposal site in the USA. Higher concentrations have been measured in landfill leachates. Information on levels of BCEE in foodstuffs is not available, but bioaccumulation is not expected to occur.

Quantitative data on levels of BCME or CMME in environmental media are not available.

Based on the maximum reported level of BCEE in drinking-water, i.e., 0.42 μg/litre, the average human (64 kg) consuming 1.4 litres/day would have an intake of about 0.01 μg/kg body weight per

day from this source, with unknown amounts from other environmental sources. No estimates can be made on the daily intake of BCME and CMME from environmental sources. However, based upon the lack of persistence of BCME and CMME in the environment, average human exposure to these compounds is likely to be very low.

Based on limited older data, workers in industries related to plastics and textile production could have been exposed to between 1.2 and 72.9 μg BCME/m^3 in workroom air. However, a recent study of a resin-manufacturing plant reported average occupational exposures ranging from 2.4 to 20.6 μg/m^3. Data from other studies reported levels of BCME as low as 0.01 μg/m^3. Higher occupational exposure to BCME occurred in China up until 1975 and still occurs on a lower level in the manufacture of octachlorodipropyl ether. General population exposure to BCME and CMME occurs where they are produced by the widespread burning of this synergist in mosquito coils.

The highest reported concentrations of BCEE in the USA for industrial effluents are 8 to 170 μg/litre and for municipal and industrial waste landfill leachates 12 400 μg/litre.

1.5 Kinetics and metabolism

Quantitative information on the kinetics and metabolism of BCEE, BCME and CMME in humans is not available. However, it is anticipated that although *in vivo* BCME and CMME would be rapidly hydrolysed in tissues to formaldehyde and hydrogen chloride, and methanol, formaldehyde and hydrogen chloride, respectively, there should be alkylation activity.

Limited data show that radioactive BCEE administered to rats by inhalation or gavage is rapidly absorbed. Less than 3% of the radioactivity was retained 48 h after gavage dosing.

BCEE is readily metabolized in rats. The principal metabolite is thiodiglycolic acid (TDGA). After rats were given a single gavage dose of [^{14}C]-BCEE, approximately 12% of the administered radioactivity was present as $^{14}CO_2$.

BCEE is eliminated quickly in both rats and rhesus monkeys. Less than 2% of the radioactivity was recovered in the faeces of monkeys 72 h after oral administration of [^{14}C]-BCEE; approximately 2.3% of the administered radioactivity was found in rat tissues or faeces 48 h after dosing. Over 50% of the radioactivity was recovered in the urine and exhaled air 12 h after a gavage dose of [^{14}C]-BCEE was administered to rats. Less than 2% of the radioactivity expired through the lungs was exhaled as the parent compound.

1.6 Effects on laboratory animals and *in vitro* test systems

BCEE is acutely toxic by the oral, inhalation or dermal routes of exposure. Reported LD_{50} values for the oral exposure of animal species to BCEE range from 75 to 215 mg/kg body weight. BCME and CMME are acutely toxic by inhalation or ingestion. Reported LC_{50} values for the inhalation exposure of laboratory animals to BCME or CMME range from 25 to 48 mg/m^3, and from 182 to 215 mg/m^3, respectively.

Exposure of laboratory animals by inhalation to high single concentrations of BCEE (>320 mg/m^3) resulted in eye irritation as well as congestion, oedema, and haemorrhage in the lungs. During inhalation of BCME, irritation of the eyes and respiratory tract were noted as well as necrotizing bronchitis. Skin application resulted in erythema and necrosis, and application to the eye resulted in corneal necrosis. Similar effects were noted after exposure to CMME.

Increased mortality and tracheal hyperplasia were observed in rats and hamsters following multiple inhalation exposure to 4.7 mg BCME/m^3. Similar results were observed in rats repeatedly exposed by inhalation to 3.3 or 33 mg CMME/m^3.

In general, positive results were obtained when BCEE, BCME and CMME were tested for mutagenicity *in vitro*. However, interpretation of the results is difficult given the lack of details in the reports available. BCME and CMME have been reported to increase unscheduled DNA synthesis *in vitro*, and BCME increased the level of transformed cells in *in vitro* assays.

In small groups of males from two strains of hybrid F_1 mice (and in females from one F_1 strain) treated orally with BCEE (time-weighted dose 41.3 mg/kg body weight over 18 months), there was a significant increase in the incidence of hepatomas (combined benign hepatomas and malignant tumours) compared to unexposed controls. Four other limited studies in rats and mice using oral gavage, subcutaneous or intraperitoneal injection and skin painting failed to confirm these findings.

Carcinogenicity studies in experimental animals (mice and rats) exposed to BCME showed significantly elevated incidence of pulmonary adenomas and respiratory tumours. In mice, inhalation exposure also showed evidence of an elevated incidence of lung tumours.

Studies with CMME have shown an increased incidence of tracheal metaplasia and bronchial hyperplasia in a dose-dependent manner in rats. However, results of carcinogenicity bioassays are inconclusive in animal studies.

Information regarding the reproductive, developmental, immunological or neurological toxicity of BCEE, BCME or CMME is not available.

1.7 Effects on humans

BCEE was found to be irritating to the eyes and nasal passages of humans at levels >150 mg/m^3 following short-term exposure.

No epidemiological studies on the effects of long-term exposure to BCEE have been reported.

In eight epidemiological studies, exposure of workers to BCME (CMME) was associated with increased risk of lung cancer. Workers exposed to commercial grade CMME were probably also exposed to BCME. The predominant tumours in exposed workers were small cell carcinomas, quite distinct from the chiefly squamous cell carcinomas usually found in smokers. The association between exposure to BCME (CMME) and lung cancer was strong, with standardized mortality ratios ranging up to 21. The type of lung cancer, latency period and average age of appearance of lung tumours in workers exposed to

BCME (CMME) have been remarkably consistent. For CMME, there is also evidence of a positive relationship between a qualitative measure of exposure and mortality due to lung cancer.

Even concentrations of 0.01 μg BCME/m^3 and 20 μg CMME/m^3, in the course of occupational exposure, increased the frequency of chromosomal aberrations in the peripheral lymphocytes of exposed workers.

Information has not been reported regarding the neurological, immunological, developmental or reproductive effects of BCME or CMME in humans.

1.8 Effects on other organisms in the laboratory and field

There have been few studies on the effects of BCEE on environmental organisms; most are restricted to aquatic species. For BCEE a 7-day LC_{50} concentration in the guppy of 56.9 mg/litre, a 96-h LC_{50} in fish of 600 mg/litre and a 48-h LC_{50} in *Daphnia magna* of 240 mg/litre have been reported.

Anaerobic microbial activity was not inhibited at concentrations of BCEE up to 100 mg/litre and an LC_{10} of 600 μg/litre has been reported for microbes indigenous to waste stabilization ponds.

No information on the toxicological effects of BCME and CMME on environmental organisms has been reported.

1.9 Conclusions

1.9.1 BCEE

- Exposure of terrestrial organisms to BCEE is considered to be negligible because of the low rate of release and its short persistence in the atmosphere.

- Although it is more persistent in water, the highest reported concentration of BCEE in surface water is approximately five orders of magnitude lower than the concentration found to induce adverse effects in the guppy, the most sensitive aquatic species identified among existing toxicity studies.

- Owing to the lack of available information on concentrations of BCEE in several environmental media to which humans are exposed, it is not possible to estimate quantitatively the total daily intake of BCEE.

- Available data on the toxicity of BCEE in humans are limited. Information on the developmental and reproductive effects of BCEE in laboratory animals has not been identified, and none of the long-term studies in laboratory animals is of sufficient quality to provide quantitative information on either the potential of BCEE to cause cancer or the toxicological effects produced by long-term exposure to this substance.

- In the absence of adequate toxicological and carcinogenicity data, it is prudent to minimize human exposure to BCEE.

1.9.2 BCME and CMME

- If these substances were to enter the environment, they would both be rapidly broken down by hydrolysis and photo-oxidation. Data concerning concentrations of BCME and CMME in the ambient environment have not been reported.

- BCME and technical grade CMME (which contains BCME) are proven human carcinogens. In addition, both of these chemicals are carcinogens in laboratory animals. Both chemicals cause chromosomal aberrations in occupationally exposed workers. Occupational and general population exposure to these compounds should be eliminated.

- Based on the fate of these substances in the environment and the lack of exposure, there is no reason to suspect that adverse effects on aquatic and terrestrial organisms would occur.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND ANALYTICAL METHODS

2.1 Identity

Bis(2-chloroethyl) ether (BCEE), bis(chloromethyl) ether (BCME) and chloromethyl methyl ether (CMME) are included in a large class of chemical substances known as the chloroalkyl ethers. Identifying features of BCEE, BCME and CMME are summarized in Table 1.

2.2 Physical and chemical properties

BCEE, a β-chloroalkyl ether, is a colourless, volatile liquid with a "chlorinated solvent-like" odour (Sittig, 1981). BCME and CMME, both α-chloroalkyl ethers, are also colourless, volatile liquids with characteristic odours. The odour of BCME has been described as "suffocating" (Sittig, 1981; Verschueren, 1983), while that of CMME has been described as "irritating" (Verschueren, 1983). Technical grade CMME contains from 1 to 8% BCME (Travenius, 1982) and, unless otherwise indicated in this monograph, CMME refers to the technical grade material. In general, the vapour pressure and water solubility of these compounds are high, and the log octanol/water partition coefficients (log K_{ow}) are low. The β-chloroalkylethers like BCEE are only slightly reactive towards water, but the α-chloroalkyl ethers like BCME and CMME are rapidly hydrolysed by water, and their solubility, K_{ow}, K_{oc} and Henry's Law constant cannot be experimentally determined. The physical and chemical properties of the selected chloroalkyl ethers are presented in Table 2.

2.3 Conversion factors

At 25 °C and 101.3 kPa, the conversion factors for BCEE, BCME and CMME in air are as follows:

BCEE: 1 ppm (v/v) = 5.85 mg/m^3; 1 mg/m^3 = 0.17 ppm
BCME: 1 ppm (v/v) = 4.7 mg/m^3; 1 mg/m^3 = 0.21 ppm
CMME: 1 ppm (v/v) = 3.3 mg/m^3; 1 mg/m^3 = 0.30 ppm

Table 1. Information on the identity of BCEE, BCME and CMME (US NLM, 1996)

Compound (CAS number)[a]	Identification	Molecular formula	Chemical structure	Relative molecular mass	Synonyms
Bis(2-chloroethyl) ether (111-44-4)	BCEE	$C_4H_8Cl_2O$	Cl-$(CH_2)_2$-O-$(CH_2)_2$-Cl	143.02	dichloroethyl ether, dichloroethyl oxide, bis (β-chloroethyl) ether, dichloroether, 1,1'-oxybis(2-chloro)ethane, 1,5-dichloro-3-oxapentane, 1-chloro-2-(β-chloroethoxy)-ethane, 2,2'-dichloroethyl ether, β,β'-dichlorodiethyl ether, bis(chloro-2-ethyl) oxide, di(β-chloroethyl) ether, di(2-chloroethyl) ether, ether, bis(2-chloroethyl), sym-dichloroethyl ether, diethylene glycol dichloride.
Bis(chloromethyl) ether (542-88-1)	BCME	$C_2H_4Cl_2O$	Cl-CH_2-O-CH_2-Cl	114.97	chloro(chloromethoxy) methane, sym-dichloro-dimethyl ether, oxybis(chloromethane), dichloromethyl ether, bichloromethyl ether, dichlorodimethyl ether, 1,1'-dichlorodimethyl ether.

Table 1 (contd).

Compound (CAS number)[a]	Identification	Molecular formula	Chemical structure	Relative molecular mass	Synonyms
Chloromethyl methyl ether (107-30-2)	CMME	C_2H_5ClO	$Cl\text{-}CH_2\text{-}O\text{-}CH_3$	80.52	chloromethoxymethane, monochlorodimethyl ether, methoxymethyl chloride, chlorodimethyl ether, methyl chloromethyl ether, monochloromethyl methyl ether.

[a] Chemical Abstracts Services registry number.

Table 2. Physical and chemical properties of BCEE, BCME and CMME

Physical/chemical property	BCEE	BCME	CMME
Melting point (°C)	-50[a]	-41.5[a]	-103.5[b]
Boiling point (°C)	178.67[a]	104[a]	59.5[b]
Vapour pressure (mmHg)	0.71 at 20 °C[b]	30 at 22 °C[c]	122 at 20 °C[d]
Vapour density	4.93[a]	3.97[b]	2.8[d]
Water solubility (mg/litre)	10 200[b]	NA	NA
Log octanol/water partition coefficient (log K_{ow})	1.46[c]	NA	NA
Henry's Law constant ($atm \cdot m^3/mol$)	1.31×10^{-5}[c]	NA	NA
Soil sorption coefficient (log K_{oc})	1.1[c]	NA	NA
Hydrolysis rate constant			
in water	4×10^{-6} h^{-1} at 25 °C[e]	0.05 sec^{-1}[h]	>90 sec^{-1} at 25 °C[e]
in air	not available	1.7×10^{-1} sec^{-1} at 45 °C[i]	0.0018 min^{-1} at 29 °C[k]

Table 2 (contd).

Physical/chemical property	BCEE	BCME	CMME
Photolysis rate constant			
in water	24 to <360 $mol^{-1} \cdot h^{-1}$ [c]	3 to <360 $mol^{-1} \cdot h^{-1}$ [c]	not available
in air	1.79×10^{-11} $cm^3 \cdot mol^{-1} \cdot sec^{-1}$ [f]	not available	1.0×10^{-10} $mol^{-1} \cdot sec^{-1}$ [e]
Half-life			
in water	20 years at 25 °C (hydrolysis) [c]	38 sec at 20 °C (hydrolysis) [i]	<0.007 sec at 25 °C [e]
in air	13.44 h at 25 °C (indirect photolysis) [f]	>25 h at 25 °C (hydrolysis) [k]	3.5 to 6 min at 25 °C (hydrolysis) [i]
in soil	1 to 6 months (estimate) [g]	not available	not available

[a] Weast & Astle (1985)
[b] Verschueren (1983)
[c] Mabey et al. (1982)
[d] CCINFO (1991)
[e] Radding et al. (1977)
[f] US EPA (1987b)
[g] Howard et al. (1991)
[h] Tou & Kallos (1974a)
[i] Nichols & Merritt (1973)
[j] US EPA (1980)
[k] Tou & Kallos (1974b)

NA = not applicable. Due to the extremely rapid hydrolysis of this substance in water, it is not possible to obtain an experimental value, and calculated values are meaningless.

2.4 Analytical methods

2.4.1 BCEE

One method for the analysis of BCEE in water involves solvent extraction (using diethyl ether in pentane, methylene chloride, or ethyl ether in hexane), concentration with a Kuderna-Danish (K-D) apparatus, and separation and analysis by gas chromatography with electron capture detection (GC/EC) or gas chromatography mass spectrometry (GC/MS) (Dressman et al., 1977; Quaghebeur et al., 1986). This method has been expanded to include clean-up with Florisil and K-D concentration of the sorbed fraction prior to analysis by GC/EC (McMillin et al., 1984). Vapour stripping using helium or nitrogen gas has also been used to extract BCEE from samples of ground and surface water. Typically, this step is followed by concentration of the extract with a cold or lipophilic vapour trap, and analysis by GC/MS (Hites et al., 1979; DeWalle & Chian, 1981). An additional technique has been described by Kleopfer & Fairless (1972), in which samples of water are passed through an activated carbon filter, followed by Soxhlet extraction of the carbon, drying of the extract with sodium sulfate, K-D concentration, Shriner-Fuson separation of the acidic, basic and neutral fractions, and analysis of the last by GC/MS. Determination of BCEE in air involves passing air samples through a sorbent, followed by elution and analysis by gas chromatography (NIOSH, 1984).

Reported detection limits for these methodologies differ by up to two orders of magnitude. Detection limits for the procedure described by Dressman et al. (1977) and Quaghebeur et al. (1986) range from 0.005 to 0.04 µg/litre, respectively. Limits of detection for the methods described by McMillin et al. (1984) and Kleopfer & Fairless (1972) are 0.3 and 0.2 µg/litre, respectively.

2.4.2 BCME

While information concerning the sampling and analysis of BCME in water, soil or foodstuffs was not available, considerable data on techniques for the analysis of low levels (µg/m^3) of BCME in air have been identified (Collier, 1972; Evans et al., 1975; Frankel & Black, 1976; Parkes et al., 1976; Kallos, 1981; Muller et al., 1981; Galvin & House, 1988; Blease et al., 1989). Typically, air samples are drawn into a (Poropak or Tenax) sorption tube, thermally eluted, and

analysed by GC/MS or GC/EC. Two additional methods have been described which involve the direct derivatization of BCME (with 2,4,6-trichlorophenol or sodium pentafluorophenolate), and subsequent analysis by GC/EC (Sawicki et al., 1976; Langelaan & Nielen, 1989). Norpoth et al. (1981) reported a spectrophotometric method for the determination of BCME.

Collier (1972), Frankel & Black (1976) and Galvin & House (1988) reported a detection limit of 470 ng/m^3 for BCME in air, while Evans et al. (1975) and Langelaan & Nielen (1989) achieved detection limits as low as 50 and 14 ng/m^3, respectively. Muller et al. (1981) did not report a detection limit, but quantified BCME at a concentration of 2.35 μg/m^3 in air. A detection limit of 0.94 μg/m^3 was reported for the spectrophotometric quantification method described by Norpoth et al. (1981). The methods described by Sawicki et al. (1976) and Parkes et al. (1976) have a detection limit of 2.35 μg/m^3, while a detection limit of approximately 4.7 ng/m^3 was established for the method described by Blease et al. (1989), in which high resolution was achieved with the combined use of gas chromatography and tandem mass spectrometry (GC/MS/MS).

2.4.3 CMME

Identified methods for the sampling and analysis of CMME in environmental media are limited to techniques developed for monitoring low levels (μg/m^3) in air. Several methods have been described which involve the derivatization of CMME (with 2,4,6-trichlorophenol or sodium pentafluorophenolate) and subsequent analysis by GC/EC (Sawicki et al., 1976; Kallos et al., 1977; Langhorst et al., 1981; Langhorst, 1985; Langelaan & Nielen, 1989). The limits of detection for these methodologies are 49 ng/m^3 (Langelaan & Nielen, 1989), 1.65 μg/m^3 (Sawicki et al., 1976; Langhorst et al., 1981) and 3.29 μg/m^3 (Kallos et al., 1977).

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural occurrence

Natural sources of BCEE, BCME or CMME in the environment have not been identified. While BCME could be formed spontaneously from the reaction of formaldehyde and chloride ions in an acidic atmosphere, this reaction is unlikely in the general environment, although it may be important in occupational settings (Durkin et al., 1975; Tou & Kallos, 1976; Kallos & Tou, 1977; Travenius, 1982).

3.2 Anthropogenic sources

3.2.1 Production

Only limited information on the production of BCEE, BCME or CMME has been reported.

3.2.1.1 BCEE

BCEE used to be prepared commercially in the USA as a by-product in the manufacture of ethylene oxide by the chlorohydrin process, but this process went out of use in the USA in 1973 (IARC, 1975). Other methods of production also involving ethylene glycol or ethylene, ethylene chlorohydrin and chlorine as reagents have been mentioned (Durkin et al., 1975; IARC, 1975; ATSDR, 1989a). In 1975, two US companies, one German and one Japanese company manufactured BCEE for captive use as a solvent or chemical intermediate (IARC, 1975).

3.2.1.2 BCME

BCME is formed when formaldehyde reacts with chloride ions in an acidic medium (Travenius, 1982). In China, BCME is produced by the reaction of paraformaldehyde and hydrogen chloride gas as an intermediate in the synthesis of the insecticide synergist S-2, octachlorodipropyl ether [bis(1,2,3,3-tetrachloropropyl)ether] to which it is converted in a one-part process. The scale of S-2 production is believed to be around 700 tonnes/year, which would require over 200 tonnes of BCME. Specific synthesis reactions include the reaction

between paraformaldehyde and chlorosulfonic acid (Durkin et al., 1975) and the saturation of a paraformaldehyde solution in cold sulfuric acid with hydrogen chloride (US EPA, 1980). Small amounts (several percent) of BCME are also produced during the synthesis of CMME from gaseous hydrogen chloride and heated methanol and formaldehyde (Durkin et al., 1975). In addition, the decomposition products of commercial forms of CMME can combine to produce 1 to 8% BCME as an impurity (Travenius, 1982). While BCME is not produced in commercial quantities in Canada or the USA, it has been produced in small quantities for use as a chemical intermediate in laboratory applications (IARC, 1974).

3.2.1.3 *CMME*

CMME is produced by the reaction of anhydrous hydrogen chloride, methanol and formaldehyde (Fishbein, 1979) or by the direct chlorination of dimethyl ether (Durkin et al., 1975). An additional method, which is designed to produce CMME that is free of BCME impurities, involves the addition of actinium chloride to a slight excess of anhydrous dimethoxymethane at room temperature (CCINFO, 1991). Production of CMME in the USA was estimated to be at least 4590 tonnes in 1977 and about 2.27 tonnes in 1982 (HSDB, 1996).

3.2.2 *Uses*

Only information concerning the use of BCEE, BCME or CMME in Canada and the USA is available.

3.2.2.1 *BCEE*

In the USA, BCEE was formerly used in the process for the manufacture of methyldithiocarbamic acid fungicide commonly known as metham-sodium. Besides this use, approximately 20% of the BCEE sold in the USA was used in the production of polymers, and 7% was either used to synthesize a derivative of diquat or recycled for use as a co-solvent (S. Helmhout, personal communication to the IPCS, 1992). Other applications have included its use as a solvent for fats, waxes, greases and esters; as a constituent of paints, varnishes and lacquers; as a solvent for the removal of fatty substances from various textiles, and as a penetrant and wetting agent in the textile industry. It has also been used in the purification of oils and gasoline, as a soil fumigant, insecticide and acaricide, and as an intermediate in the

manufacture of pharmaceuticals and other chemicals (Durkin et al., 1975; IARC, 1975; US EPA, 1987a; ATSDR, 1989a).

3.2.2.2 *BCME*

In the USA, industrial use of BCME has been restricted since the early 1980s to specific intermediate chemical reactions (Travenius, 1982). In China, BCME is an intermediate in the production of the insecticide synergist S-2, octachlorodipropylether (see section 3.2.1.2). In the past, BCME has been used as a chloromethylating agent in the production of ion exchange resins, water repellents and other textile-treating agents, the manufacture of polymers, and a solvent for polymerization reactions (Fishbein, 1979). Specific minor uses of BCME have included the crosslinking of cellulose, the preparation of three-block styrene-butadiene-styrene polymers, and the surface treatment of vulcanized rubber to increase adhesion of epoxy resin and polyurethane elastomers (Durkin et al., 1975).

Available data indicate that there is currently no commercial activity involving more than one kilogram of BCME in Canada (Government of Canada, 1993b).

3.2.2.3 *CMME*

In the USA, industrial use of CMME has been restricted since the early 1980s to specific intermediate chemical reactions (Travenius, 1982). Based on available data, there is currently no commercial activity in Canada involving more than one kilogram of CMME (Government of Canada, 1993b).

In the past, CMME has been used as a chloromethylating agent in many synthetic processes, most notably in the production of anion exchange resins (Durkin et al., 1975). It has also been used as a solvent for polymerization reactions (Fishbein, 1979), in the synthesis of methoxymethyl ethers of phenols, the crosslinking of polystyrene, and the surface treatment of vulcanized rubber (Durkin et al., 1975).

3.2.3 Sources in the environment

Information on the release of BCEE, BCME and CMME in countries other than the USA and Canada has not been reported.

3.2.3.1 BCEE

BCEE may enter the environment as a by-product from the chlorination of waste streams containing ethylene or propylene, and as a contaminant in the fungicide metam-sodium. It has been estimated, based on the quantities imported and the known level of contamination, that less than 100 g of BCEE would have been released into the Canadian environment in 1990 from metam-sodium (Government of Canada, 1993a). In the USA, a total of 2700 kg/year was estimated to be released into the environment from chemical plants in 1989. Seventy percent of this amount was reported to be emitted to the air, while the remaining 30% was released in water (US EPA, 1990). The chlorination of drinking-water containing diethyl ether can result in the formation of BCEE (NRC, 1977); however, quantitative data have not been identified.

3.2.3.2 BCME and CMME

It was reported in the Toxic Release Inventory Database (US EPA, 1990) that less than 1 kg of BCME and 50 kg of CMME were released into the atmosphere in the USA from industrial producers and users during 1989. However, release occurred in the two-step production of octachlorodipropyl ether in China (Chen et al., 1996). This process ceased in 1975, but manufacture of octachlorodipropyl ether was revived in 1987 using a one-step process, from which gas releases and accidental liquid spills occur. There is no information on the amount of BCME that may remain as a contaminant of the product, which contains formaldehyde and hydrogen chloride (BCME's precursors). There is, however, gas-chromatographic evidence that CMME and BCME are released into the air by the burning of octachlorodipropyl ether in mosquito coils. No information is available from these sources concerning the release of BCME or CMME into other media (water, soil, underground injection), but, owing to their rapid rate of hydrolysis, these compounds are not expected to remain as such for prolonged periods in waste streams from plants where they are produced or used (IARC, 1974).

The spontaneous formation of BCME or CMME in drinking-water from the chlorination of ethers has not been investigated. However, in view of their rapid rate of hydrolysis (see section 4.2.2), it is unlikely that BCME or CMME would be present as contaminants in drinking-water (Durkin et al., 1975).

No information has been identified concerning the quantities of BCME or CMME released into the environment during storage or transportation. However, these amounts are likely to be insignificant since BCME and CMME have been usually produced and used in "closed system" operations where containment prevents the release of these chemicals into the environment (Durkin et al., 1975).

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

4.1 Transport and distribution between media

4.1.1 BCEE

Based on the low-to-moderate Henry's Law constant (1.3×10^{-5} atm·m^3/mol), BCEE would tend to remain in water. The air/water ratio, as well as the Henry's Law constant, will determine the amounts of BCEE distributed between the two compartments. Rainfall would probably result in the removal of BCEE from the atmosphere (Durkin et al., 1975). Using the approach of Mackay & Wolkoff (1973), Durkin et al. (1975) calculated the half-life with respect to volatilization of BCEE from a body of water to be 5.78 days at 25 °C. Similarly, a volatilization half-life of 3.4 days (from water) was calculated by the US EPA (1987b). Thus the removal of BCEE from surface water will probably occur within a week, although it will persist in bottom water. Based upon its low log K_{oc} (organic carbon partition coefficient) and high water solubility, BCEE is not expected to adsorb to soil or sediment and is therefore considered to be mobile in these media (US EPA, 1987b). The US EPA (1987b) reported that, because of its vapour pressure, BCEE should volatilize relatively rapidly from dry surfaces. In the only study dealing with soil volatilization (a 7-day microcosm study by Piwoni et al. (1986) in which the soil was kept moist), an insignificant amount (3%) of applied BCEE was calculated to have volatilized.

4.1.2 BCME and CMME

Information regarding the mobility and distribution of BCME and CMME in environmental media is limited. Callahan et al. (1979) suggested that BCME could volatilize rapidly from an aquatic system only if it were discharged in a water-immiscible solvent with a high vapour pressure. Once in the atmosphere, these substances would be rapidly degraded by photo-oxidation or hydrolysis. Very little information was identified concerning the behaviour of BCME or CMME in soil. It is unlikely that BCME and CMME are mobile in soil as both compounds hydrolyse rapidly in an aqueous environment.

4.2 Abiotic degradation

4.2.1 BCEE

At a temperature of 20 °C in water, a hydrolysis half-life of 20 to 22 years was estimated for BCEE (Mabey et al., 1982; Milano et al., 1989). The US EPA estimated the half-life for the reaction of BCEE with hydroxyl radicals in the atmosphere to be approximately 2.8 days (A. Leifer, Office of Toxic Substances, US EPA, personal communication, 1992). A half-life of 13.4 h has been reported for the indirect photolysis of BCEE in the gaseous phase (US EPA, 1987b). Photolysis products of BCEE include 2-chloroethanol, ethyl alcohol, methyl alcohol, 2-chloroethyl ethyl ether, peracetic acetic acid, 1-(2-chloroethoxy)-1,2-epoxyethane, acetaldehyde and chloracetaldehyde (Milano et al., 1989).

4.2.2 BCME and CMME

BCME and CMME are removed from environmental media via abiotic processes. In the atmosphere, these substances are degraded by photo-oxidation or hydrolysis. Cuppit (1980) reported atmospheric half-lives of < 2.9 days for BCME and < 3.9 days for CMME. Tou & Kallos (1974a) reported half-lives for atmospheric hydrolysis of > 1 day for BCME and between 0.0024 (Nichols & Merritt, 1973) and 0.27 days for CMME, in humid air. At low humidity levels, however, BCME may be degraded by oxidative as well as hydrolytic pathways. In air, the decomposition products for BCME include hydrogen chloride, formaldehyde and chloromethylformate, while those of CMME include chloromethyl and methyl formate (Cupitt, 1980).

BCME and CMME hydrolyse rapidly in water. At 20 °C, half-lives in water of 38 seconds for BCME and < 1 second for CMME have been reported (Tou et al., 1974; Radding et al., 1977; US EPA, 1980). Although BCME may be degraded by oxidation, the extremely rapid hydrolysis of BCME in aqueous media precludes any significant oxidative degradation of this substance in aquatic systems (Callahan et al., 1979). BCME is hydrolysed to formaldehyde and hydrogen chloride (ATSDR, 1989b), while CMME is hydrolysed to hydrogen chloride, methanol and formaldehyde (Travenius, 1982).

4.3 Biodegradation, biotransformation and bioaccumulation

4.3.1 BCEE

In the only study identified, Tabak et al. (1981) reported that BCEE was completely biodegraded within 7 days in an aqueous medium inoculated with sewage sludge. Although data on the biodegradation of BCEE in soil are limited, this process may play some role in the fate of this substance in soil. Kincannon & Lin (1986) reported a half-life of BCEE in soil of approximately 16.7 days, based on the results of a 97-day soil column study in which the degradation of BCEE mixed with hexachloroethane (as a constituent of a hazardous waste sludge) was quantified.

For biota, Barrows et al. (1978) reported a bioconcentration factor (BCF) of 11 and a biological half-life of between 4 and 7 days for BCEE in bluegill sunfish (*Lepomis marochirus*) based on the results of a study in which the fish were exposed to BCEE (under flow-through conditions) for 14 days at a mean water concentration of 10 µg/litre.

4.3.2 BCME and CMME

No information on the biodegradation of either BCME or CMME in soil was identified. However, their high rates of hydrolysis in aqueous media preclude any possibility of BCME or CMME bioaccumulating in organisms.

4.4 Ultimate fate following use

Owing to the highly reactive nature of the α-chloroalkylethers in water and air, CMME and BCME are not expected to be present in the general environment (Durkin et al., 1975). However, owing to the relative stability of ß-chloroalkylethers in environmental media, BCEE may be persistent in the general environment (Durkin et al., 1975).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

5.1.1 BCEE

Quantitative information on the levels of BCEE in air is limited to a single study in the USA in which this substance was detected (but not quantified) in the atmosphere above two landfill sites in New Jersey (US NLM, 1996).

Available data concerning the levels of BCEE detected in surface water and drinking-water are summarized in Tables 3 and 4, respectively. BCEE has been detected in samples of municipal drinking-water at mean concentrations of up to 0.42 µg/litre in the USA (Kraybill, 1977). The highest concentration reported for selected surface waters was 58 µg/litre in Belgium, in the vicinity of industrial discharges (Quaghebeur et al., 1986).

Identified studies concerning the levels of BCEE in groundwater were limited to surveys conducted in the vicinity of contaminated areas; concentrations of BCEE ranged from 0.001 µg/litre in samples collected at an industrial gypsum waste disposal site in Belgium (Quaghebeur et al., 1986) to 840 µg/litre in samples collected near a municipal and industrial waste landfill site in the USA (DeWalle & Chian, 1981).

Identified studies on the levels of BCEE in soil were limited to two investigations in which this compound was detected in samples collected from contaminated areas in the USA. BCEE was monitored (but not quantified) in samples of soil collected at Love Canal, New York (Hauser & Bromberg, 1982), and measured at a mean concentration of 140 mg/kg in samples of soil from waste disposal sites in the USA (ATSDR, 1989a).

No information is available on the levels of BCEE in foodstuffs. Based on its high water solubility and low K_{ow}, BCEE is not expected to bioaccumulate in fish or other aquatic species (ATSDR, 1989a).

Table 3. Bis(2-chloroethyl) ether levels in surface water

Location	Number of samples[a]	Concentration[b] mean (range) (µg/litre)	Remarks	Reference
Philadelphia, USA	NR	ND	samples collected from April 1975 to July 1975 from the Delaware River, upstream from a water treatment plant	Manwaring et al. (1977)
	NR	trace	samples collected in April 1975 from the Delaware River, upstream from a chemical plant	Manwaring et al. (1977)
	2	trace	samples collected in October 1976 from the Delaware River	Sheldon & Hites (1978)
	5	(ND - trace)	samples collected in March 1977 from the Delaware River	Sheldon & Hites (1978); US EPA (1980)
New Orleans and Baton Rouge, USA	3	0.11 (0.04 - 0.16)		Pellizzari et al. (1979)
Houston, USA	1 (1)	1.4		Pellizzari et al. (1979)
Nitro, USA	NR	0.041	samples collected from the Kanawha River	Rosen et al. (1963); Durkin et al. (1975)
USA[c]	808 (3)	< 10.0 median	limit of detection, 10.0 µg/litre	Staples et al. (1985)
Belgium[c]	NR	(7 - 58)	samples collected from Haine River adjacent to industrial discharges	Quaghebeur et al. (1986)
Belgium[c]	NR	(trace - 7.9)	samples collected from Durme River, Scheldt River and Gheut-Terneuzen Channel downstream from industrial discharges	Quaghebeur et al. (1986)

[a] Value in parenthesis indicates the number of samples with detectable levels of bis(2-chloroethyl) ether.
[b] Mean and/or (range) of concentrations, unless otherwise indicated; detection limits were reported, when possible.
[c] Locations were not specified.
NR = not reported; ND = not detected

Table 4. Bis(2-chloroethyl) ether levels in drinking water

Location	Number of samples[a]	Concentration[b] mean (range) (µg/litre)	Detection limit (µg/litre)	Remarks	Reference
Toronto, Canada	50 (0)	ND	0.00003	finished drinking-water	Kendall (1990)
Toronto, Canada	8 (0)	ND	0.001	bottled spring water	Kendall (1990)
Alberta, Canada[c]	1512 (1)	ND (ND - trace)	1	samples of treated (from 215 sites) and raw (from 14 sites) drinking-water collected from January 1986 to June 1991	Alberta Ministry of the Environment (1991)
Nitro, USA	1 (1)	0.2	NR	tap water	DeWalle & Chian (1981)
Evansville, USA	1	NQ	NR	finished drinking-water	Kleopfer & Fairless (1972)
Philadelphia, USA	NR	NQ	NR	finished drinking-water collected between 1975 and 1977	Suffet et al. (1980)
Philadelphia, USA	NR	< 0.1 (0.04 - 0.6)	NR	finished drinking-water collected between February 1975 and July 1975	Manwaring et al. (1977)
New Orleans, USA	NR	(0.04 - 0.16)	NR	finished drinking-water collected in August 1974	Keith et al. (1976)

Table 4 (contd).

Location	Number of samples[a]	Concentration[b] mean (range) (µg/litre)	Detection limit (µg/litre)	Remarks	Reference
Philadelphia, USA	NR	(0.03 - < 1)	NR	raw drinking-water collected between April 1975 and July 1975	Manwaring et al. (1977)
Philadelphia, USA	NR	(0.4 - 0.5)	NR	raw drinking-water	Durkin et al. (1975)
USA[c]	NR	0.42	NR	finished drinking-water	Kraybill (1977)
	NR	ND	5	finished drinking-water collected (between March 1976 and April 1976) from 112 cities during the National Organics Monitoring Survey (NOMS) (Phase I)	US EPA (1980)
	NR	0.0115 (ND - 0.36)	0.005	finished drinking-water collected (between May 1976 and June 1976) from 113 cities during the NOMS (Phase II); BCEE was detected in drinking-water from 13 cities at a mean concentration of 0.10 µg/litre	Dressman et al. (1977)

Table 4 (contd).

Location	Number of samples[a]	Concentration[b] mean (range) (µg/litre)	Detection limit (µg/litre)	Remarks	Reference
USA[c]	NR	0.0017	NR	finished drinking-water collected (between November 1976 and June 1977) from 110 cities during the NOMS (Phase III); BCEE was detected in drinking-water from 8 cities at a mean concentration of 0.024 µg/litre	US EPA (1980)
	NR	(0.02 - 0.12)	NR	drinking-water from 80 cities	Fishbein (1979)
Netherlands[c]	NR	0.1 maximum	NR		Kraybill (1977)

[a] Values in parenthesis indicate the number of samples with detectable levels of bis(2-chloroethyl) ether.
[b] Mean and/or (range) of concentrations, unless otherwise indicated.
[c] Locations were not specified
ND = not detected
NR = not reported
NQ = not quantified

The concentration of BCEE in in-plant effluents in Canada has been reported to range from 6.1 to 1057 µg/litre (Government of Canada, 1993a). These effluents are diluted with cooling water before being discharged to the environment and, although levels of BCEE at the outflow pipe were not monitored, they were probably below the limit of detection.

The highest concentrations of BCEE in the USA were reported for industrial effluents (8 to 170 µg/litre), and municipal and industrial waste landfill leachates (12 400 µg/litre) (DeWalle & Chian, 1981).

5.1.2 BCME and CMME

No information has been reported on levels of BCME or CMME in ambient air or the indoor air of homes or offices. In a small survey of outdoor air in the Netherlands, BCME and CMME were not detected (detection limits, 14.1 µg/m^3 and 49.5 µg/m^3, respectively) in samples collected in the neighbourhood of a potential emission source (distance and source were not specified) (Langelaan & Nielen, 1989).

Available data on the levels of BCME or CMME in drinking-water, surface water or ground water are limited to one investigation in which BCME was not detected (detection limit, 10 µg/litre) in a total of 317 samples of surface and groundwater from unspecified locations in the USA (Staples et al., 1985).

Quantitative data concerning the levels of BCME or CMME in soil have not been reported. However, in view of their rapid rate of hydrolysis, these compounds are not expected to persist as contaminants in moist soil (US NLM, 1996). Similarly, while no studies on the levels of BCME or CMME in foodstuffs have been reported, the high rates of hydrolysis reduce the likelihood of BCME or CMME bioaccumulating in the food chain (US NLM, 1996).

No reliable data on levels of either BCME or CMME in industrial effluents have been reported.

5.2 General population exposure

Quantitative data concerning the levels of BCEE in the general environment are restricted to the results of studies in which the levels of this substance in surface water and drinking-water have been

assessed. Based on a daily volume of ingestion for adults of 1.4 litres, a mean body weight for males and females of 64 kg (IPCS, 1994), and the highest mean concentration of BCEE in drinking-water presented in Table 4 (0.42 μg/litre), the estimated intake of BCEE from drinking-water for adults would be approximately 0.01 μg/kg body weight per day.

Adequate information on the concentrations of BCME and CMME in air, drinking-water, soil, or foodstuffs have not been reported, and therefore it is not possible to estimate the intake of these substances. No quantitative data are available for the exposure of populations that use mosquito coils containing octachlorodipropyl ether (see section 3.2.3.2), but the number of users of such coils is of the order of millions in China.

5.3 Occupational exposure

5.3.1 BCEE

Occupational exposure to BCEE (via inhalation or dermal contact) may occur in individuals involved in the dry cleaning and textile industries, or in the processing of gum, lacquer, oil, paint, soap and tar (Tabershaw et al., 1977). However, no investigations concerning quantitative levels of exposure to BCEE in the workplace have been reported.

5.3.2 BCME and CMME

Occupational exposure to BCME or CMME may occur in laboratory and textile workers, and in individuals involved in the production of anion-exchange resins, organic chemicals and polymers (Lemen et al., 1976; US EPA, 1980). In China, occupational exposure to BCME occurs in the manufacture of octachlorodipropyl ether. Under conditions where vapours of formaldehyde and hydrochloric acid co-exist, BCME may form spontaneously in air. Available quantitative data concerning occupational exposure to either BCME or CMME are limited to investigations of the levels of BCME in workroom air (Table 5).

Table 5. Concentrations of bis(chloromethyl) ether in workroom air

Industry	Sampling period	Concentration[a] (µg/m³)	Detection limit (µg/m³)	Reference
Dye auxiliaries (resin) production; dye manufacture; fertilizer production; textile finishing on woven goods; hospital procedures; foundry products (research plant); foundry products (full-scale plant) (USA)	Jan. 1976 - Aug. 1976	ND	0.5 or 0.9	Yao & Miller (1979)
Plastics industry[b] (USA)	Jan. 1973	<4.7 - 72.9	NR	Eisner (1974)
Textile finishing plants (4) (USA)	Nov. 1974 - Dec. 1974	<0.5 - 37.6	0.5	Marceleno (1974)
Chemical plant (UK)	1978	≤4.7	NR	Travenius (1982)
Chemical plant (Netherlands)	NR	1.2 - 3.8	0.5	van der Ven & Venema (1979)
Resin manufacturing plant[d] (France)	1979 - 1984	2.8 - 20.6	NR	Gowers et al. (1993)

[a] Concentrations of bis(chloromethyl) ether measured in workroom air
[b] Samples of air collected at the Diamond Shamrock Chemical Company in California, in the vicinity of reactors used to condense phenol and formaldehyde
[c] Unspecified industrial operations; location of sample acquisition was not reported
[d] Range of average concentrations from various areas in the plant
ND - not detected
NR - not reported

BCME may be produced in solution from a variety of sources of formaldehyde and chloride ions, and has been detected in the vapours above these solutions (Frankel et al., 1974). In one study, the concentration of BCME in the headspace above formalin slurries containing Freidel-Crafts (chloride) salts ranged from 0.99 to 7.1 mg/m^3 (210 to 1500 ppb) (Frankel et al., 1974).

While no recent studies have been identified where levels of occupational exposure to CMME have been reported, it has been estimated that in the past, concentrations of CMME in workroom air may have ranged from 4.7 to 47 mg/m^3 (1-10 ppm) (Travenius, 1982).

6. KINETICS AND METABOLISM IN LABORATORY ANIMALS

Quantitative information on the absorption, distribution, elimination and metabolism of BCEE, BCME or CMME in humans is not available.

6.1 Absorption and distribution

Gwinner et al. (1983) reported that more than 95% of the total [^{14}C]-BCEE vapour (calculated to be approximately 75 mg) introduced into an inhalation chamber containing three male Wistar rats was absorbed by the animals after an 18-h exposure. When the tissue (protein)-associated radioactivity (per gram of tissue) was examined after this exposure period, approximately 0.32% of the administered radioactivity was present in the liver, while 0.17 and 0.12% were found in the kidney and small intestine, respectively. Only 0.07% of the administered radioactivity was present in the lungs. Lingg et al. (1982) administered by gavage a single dose of [^{14}C]-BCEE (40 mg/kg body weight, dissolved in corn oil) to male Sprague-Dawley rats and monitored the amount of radioactivity present in a limited number of tissues during the subsequent 48-h period. After 48 h, the percentage of administered ^{14}C was found to be 11.5 in expired CO_2, 64.7 in urine, 2.4 in faeces, and 2.3 in organs and tissues. In tissues, approximately 1, 0.56, 0.49 and 0.19% of the radioactivity was retained in muscle, kidney, blood and liver, respectively. Quantitative data on the absorption and distribution of BCME or CMME in animal species have not been reported.

6.2 Metabolism

BCEE is readily metabolized following absorption. Thiodiglycolic acid (TDGA) was the principal metabolic product (representing 50 to 80% of the total metabolites) in the urine of rats administered BCEE either orally, by intraperitoneal injection or by inhalation (Lingg et al., 1979, 1982; Muller et al., 1979; Norpoth et al., 1986). 2-Chloroethoxy-acetic acid, N-acetyl-S-[2-(2-chloroethoxy)-ethyl]-L-cysteine, 1-(2-chloroethyl)-β-D-glucopyranosiduronic acid and S-carboxymethyl-L-cysteine have been reported to be minor metabolites (each comprising less than 10% of the total) in the urine of rats administered BCEE (Lingg et al., 1979, 1982; Muller et al.,

1979). Lingg et al. (1982) reported that in male Sprague-Dawley rats administered (by gavage) a single dose of [^{14}C]-BCEE (40 mg/kg body weight, dissolved in corn oil), approximately 12% of the radioactivity was metabolized to $^{14}CO_2$.

The formation of TDGA from BCEE involves a number of steps (Lingg et al., 1979, 1982; Muller et al., 1979; Gwinner et al., 1983; Norpoth et al., 1986). BCEE is believed to undergo oxidative degradation (involving ether cleavage) to produce chloroacetaldehyde and chloroethanol (which itself is rapidly converted to chloroacetaldehyde) (Gwinner et al., 1983). It is believed that chloroacetaldehyde is subsequently converted to chloroacetic acid, which after conjugation with glutathione and further modification, produces TDGA. The formation of N-acetyl-S-[2-(2-chloroethoxy)ethyl]-L-cysteine is believed to involve the direct substitution of one of the chlorine atoms in BCEE with cysteine (Lingg et al., 1982). S-Carboxymethyl-L-cysteine, although not detected in all studies in which the metabolism of BCEE was examined, has been postulated to be an intermediate in the synthesis of TDGA (Lingg et al., 1982). 1-(2-Chloroethyl)-β-D-glucopyranosiduronic acid is evidence of the occurence of 2-chloroethanol among metabolic products, while S-carboxymethyl-*n*-cysteine may be produced by alkylation of glutathione by chloroacetaldehyde (Lingg et al., 1982), and 2-chloroethoxy-acetic acid is believed to be produced via the oxidative dehalogenation of BCEE (Lingg et al., 1982).

Information on the metabolism of BCME or CMME in laboratory animals has not been reported; however it is anticipated that BCME and CMME would be rapidly hydrolysed in the aqueous environment of tissues, forming formaldehyde and hydrogen chloride, and methanol, formaldehyde and hydrogen chloride, respectively. However, the effects of BCME (CMME) are most likely attributable to their direct alkylating activity (van Duuren, 1989).

6.3 Elimination

Although quantitative information on the elimination of BCME or CMME in laboratory animals is not available, limited quantitative data concerning the elimination of BCEE (administered orally) in laboratory animals have been reported. Lingg et al. (1982) administered (by gavage) a single dose of [^{14}C]-BCEE (40 mg/kg body

weight, dissolved in corn oil) to male Sprague-Dawley rats and monitored the amount of radioactivity appearing in the faeces, urine and expired air during the subsequent 48-h period. Twelve hours after the administration of [^{14}C]-BCEE, 50% of the radioactivity had been lost in the urine and exhaled air (as $^{14}CO_2$). Lingg et al. (1979) estimated that less than 2% of the administered radioactivity that was expired through the lungs was exhaled as the parent compound. Forty-eight hours after the oral administration of [^{14}C]-BCEE, approximately 65% of the radioactivity was excreted in the urine and 11.5% exhaled from the lungs (total loss of 76%); approximately 2.3 and 2.4% of the administered radioactivity remained in the organs (and tissues) and faeces, respectively.

Smith et al. (1985) reported that 24, 48 and 72 h after the oral administration (by gavage) of [^{14}C]-BCEE (10 mg/kg body weight, in a solution containing ethanol, Emulphor and distilled water) to two female Rhesus monkeys, approximately 43, 56 and 58% of the administered radioactivity had been eliminated in the urine. Seventy-two hours after the administration of [^{14}C]-BCEE, less than 2% of the radioactivity was recovered in the faeces.

7. EFFECTS ON EXPERIMENTAL MAMMALS AND *IN VITRO* TEST SYSTEMS

7.1 Single exposure

Information on the acute toxicity of BCEE, BCME and CMME is summarized in Table 6.

7.1.1 BCEE

Although the acute toxicity of BCEE has been examined in a number of studies, complete experimental details were not always provided. Reported LD_{50} values for the oral exposure of animal species to BCEE range from 75 to 215 mg/kg body weight. An LC_{50} of 5850 mg/m^3 (1000 ppm) was estimated from studies in which Sherman strain rats were exposed to BCEE for 0.75 h (Smyth & Carpenter, 1948). The exposure of guinea-pigs to 5850 mg/m^3 for 3.8 to 5.5 h resulted in the death of the animals (Schrenk et al., 1933). Exposure to 1521 mg/m^3 (260 ppm) resulted in the death of the animals after 7.5 to 12.3 h of continuous exposure. No deaths were observed after exposure to 205 mg/m^3 (35 ppm) for up to 13.5 h, although slight nasal irritation was observed within 3 to 10 min of exposure to this concentration. Acute exposure of guinea-pigs to BCEE vapour (320 mg/m^3) caused eye irritation (as indicated by squinting and lacrimation) as well as congestion, oedema and haemorrhage in the lungs; liver, kidney and brain congestion was also noted (Schrenk et al., 1933). The severity of the toxicological effects produced by exposure to the higher concentrations of BCEE was also related to the length of the exposure period. Effects in Sprague-Dawley rats or CD-1 mice administered a single oral dose of BCEE (dissolved in cottonseed oil) included ptosis, increased salivation, diarrhoea, decreased activity and ataxia (Drake & Myer, 1992).

Smyth & Carpenter (1948) reported that the dermal exposure of guinea-pigs to BCEE caused skin irritation; the LD_{50} was 366 mg/kg body weight.

7.1.2 BCME and CMME

Reported LC_{50} values for the exposure (by inhalation) of laboratory animals to BCME range from 25 to 48 mg/m^3 (5.3 to 10.3 ppm).

Table 6. Acute toxicity of BCEE, BCME and CMME

Species[a]	Route (duration)	LC_{50} or LD_{50}	Reference
BCEE			
Rat (Sherman)	inhalation (0.75 h)	LC_{50}: 5850 mg/m³ (1000 ppm)	Smyth & Carpenter (1948)
Rat (Sherman)	oral	LD_{50}: 75 mg/kg bw	Smyth & Carpenter (1948)
Rat	oral	LD_{50}: 105 mg/kg bw	Spector (1956)
Rat (Sprague-Dawley)	oral	LD_{50}: 175 mg/kg bw	Drake & Myer (1992)
Mouse	oral	LD_{50}: 136 mg/kg bw	Spector (1956)
Mouse (CD-1)	oral	LD_{50}: 215 mg/kg bw	Drake & Myer (1992)
Rabbit	oral	LD_{50}: 126 mg/kg bw	Spector (1956)
Guinea-pig	dermal (poultice; 24 h)	LD_{50}: 366 mg/kg bw	Smyth & Carpenter (1948)
BCME			
Rat (Sprague-Dawley)	inhalation (7 h)	LC_{50}: 33 mg/m³ (7 ppm)	Drew et al. (1975)
Rat	inhalation[b]	LC_{50}: 48 mg/m³ (10.3 ppm)	Union Carbide (1968)
Mouse (A/Heston)	inhalation (6 h)	LC_{50}: 25 mg/m³ (5.3 ppm)	Leong et al. (1971)
Hamster (Syrian)	inhalation (7 h)	LC_{50}: 33 mg/m³ (7 ppm)	Drew et al. (1975)
Rat (Wistar)	oral (undiluted)	LD_{50}: 0.21 ml/kg bw (278 mg/kg bw)	Union Carbide (1968)
Rabbit (New Zealand)	dermal (undiluted; 24 h)	LD_{50}: 0.28 ml/kg bw (370 mg/kg bw)	Union Carbide (1968)
CMME[c]			
Rat	inhalation (7 h)	LC_{50}: 182 mg/m³ (55 ppm)	Drew et al. (1975)
Hamster	inhalation (7 h)	LC_{50}: 215 mg/m³ (65 ppm)	Drew et al. (1975)
Rat	oral	LD_{50}: 817 mg/kg bw	NIOSH (1974)

[a] Data on strain presented if reported in study.
[b] Duration not specified.
[c] Containing BCME.

The acute exposure (by inhalation) of animals to BCME produced severe irritation of the eyes and respiratory tract (congestion, oedema and haemorrhage (mainly of the lungs) and acute necrotizing bronchitis (Union Carbide, 1968; Drew et al., 1975). The median life span of rats exposed (by inhalation) to 0, 3.3, 9.9, 32.4 or 44.7 mg/m^3 (0, 0.7, 2.1, 6.9 or 9.5 ppm) was 462, 420, 36, 2 and 2 days, respectively. For hamsters exposed (by inhalation) to these concentrations of BCME, the median life span was 675, 657, 68, 16 and 4 days, respectively (Drew et al., 1975). Exposure to 9.9 mg/m^3 (2.1 ppm) for 7 h increased the incidence of tracheal and bronchial hyperplasia 2- to 3-fold in rats and 4- to 5-fold in hamsters, compared to unexposed controls (Drew et al., 1975).

Reported LC_{50} values for the exposure (by inhalation) of laboratory animals to CMME range from 182 to 215 mg/m^3 (55 to 65 ppm). Exposure to CMME produced pulmonary congestion, oedema, haemorrhage and acute necrotizing bronchitis (Drew et al., 1975); however the toxic effects produced by CMME may be due, at least in part, to contaminating BCME.

Application of BCME to the skin of rabbits produced erythema and necrosis, while exposure of the eye to this substance produced severe corneal necrosis (Union Carbide, 1968).

7.2 Short-term exposure

7.2.1 BCEE

Information on the effects of short-term or subchronic exposure of animals to BCEE is limited primarily to range-finding studies for carcinogenicity bioassays. Theiss et al. (1977) reported that the maximum tolerated dose (MTD) of BCEE in A/St male mice (receiving 6 intraperitoneal injections over a 2-week period) was 40 mg/kg body weight. The administration (route not clearly specified) of 19 daily doses (100 mg/kg body weight) of BCEE (deemed to be the MTD) to two strains of hybrid F_1 mice [strain (C57BL/6 x C3H/Anf)F_1 and strain (C57BL/6 x AKR)F_1] had no effect on mortality, although other toxicological effects were not reported (Innes et al., 1969).

7.2.2 BCME

In one study (Drew et al., 1975) on the short-term toxicity of BCME, groups of 50 male Sprague-Dawley rats and Syrian hamsters were exposed by inhalation to 0 or 4.7 mg/m^3 (0 or 1 ppm) for 1, 3, 10 or 30 multiple 6-h exposures (duration between exposures not specified), after which time the animals were observed for their entire life span and the trachea and bronchi examined histopathologically. In groups of rats exposed to BCME for 0, 1, 3, 10 or 30 occasions, 50% mortality was observed after 66, 66, 20, 4 and 4 weeks, respectively. The incidence of tracheal hyperplasia, with and without atypias, increased from 27% after 1 exposure to 89% after 30 exposures to BCME. The incidence of tracheal squamous metaplasia increased after 3 to 30 exposures. The incidence of bronchial hyperplasia and squamous metaplasia increased with greater exposure to BCME. In hamsters subjected to 0, 1, 3, 10 or 30 exposures (6-h) to BCME, 50% mortality was observed after 95, 95, 70, 22 and 8 weeks, respectively. The incidence of tracheal hyperplasia, with and without atypias, tracheal squamous metaplasia and alveolar metaplasia with atypia increased with more frequent exposure to BCME. Exposure to BCME also produced bronchoalveolar metaplasia, squamous metaplasia with atypia and atypical alveolar epithelium. Evidence of subarachnoid haemorrhage was observed in 24% of the rats and 8% of the hamsters that received 30 exposures (6-h) to 4.7 mg/m^3 (1 ppm) (Drew et al., 1975).

7.2.3 CMME

In one study on the short-term toxicity of CMME, groups of 25 male Sprague-Dawley rats were exposed (by inhalation) to 3.3 or 33 mg/m^3 (1 or 10 ppm) for 30 days (duration and frequency of exposure not specified) (Drew et al., 1975). Exposure to 3.3 mg/m^3 resulted in 8% mortality, but no effect on body weight, within 30 days (data for unexposed controls were not presented). Regenerative hyperplasia and squamous metaplasia in bronchial epithelium were observed in rats killed 2 weeks after the last exposure. Exposure to 33 mg/m^3 resulted in 88% mortality within 30 days (data for controls not presented); marked (not quantified) weight decrease was observed with some recovery towards the end of exposure. Significant (not quantified) increases in lung/body weight ratios were observed in rats that died after exposure to CMME; regenerative hyperplasia of bronchial epithelium was also observed.

7.3 Long-term exposure/carcinogenicity

Studies on long-term exposure and carcinogenicity are given in Table 7.

7.3.1 BCEE

Studies on the toxicological effects produced by the long-term exposure of laboratory animals to BCEE have focused on its carcinogenic potential. However there are numerous deficiencies in all of these studies, compared to the more stringent protocols used in current carcinogenicity bioassays.

Innes et al. (1969) assessed the carcinogenicity of BCEE in mice following ingestion. Groups of 18 males and 18 females from two strains of hybrid F_1 mice [(C57BL/6 X C3H/Anf) and (C57BL/6 X AKR)] were administered by stomach tube approximately 100 mg/kg body weight BCEE (dissolved in distilled water) from the age of 7 to 28 days (although the amount of BCEE was not adjusted during this period to account for weight gain). Once the mice had reached four weeks of age, the BCEE was then provided in the diet at a concentration of 300 mg/kg diet until the mice were 18 months of age, after which time they were killed and necropsied. The time-weighted average dose for these studies was calculated to be 41.3 mg/kg body weight per day (US EPA, 1987a). There were multiple groups of controls consisting of animals of both strains and sexes. "Hepatomas" (representing benign hepatomas and malignant tumours), tumours of the pulmonary system (adenomas and adenocarcinomas) and lymphomas (Type-B reticulum cell sarcomas and leukaemias) were the predominant types of tumours observed in these animals. Compared to unexposed controls, the incidence of "hepatomas" was significantly ($p = 0.01$) increased in the treated (C57BL/6 X C3H/Anf)F_1 mice (in males, 8/79 versus 14/16; in females, 0/87 versus 4/18; in control and exposed animals, respectively) and in (C57BL/6 X AKR)F_1 males (5/90 versus 9/17 in control and exposed animals, respectively). However the incidence of pulmonary tumours or lymphomas was not significantly increased in the BCEE-exposed animals of either sex. Clinical, biochemical or haematological effects were not addressed in the published account of this study.

Table 7. Long-term exposure/carcinogenicity of BCEE, BCME and CMME

Protocol	Result	Comments	Reference
BCEE			
Groups of 18 males and 18 females from two strains of F_1 hybrid mice [(C57BL/6 x C3H/Anf) and (C57BL/6 x AKR)] were given (by gavage) approximately 100 mg/kg bw BCEE (dissolved in distilled water) from the age of 7 to 28 days. Once the mice had reached four weeks of age, BCEE was then provided in the diet at a concentration of 300 mg/kg until the mice were 18 months of age, after which time they were sacrificed and necropsied. The time-weighted-average dose for these studies was calculated to be 41.3 mg/kg bw/day (US EPA, 1987a). Controls consisted of multiple groups of animals of both strains and sexes.	The incidence of "hepatomas" (benign and malignant tumours), "pulmonary tumours" and lymphomas in the male control and BCEE-exposed (C57BL/6 x C3H/Anf)F_1 mice was 8/79 and 14/16 ($p = 0.01$), 5/79 and 0/16 and 5/79 and 2/16, respectively; the incidence of these tumours in the female control and (C57BL/6 x C3H/Anf)F_1 mice was 0/87 and 4/18 ($p = 0.01$), 3/87 and 0/18 and 4/87 and 0/18, respectively. The incidence of "hepatomas" (benign and malignant tumours), "pulmonary tumours" and lymphomas in the male control and BCEE-exposed (C57BL/6 x C3H/AKR)F, mice was 5/90 and 9/17 ($p = 0.01$), 10/90 and 2/17 and 1/90 and 0/17, respectively; the incidence of these tumours in the female control and BCEE-exposed mice was 1/82 and 0/18, 3/82 and 0/18 and 4/82 and 1/18, respectively.	Evidence of increased incidence of liver tumours. However, study limited owing to small number of BCEE-exposed animals, use of single dose level and inadequate reporting of tumour pathology. Amount of BCEE was not adjusted during initial period to account for weight gain.	Innes et al. (1969)

Table 7 (contd).

BCME (dissolved in a solution containing sodium chloride, Polysorbate 80, carboxymethylcellulose and benzyl alcohol) was administered by gavage to groups of 26 male and 26 female Charles River CD rats (at doses of 50 and 25 mg/kg bw) twice weekly for 78 weeks, after which time the animals were observed for a further 26-week period. The animals were necropsied and tissues examined histopathologically, either at the end of the study or when the animals became moribund. Groups of controls of each sex were administered vehicle alone.	The authors reported that BCEE was not carcinogenic in these male or female rats; however, there was a "substantial difference" between the mean weight of the females administered BCEE and corresponding controls, as well as "a reduction" in the mean weight of the high-dose male rats, compared to the controls. Notably, survival after 52 weeks on the study was only 65% for the high-dose females and 96-100% for the other BCEE-exposed animals. The survival for the control animals at 52 weeks was 97% and 99% for males and females, respectively.	No reported evidence of carcinogenicity. However, study limited due to small number of BCEE-exposed animals and relatively short exposure period. The size of control groups was not clearly stated, and quantitative data on tumour incidence were not presented.	Weisburger et al., 1981
Groups of 20 male A/St mice were injected intraperitoneally three times a week with 8, 20 or 40 mg/kg bw BCEE (dissolved in tricaprylin). Mice injected with 8 and 20 mg/kg bw BCEE received a total of 24 injections while animals administered 40 mg/kg bw BCEE only received 4 injections. Controls (n = 20) were injected with vehicle alone. The mice were sacrificed 24 weeks after the initial injection and the number of surface lung tumours (adenomas) determined.	The incidence of lung tumours (expressed as the number of lung tumours/mouse) in the BCEE-exposed animals (approximately 0.13 lung tumours/mouse) was lower than that observed in animals injected with vehicle alone (0.39 lung tumours/mouse).	No evidence of carcinogenicity in a limited study of carcinogenic potential.	Theiss et al., 1977

Table 7 (contd).

Protocol	Result	Comments	Reference
Thirty female ICR/Ha Swiss mice were injected subcutaneously with 1 mg BCEE (suspended in 0.05 ml mineral oil) once a week for life (median survival time of animals was 656 days). Controls (n = 30) were administered vehicle alone.	Compared to animals injected with vehicle alone, where no tumours developed at the site of injection, 2/30 animals injected with BCEE developed sarcomas at the site of injection.	Inconclusive evidence of carcinogenicity in a limited study involving small numbers of animals administered one dose-level with inadequate reporting of data on other effects.	van Duuren et al., 1972
Groups of 50 male and 50 female Sprague-Dawley rats were injected subcutaneously with either 4.36 µmole (0.62 mg) or 13.1 µmole(1.87 mg) BCEE (dissolved in 0.25 ml DMSO) once a week for two years. Controls were administered DMSO or left untreated.	The incidence of all malignant and benign tumours (e.g., mesenchymal, epithelial, sarcomas, carcinomas, unclassified) in the untreated controls, vehicle-treated controls, low- and high-dose males and females was 2/35, 4/35, 4/50 and 6/50, and 24/50, 24/50, 23/50 and 22/50, respectively. The median survival time of the untreated control, vehicle-treated control, low- and high-dose groups was 696, 605, 590 and 643 (for males), and 639, 668, 629 and 654 days (for females), respectively.	No evidence of carcinogenicity in a study involving limited exposure to BCEE with limited reporting of toxicological effects.	Norpoth et al., 1986
One milligram of BCEE (in 0.1 ml benzene) was applied to the skin of 20 female ICR/Ha Swiss mice. Two weeks later the secondary (promotion) treatment (2.5 µg phorbol myristate acetate (PMA) in 0.1 ml acetone, three times weekly) commenced and was maintained for the lifespan of the animals. Controls were administered PMA alone.	The incidence of skin papillomas at the site of application was 2/20 and 3/20 in the control and BCEE-initiated animals, respectively.	No evidence of skin tumour initiating activity by BCEE.	van Duuren et al., 1972

Table 7 (contd).

BCME			
Fifty A/Heston male mice were exposed (by inhalation) to 0 or 5 mg/m^3 BCME (industrial grade) for 6 h/day, 5 days/week for 82 days, after which exposure was terminated and survivors observed for a further 10 weeks. The animals were necropsied and lungs examined pathologically.	Exposure to BCME produced loss of body weight, respiratory distress and death. Survival of control and BCME-exposed mice was 90% and 28%, respectively. The incidence of pulmonary adenomas was 20/49 and 26/47 in control and BCME-exposed mice respectively (statistical significance not specified). The average number of pulmonary adenomas/animal among tumour-bearing mice was 2.2 for controls and 5.2 for the BCME-exposed group.	Limited evidence of increased pulmonary tumour burden in mice exposed to one concentration of BCME for a relatively short period.	Leong et al., 1971
Groups of 120 male Sprague-Dawley rats were exposed (by inhalation) to 0, 1, 10 or 100 ppb (0, 0.0047, 0.047, 0.47 mg/m^3) BCME 6 h/day, 5 days/week for 6 months, after which exposure was terminated and the rats observed for a further 22 months. Eight rats from each group were sacrificed after 6 months for haematological, cytological, cytogenetic and histopathological analyses.	Six-month survival was greater than 97% for control and BCME-exposed rats. Nineteen-month survival for animals exposed to 0, 0.0047 or 0.047 mg/m^3 was approximately 45%, while no animals exposed to 0.47 mg/m^3 survived. After 6 months there was no significant difference in the weights of the total body, liver, kidneys, brain, heart and testes; exposure to BCME produced no adverse haematological or cytogenetic effects. The incidence of "respiratory tract" tumours was 0/112, 0/113, 0/111 and 102/111, respectively; in the highest-concentration group, there were 96 esthesioneuroepitheliomas (significantly different [$p < 0.05$] than controls), four pulmonary adenomas, one carcinoma of the nasal passage and an esthesio-neuroepithelioma metastasis in the lung.	Increased incidence of respiratory tract tumours in rats exposed to BCME.	Leong et al., 1981

Table 7 (contd).

Protocol	Result	Comments	Reference
Groups of 20 to 50 male Sprague-Dawley rats were exposed (by inhalation) to 0 or 0.1 ppm (0 or 0.47 mg/m^3) BCME 6 h/day, 5 days/week for 2, 4, 8, 12, 16 and 20 weeks (10, 20, 40, 60, 80 or 100 exposures), after which the rats were necropsied and examined histopathologically.	Sixty exposures to BCME had no effect upon mortality, although the time at which 50% mortality was reached was reduced by approximately 24% in animals receiving 80 or 100 exposures to BCME. Animals surviving 30 weeks had "respiratory tract cancers" (26 in the nasal cavity and 13 in the lung). The incidence of "respiratory tract cancer" in animals surviving for more than 210 days and receiving 10, 20, 40, 60, 80 or 100 exposures of BCME was, 1/41 (2.4%), 3/46 (6.5%), 4/18 (22.2%), 4/18 (22.2%), 15/34 (44.1%) and 12/20 (60.0%), respectively (statistical significance not specified). No lung tumours were observed following up to 40 exposures to BCME. The incidence of squamous cell carcinomas of the lung was 2/20, 3/50 and 8/30, after 60, 80 and 100 exposures, respectively.	Increased incidence of respiratory tract tumours in rats exposed to BCME.	Kuschner et al., 1975
Groups of 20 female Sprague-Dawley rats were injected subcutaneously once per week with 3 mg BCME (dissolved in 0.1 ml mineral oil) or vehicle alone for approximately 300 days. (Because of the corrosive effects produced by BCME, after 114 days the dose was reduced to 1 mg, and injections performed only three times per month; however because of severe weight loss of the animals, the injections were terminated after 300 days).	The incidence of malignant tumours at the site of injection (i.e., fibrosarcoma) and in the breast (i.e., adenocarcinoma) in the control and BCME-exposed animals was 0/20 and 1/20, and 5/20 and 0/20, respectively.	Limited evidence of carcinogenicity in rats injected subcutaneously with BCME.	van Duuren et al., 1969

Table 7 (contd)

Fifty female and 50 male newborn ICR Swiss mice received a single subcutaneous injection of 12.5 µl/kg bw (16.6 mg/kg bw) BCME (dissolved in peanut oil) and the animals were observed for a period of six months, after which the survivors were necropsied and the number of lung tumours (adenomas, based on histopathological analysis) quantified. Controls (20 females and 30 males) received a single subcutaneous injection of vehicle alone.	Exposure to BCME had no effect upon growth or survival of the mice. The incidence of pulmonary adenomas in the control and BCME-exposed males was 2/30 and 25/50, respectively; 5/20 controls and 20/50 of the BCME-exposed females had lung adenomas.	Increased incidence of lung tumours in mice injected subcutaneously with BCME.	Gargus et al., 1969
Thirty male and 30 female XVIInc/Z mice received 32 subcutaneous injections of 0.3 mg BCME (dissolved in mineral oil) over a period of 42 weeks. Controls consisted of 30 XVIInc/Z male mice injected with vehicle alone.	Approximately 0%, 44% and 42% of the male controls and male and female BCME-exposed mice, respectively, had tumours (e.g., fibrosarcomas and squamous carcinomas) at the site of injection.	Evidence of carcinogenicity in mice injected subcutaneously with BCME.	Zajdela et al., 1980
Groups of 20 female ICR/Ha mice which received 2 mg BCME (applied dermally) or solvent (i.e., benzene) alone (controls) thrice weekly for 325 days.	The incidence of squamous cell carcinomas of the skin in the controls and BCME-exposed animals was 0/20 and 12/20, respectively.	Evidence of carcinogenicity in mice exposed dermally to BCME.	van Duuren et al., 1969
CMME			
Fifty A/Heston male mice were exposed (by inhalation) to 0 or 2 ppm (0 or 6.6 mg/m^3) (industrial grade) CMME for 6 h/day, 5 days/week for 101 days, after which time exposure was terminated and survivors observed for a further 7 weeks. The animals were necropsied and lungs examined histopathologically.	The incidence of pulmonary tumours in CMME-exposed mice (25/50) was not significantly (i.e., $p > 0.05$) different from that in the unexposed controls (20/49). The average number of pulmonary tumours/animal among tumour-bearing mice was 2.2 and 3.1 for the control and CMME-exposed group, respectively.	Suggestion of increased pulmonary tumour burden in mice exposed to one concentration of CMME for a relatively short period.	Leong et al., 1971

Table 7 (contd).

Protocol	Result	Comments	Reference
Seventy-four male Sprague-Dawley rats were exposed (by inhalation) to 0 or 1 ppm (0 or 3.3 mg/m^3) (industrial grade) CMME for 6 h/day, 5 days/week for their entire lifespan (up to 852 days). The rats were necropsied and tissues examined histopathologically.	Exposure to CMME had no effect upon mortality or body weight gain. The incidence of tracheal squamous metaplasia and bronchial hyperplasia was 3% and 10%, and 35% and 59%, in the control and BCME-exposed animals respectively (statistical significance not stated). Two respiratory tract cancers (lung squamous cell carcinoma and an esthesioneuroepithelioma of olfactory epithelium) were found in animals exposed to CMME (but presumably not in unexposed controls).	No clear evidence of carcinogenicity in a limited study.	Laskin et al., 1975
Ninety male Syrian hamsters were exposed (by inhalation) to 1 ppm (3.3 mg/m^3) (industrial grade) CMME for 6 h/day, 5 days/week for their entire lifespan (up to 852 days). The hamsters were necropsied and tissues examined histopathologically. Eighty-eight unexposed animals served as controls.	Exposure to CMME had no effect upon mortality or body weight gain. The incidence of tracheal squamous metaplasia was 0% and 2%, and incidence of bronchial hyperplasia was 5% and 8%, in the control and BCME-exposed animals respectively (statistical significance not stated). One lung adenocarcinoma and a tracheal squamous papilloma were observed in two animals exposed to CMME.	No clear evidence of carcinogenicity in a limited study.	Laskin et al., 1975
Groups of 20 female Sprague-Dawley rats were injected subcutaneously once per week with 3 mg laboratory purified CMME (dissolved in 0.1 ml mineral oil) or vehicle alone for approximately 300 days. Because of moderate corrosive effects, the injections were terminated after this time.	The incidence of malignant tumours at the site of injection (i.e., fibrosarcoma) and in the breast (adenocarcinoma) in the control and CMME-exposed animals was 0/20 and 1/20, and 1/20 and 0/20, respectively.	No evidence of carcinogenicity in rats injected subcutaneously with laboratory purified CMME.	van Duuren et al., 1969
Thirty female ICR/Ha Swiss mice were injected (subcutaneously) with 0.3 mg of laboratory purified CMME (suspended in 0.05 ml mineral oil) once a week for life. Controls (n = 30) received vehicle alone.	Compared to the animals injected with vehicle alone, where no tumours developed at the site of injection, 10/30 animals injected with CMME developed sarcomas at the site of injection.	Evidence of carcinogenicity in mice injected subcutaneously with CMME.	van Duuren et al., 1972

Table 7 (contd).

Forty-eight female and 51 male newborn ICR Swiss mice received a single subcutaneous injection of 125 µl/kg bw (132.5 mg/kg bw) CMME dissolved in peanut oil; the animals were observed for a period of six months, after which time the survivors were necropsied and the number of lung tumours (adenomas, based on histopathological analysis) quantified. Controls (20 females and 30 males) received a single subcutaneous injection of vehicle alone.	The numbers of female mice with lung adenomas in the control (vehicle) and CMME-exposed groups were 5/20 and 8/48, respectively. The numbers of male mice with lung adenomas in the control (vehicle) and CMME-exposed groups were 2/30 and 9/51, respectively.	No increase in the incidence of lung tumours in mice injected subcutaneously with CMME.	Gargus et al., 1969
Groups of 20 female ICR/Ha mice received 2 mg CMME (applied dermally) or solvent (i.e., benzene) alone (controls) thrice weekly for 325 days.	No squamous cell carcinomas of the skin were observed in either the control or CMME-exposed animals.	No evidence of carcinogenicity in mice exposed dermally to CMME.	van Duuren et al., 1969

Weisburger et al. (1981) reported that the oral administration of BCEE to rats had no significant carcinogenic effect. BCEE (dissolved in a solution containing sodium chloride, Polysorbate 80, carboxymethylcellulose and benzyl alcohol) was administered (by gavage) to groups of 26 male and 26 female Charles River CD rats (at doses of 50 and 25 mg/kg body weight) twice weekly for 78 weeks, after which time the animals were observed for a further 26-week period. Control groups of each sex (the size of which was not clearly stated) were administered vehicle alone. The authors reported (although no data on tumour incidence were presented) that BCEE was not carcinogenic in these male or female rats. However, the authors indicated (but results were not quantified) that there was a "substantial difference" between the mean body weight of the females administered both doses of BCEE and that of the corresponding controls, as well as "a reduction" in the mean body weight of the high-dose male rats, compared to controls. Notably, survival after 52 weeks on the study was only 65% for the high-dose females and 96 to 100% for the other BCEE-exposed animals. The survival for the control animals at 52 weeks was 97 and 99% for males and females, respectively. Clinical, biochemical or haematological effects were not addressed in the published account of this study.

Theiss et al. (1977) assessed the potential of BCEE to produce lung tumours in groups of 20 male A/St mice injected intraperitoneally three times per week with 8, 20 or 40 mg/kg body weight BCEE (dissolved in tricaprylin). Mice injected with 8 and 20 mg/kg received a total of 24 injections while animals administered 40 mg/kg only received 4 injections. Controls (n = 20) were injected with vehicle (tricaprylin) alone. The mice were killed 24 weeks after the initial injection and the number of surface lung tumours (adenomas) determined. The incidence of lung tumours (expressed as the number of lung tumours/mouse) in the BCEE-exposed animals was less than that observed in animals injected with vehicle alone.

The potential of BCEE to induce tumours was also investigated in a study in which groups of 30 female ICR/Ha Swiss mice were injected subcutaneously with 1 mg BCEE (suspended in 0.05 ml mineral oil) once per week for life (the median survival time of animals was 656 days) (van Duuren et al., 1972). Compared to animals injected with vehicle alone, where no tumours developed at the site of injection, 2/30 animals injected with BCEE developed sarcomas at the site of injection. Norpoth et al. (1986) also examined the carcino-

genicity of BCEE in a study in which groups of 50 male and 50 female Sprague-Dawley rats were injected subcutaneously with either 4.36 µmole (0.62 mg) or 13.1 µmole BCEE (1.87 mg) (dissolved in 0.25 ml DMSO) once per week over a 2-year period. Controls were injected with DMSO (alone) or left untreated. The incidence of all malignant and benign tumours (e.g., mesenchymal, epithelial, sarcomas, carcinomas and unclassified) in the BCEE-exposed animals was not significantly different from that in the controls. The median survival time of the untreated control, vehicle-treated control, and low- and high-dose groups was 696, 605, 590 and 643 (for males), and 639, 668, 629 and 654 days (for females), respectively.

Van Duuren et al. (1972) assessed the skin-tumour-initiating potential of BCEE. One milligram BCEE (in 0.1 ml benzene) was applied to the skin of 20 female ICR/Ha Swiss mice. Two weeks later the secondary (promotion) treatment (2.5 µg PMA in 0.1 ml acetone, three times weekly) commenced and was maintained for the life span of the animals. Compared to controls (administered PMA alone) where 2/20 animals developed papillomas, 3/20 of the BCEE-initiated animals developed papillomas at the site of application.

7.3.2 BCME

Studies on the toxicological effects produced by long-term exposure (by inhalation) to BCME have been restricted primarily to limited carcinogenesis bioassays. The exposure (by inhalation) of male A/Heston mice to 5 mg/m^3 for 6 h/day, 5 days/week for a period of 82 days, followed by a 10-week observation period, produced a marked reduction in survival (90 and 28% in control and BCME-exposed mice, respectively) and an increase in the number of pulmonary adenomas (20/49 and 26/47 in control and BCME-exposed mice, respectively), although the statistical significance was not specified (Leong et al., 1971). The average number of pulmonary adenomas per animal among tumour-bearing mice was 2.2 for controls and 5.2 for the BCME-exposed group.

The exposure (by inhalation) of groups of 144 to 157 male ICR/Ha mice to concentrations of BCME from 0.0047 to 0.47 mg/m^3 (1 to 100 ppb) for 6 h/day, 5 days/week for a period of 6 months, followed by an 18-month observation period, produced a reduction in survival (55, 35, 25 and 18% in mice exposed to 0, 0.0047, 0.047 or 0.47 mg/m^3 [0, 1, 10 or 100 ppb], respectively), although no difference

in survival (> 90%) was observed between the control and BCME-exposed groups after 24 months (Leong et al., 1981). All mice developed an ascending urinary tract infection. After 6 months, the incidence of pulmonary adenomas in surviving mice exposed to 0, 0.0047, 0.047 and 0.47 mg/m^3 was 9/86, 5/45, 3/37 and 8/27 ($p < 0.05$), respectively. Exposure to these concentrations of BCME had no adverse effect on body weight and produced no nasal or eye irritation.

Groups of 120 male Sprague-Dawley rats were exposed (by inhalation) to BCME concentrations of 0, 0.0047, 0.047 or 0.47 mg/m^3 (0, 1, 10 or 100 ppb) 6 h/day, 5 days/week for 6 months, after which time exposure was terminated and the animals observed for a further 22 months (Leong et al., 1981). Although 6-month survival was greater than 97% for control and BCME-exposed rats, 19-month survival for animals exposed to 0, 0.0047 or 0.047 mg/m^3 was approximately 45%, while none of the animals exposed to 0.47 mg/m^3 survived. After 6 months there was no significant difference in the weights of the total body, liver, kidneys, brain, heart and testes, and no adverse haematological or cytogenetic effects were observed. The incidence of "respiratory tract" tumours in animals exposed to 0, 0.0047, 0.047 or 0.47 mg/m^3 was 0/112, 0/113, 0/111 and 102/111, respectively; in the highest-concentration group, there were 96 esthesioneuroepitheliomas (significantly different [$p < 0.05$] from controls), 1 carcinoma of the nasal passage and an esthesioneuroepithelioma metastasis in the lung, and 4 pulmonary adenomas.

Kuschner et al. (1975) exposed (by inhalation) groups of 20 to 50 male Sprague-Dawley rats to 0.47 mg BCME/m^3 (0.1 ppm) for 6 h/day, 5 days/week for 2, 4, 8, 12, 16 or 20 weeks (10, 20, 40, 60, 80 or 100 exposures). Sixty exposures to BCME had no effect on mortality, although the time at which 50% mortality was reached was reduced by approximately 24% in animals receiving 80 or 100 exposures to BCME. The incidence of "respiratory tract cancer" in animals surviving for more than 210 days and receiving 10, 20, 40, 60, 80 or 100 exposures of BCME was 1/41 (2.4%), 3/46 (6.5%), 4/18 (22.2%), 4/18 (22.2%), 15/34 (44.1%) and 12/20 (60.0%), respectively. No lung tumours were observed following up to 40 exposures to BCME; however, the incidence of squamous cell carcinomas of the lung was 2/20, 3/50 and 8/30 after 60, 80 and 100 exposures, respectively.

The carcinogenicity of BCME has also been examined following subcutaneous injection in rats and mice. Groups of 20 female Sprague-Dawley rats (weighing between 120 and 125 g) were injected subcutaneously once per week with 3 mg BCME (dissolved in 0.1 ml mineral oil) or vehicle alone for approximately 300 days (van Duuren et al., 1969). Because of the corrosive effects produced by BCME, after 114 days the dose was reduced to 1 mg, and injections were performed only three times per month; however, because of severe weight loss of the animals, the injections were terminated after 300 days. In the controls administered vehicle alone, no tumours were observed at the site of injection; however a fibroadenoma and an adenocarcinoma (of the breast) were observed elsewhere. In the group of animals administered BCME, two fibromas and five fibrosarcomas were observed at the site of injection, and one fibroadenoma (of the breast) was found elsewhere (van Duuren et al., 1969).

The potential of BCME to increase the incidence of spontaneous lung tumours in mice was assessed by Gargus et al. (1969). A group of 50 female and 50 male newborn ICR Swiss mice received a single subcutaneous injection of 12.5 µl/kg body weight (16.6 mg/kg body weight) BCME (dissolved in peanut oil) and the animals were observed for a period of 6 months, after which time the survivors were necropsied and the number of lung tumours (adenomas, based on histopathological analysis) quantified. A group of control animals (20 females and 30 males) received a single subcutaneous injection of vehicle alone. The numbers of female mice with pulmonary adenomas in the control (vehicle) and BCME-exposed groups were 5/20 and 20/50, respectively. The numbers of male mice with pulmonary adenomas in the control (vehicle) and BCME-exposed groups were 2/30 and 25/50, respectively. The administration of BCME had no effect upon the growth or survival of the mice.

Zajdela et al. (1980) assessed the carcinogenicity of BCME following repeated subcutaneous injection in male and female XVIInc/Z mice. Groups of 30 males and 30 females received 32 injections of 0.3 mg BCME (dissolved in mineral oil) over a period of 42 weeks. The control group consisted of 30 male mice injected with vehicle alone. After 110 days (when the first sarcoma was observed), survival in the control and male and female BCME-exposed groups was 100, 90 and 80%, respectively. The number of animals with tumours (mainly fibrosarcomas) at the site of injection was 0/30, 12/27 and 10/24, respectively ($p < 0.0001$). The incidence of tumours at

locations other than the site of injection was the same in the control and BCME-exposed groups. The incidence of pulmonary adenomas in the control and BCME-exposed groups was 2/30 and 7/30, respectively; this difference was not statistically significant (Zajdela et al., 1980).

The incidence of squamous cell carcinomas of the skin in female ICR/Ha mice that received 2 mg BCME (applied dermally) or solvent (i.e., benzene) alone thrice weekly for 325 days was 12/20 and 0/20, respectively (van Duuren et al., 1969). A two-stage skin tumour carcinogenesis bioassay was conducted in which the primary treatment involved the application of 1 mg BCME (dissolved in 80 µl benzene) to the dorsal skin of 28 male XVIInc/Z mice and the secondary treatment, commencing 14 days later, involved the application three times per week of 2 µg PMA (dissolved in acetone) to the dorsal skin of these animals for 42 weeks. The incidence of mice with squamous cell carcinomas was 0/28 and 3/28 in unexposed and BCME-initiated animals, respectively (Zajdela et al., 1980).

7.3.3 CMME

Studies on the toxicological effects produced by long-term inhalational exposure to CMME have been restricted primarily to limited carcinogenesis bioassays in mice, rats and hamsters.

A study was conducted in which 50 A/Heston male mice were exposed (by inhalation) to 0 or 6.6 mg CMME/m^3 (0 or 2 ppm) for 6 h/day, 5 days/week for 101 days, followed by an observation period of 7 weeks. Although there was no significant effect upon the incidence of pulmonary tumours, the average number of pulmonary tumours per animal among tumour-bearing mice was 3.1 and 2.2 for the CMME-exposed and control groups, respectively (Leong et al., 1971).

In a study in which 74 male Sprague-Dawley rats were exposed (by inhalation) to 0 or 3.3 mg CMME/m^3 (0 or 1 ppm) for 6 h/day, 5 days/week for their entire life span (up to 852 days), the incidence of tracheal squamous metaplasia and bronchial hyperplasia was 3 and 10%, and 35 and 59%, in the control and CMME-exposed animals, respectively. Two respiratory tract cancers (lung squamous cell carcinoma and an esthesioneuroepithelioma of the olfactory epithelium) were found in animals exposed to CMME (but presumably

not in unexposed controls) (Laskin et al., 1975). Exposure to CMME had no effect upon mortality or body weight gain.

The exposure (6 h/day, 5 days/week) of 90 male hamsters to 3.3 mg CMME/m^3 (1 ppm) for virtually their entire lives increased the incidence of tracheal metaplasia and bronchial hyperplasia compared to 88 unexposed controls. The incidence of tracheal squamous metaplasia was 0 and 2%, and the incidence of bronchial hyperplasia was 5 and 8%, in the control and CMME-exposed animals, respectively (statistical significance not stated). One lung adenocarcinoma and a tracheal squamous papilloma were observed in two animals exposed to CMME; presumably none was found in unexposed controls (Laskin et al., 1975).

The carcinogenicity of purified CMME has also been examined following subcutaneous injection of this substance in rats and mice. Groups of 20 female Sprague-Dawley rats (weighing between 120 and 125 g) were injected once per week with 3 mg (laboratory purified) CMME (dissolved in 0.1 ml mineral oil) or vehicle alone for approximately 300 days; because of moderate corrosive effects, the injections were terminated after this time (van Duuren et al., 1969). In controls administered the vehicle alone, no tumours were observed at the site of injection; however a fibroadenoma and an adenocarcinoma (of the breast) were found elsewhere. In animals administered (laboratory purified) CMME, a fibrosarcoma (at the site of injection) in one animal was the only tumour described.

Van Duuren et al. (1972) subcutaneously injected (laboratory purified) CMME (dissolved in 0.05 ml mineral oil, 300 µg/animal, once per week) to a group of 30 female ICR/Ha Swiss mice for their entire lives, and a similarly sized group of controls received vehicle alone. Median survival time was 643 days and 496 days, and the numbers of mice with sarcomas at the site of injection were 0 and 10 in the control and purified CMME-exposed groups, respectively.

The potential of CMME to increase the incidence of spontaneous lung tumours in mice was assessed by Gargus et al. (1969). A group of 48 female and 51 male newborn ICR Swiss mice received a single subcutaneous injection of 125 µl/kg body weight (132.5 mg/kg body weight) CMME dissolved in peanut oil, and subsequently observed for a period of 6 months, after which time the survivors were necropsied and the number of lung tumours (adenomas, based on histopatho-

logical analysis) quantified. Controls (20 females and 30 males) received a single subcutaneous injection of vehicle alone. The numbers of female mice with adenomas in the control (vehicle) and CMME-exposed groups were 5/20 and 8/48, respectively. The numbers of male mice with adenomas in the control (vehicle) and CMME-exposed groups were 2/30 and 9/51, respectively.

Purified CMME was not carcinogenic when applied thrice weekly (2 mg/animal for 325 days) to the skin of female ICR/Ha Swiss mice (van Duuren et al., 1969).

7.4 Mutagenicity and related end-points

7.4.1 BCEE

A small number of investigations have been performed to assess the genotoxic potential of BCEE. The *in vitro* studies have yielded somewhat equivocal results. However it should be noted that, in general, detailed descriptions of the laboratory conditions were not provided, making interpretation of the findings difficult. The mutagenic activity of BCEE in bacteria has been examined in a number of strains, in the presence and absence of metabolic activating systems. Simmon et al. (1977a,b) reported BCEE (vapour) to be strongly mutagenic in *Salmonella typhimurium* TA100 in the absence of a metabolic activating system, with the number of revertants increasing with the duration of exposure. Simmon et al. (1977a,b) also reported that in suspension assays BCEE was mutagenic in *S. typhimurium* strains TA1535 and TA100, as well as in *Saccharomyces cerevisiae* D3. Norpoth et al. (1986) reported "weak" mutagenic activity in *S. typhimurium* TA100 (in the presence of a metabolic activating system) when BCEE (up to 40 µg/dish) was added directly to culture plates. Mortelmans et al. (1986) reported BCEE (up to 10 mg/plate) had "weak" mutagenic activity in a number of *S. typhimurium* strains (TA100, TA1535, TA1537, TA98), either in the presence or absence of a metabolic activating system. Shirasu et al. (1975) reported that BCEE was mutagenic in various strains of *Escherichia coli*, *Bacillus subtilis* and *S. typhimurium*, although experimental details were not provided in the published account of this study. In contrast, Quinto & Radman (1987) reported that BCEE was not mutagenic in the MT 103, MT 119 and MT 126 tester strains of *E. coli*, although complete experimental details were not provided in this published account.

Foureman et al. (1994) considered BCEE mutagenic, based upon the results of a sex-linked recessive lethal assay in which male *Drosophila* were injected with the compound. However the response was negative when the males were fed BCEE. To examine the genotoxicity of BCEE in mammals, Jorgenson et al. (1977) performed heritable translocation assays in mice administered BCEE orally. These authors concluded that BCEE did not promote heritable translocations. However, few experimental details were provided in this published account. Gwinner et al. (1983) did not detect radioactivity bound to liver DNA or RNA isolated from male Sprague-Dawley rats exposed (by inhalation) to [1-^{14}C]-BCEE (amount not clearly specified) for 18 h.

7.4.2 BCME

The genotoxicity of BCME has been examined in a variety of limited and generally poorly documented studies. BCME (at a maximum concentration of 20 µg/plate) was mutagenic in the presence of an exogenous metabolic activating system in *S. typhimurium* strain TA100, based on a 3-fold increase in the frequency of revertants above control levels. However, similar results were not observed in *S. typhimurium* strains TA1535, TA1538 and TA98 (Anderson & Styles, 1978). BCME was also reported to be mutagenic in various strains of *E. coli* and *S. typhimurium*, but experimental details and results were not provided (Mukai & Hawryluk, 1973).

BCME (at concentrations as low as 0.16 µg/ml) was reported to increase DNA repair (unscheduled DNA synthesis) in human skin fibroblasts, although quantitative results were not provided (Agrelo & Severin, 1981). In *in vitro* assays with BHK-21 and human lung WI-38 cells, concentrations of BCME between 0.008 and 25 mg/ml (in the presence of an exogenous metabolic activating system) increased the frequency of transformed cells approximately 6.6- and 11-fold, respectively (Styles, 1978). The exposure (*in vitro*) of human neonatal foreskin fibroblasts to concentrations of BCME between 0.1 and 8 µg/ml produced a 3- to 14-fold increase in the frequency of anchorage-independent cells (Kurian et al., 1990).

BCME was reported to directly alkylate DNA (at guanine and adenine residues) when the two substances were incubated together in an *in vitro* assay (Goldschmidt et al., 1975). It was reported to damage RNA within bacteriophage R17 (Shooter, 1975).

7.4.3 CMME

CMME was reported to be mutagenic in various strains of *E. coli* and *S. typhimurium*. However, experimental details or results were not provided in this published account (Mukai & Hawryluk, 1973). In the presence of an exogenous metabolic activating system, CMME (1 and 10 mmol/litre) increased unscheduled DNA synthesis in human lymphocytes approximately 30 and 100%, respectively (Perocco et al., 1983).

7.5 Other toxicity studies

The exposure (by inhalation) of male Sprague-Dawley rats to 0.47 mg BCME/m^3 (100 ppb) for 6 h/day, 5 days/week, for a period of six months had no observable effect upon the nervous or reproductive systems, based on gross and microscopic analysis (Leong et al., 1981). No other relevant information regarding the reproductive, developmental, immunological or neurological toxicity of BCEE, BCME or CMME was identified.

8. EFFECTS ON HUMANS

8.1 General population exposure

3.1.1 *Human exposure studies*

Schrenk et al. (1933) reported that the "brief" (time not stated) exposure of men to concentrations of BCEE ranging from 3218 to 5850 mg/m^3 (550 to 1000 ppm) caused irritation to the eyes (lacrimation) and nasal passages, such that exposure was considered intolerable. Inhalation of BCEE also caused nausea. The intensity of such effects gradually declined as the concentration of BCEE was lowered from 1521 mg/m^3 (260 ppm) to 585 mg/m^3 (100 ppm); exposure to 205 mg/m^3 (35 ppm) was reported to be "only slightly offensive and practically free from irritation". No clinical studies on BCME and CMME were identified.

8.2 Occupational exposure

8.2.1 *Case reports*

The death of a worker in a fulling mill (textile factory) was attributed to the inhalation of BCEE, but details were not provided (Elkins, 1959). One anecdotal report on the occurrence of dermatitis in textile workers exposed to resins containing BCEE was identified (Kirwin & Sandmeyer, 1981).

Sakabe (1973) reported that 5 out of 32 Japanese males employed in dyestuffs factories who had been exposed to BCME died of "lung cancer" (between 1963 and 1969). Small (oat) cell carcinoma was identified in one of the cases. Quantitative information on exposure was not provided in this published account and these individuals were exposed to a number of chemical substances in addition to BCME (smoking habits could not be confirmed). However, because a large proportion (approximately 16%) of the individuals exposed to BCME developed lung cancer, and those exposed to chemicals other than BCME did not, the authors attributed the occurrence of these pulmonary tumours to exposure to BCME.

Reznick et al. (1977) reported the case of a 45-year-old male chemist who had died of a slightly differentiated adenocarcinoma of

the lung. Twelve years earlier this individual had been exposed to BCME and CMME over a period of two years. Although quantitative information on exposure was not presented (and the individual was also exposed to vinyl chloride), the lung adenocarcinoma was attributed to his exposure to BCME and CMME.

Roe (1985) reported the case of three males (between 35 and 40 years of age) who had died of lung cancer (small (oat) cell and squamous cell carcinomas) after having been occupationally exposed to BCME. Although quantitative or qualitative information on exposure was not provided and the individuals had been smokers, the relatively young age at which these individuals died was attributed to their exposure to BCME.

8.2.2 *Epidemiological studies*

Data on the effects of long-term exposure to BCEE on human health were not identified. In a number of epidemiological studies, mortality and morbidity due to cancer in workers occupationally exposed to BCME and CMME have been examined. Lemen et al. (1976) examined the incidence of lung cancer in a group of workers employed at a chemical plant in California, USA, where BCME was used in the production of ion-exchange resins. The authors identified 136 individuals who had been employed for at least 5 years between 1955 and 1972. The number of cases of lung cancer (5) was significantly greater ($p < 0.01$) than the number expected (0.54), based on age-respiratory cancer-specific incidence rates for white males in the state of Connecticut in 1960-1962. Notably, 80% of the tumours were small cell undifferentiated cancers. Importantly, lung tumours in persons occupationally exposed to BCME and CMME are predominantly small (oat) cell carcinomas (Weiss, 1976; Pasternack et al., 1977). The occurrence of this type of lung cancer in these individuals is quite distinct from that caused by tobacco, one of the potential confounders in such studies, where the lung tumours are predominantly squamous cell carcinomas (Weiss, 1976; Pasternack et al., 1977). Individuals (80% were smokers) with cancer averaged 47 years of age, and the average latency period was approximately 10 years. Quantitative or qualitative information on exposure was not provided in this published account. The incidence of metaplastic and atypical cells in the sputum of workers exposed to BCME was greater than in controls (uranium miners), based on cytological analysis.

Nishimura et al. (1990) examined the incidence of lung cancer in a group of Japanese workers employed in two dyestuff factories where BCME was used. The study group consisted of 35 males employed at these plants between 1955 and 1970. The number of cases (13) of lung cancer (11 cases were in smokers) was significantly ($p < 0.001$) higher than the number expected (0.62). Tumours from eight of the individuals were examined histopathologically; four were diagnosed as small cell undifferentiated carcinomas, two were adenocarcinomas and one a large cell carcinoma; in one individual, both a small cell carcinoma and an adenocarcinoma were found. The average age at which individuals with lung cancer died was 46 years, and the latency period was approximately 13.5 years. The average duration of exposure to BCME was approximately 7.2 years, although no other quantitative or qualitative information on exposure was provided.

Since technical grade CMME contains between 1 and 8% BCME (Travenius, 1982), in epidemiological studies in which mortality and the incidence of cancer in workers exposed to CMME were examined, the effects may have been due (at least in part) to BCME. Weiss (1976) reported the results of a 10-year prospective study (1963-1973) in which 125 male employees of a chemical plant in the USA who had been occupationally exposed to CMME(BCME), were examined with respect to the "incidence" of pulmonary cancer. No quantitative or qualitative information on exposure was provided. However, an exposure index (low, medium and high) based on type and duration of job associated with potential exposure to CMME(BCME) was developed. Eleven cases of lung cancer were reported in 49 individuals with medium or high exposure to CMME(BCME); no "incidence" of lung cancer was reported in 76 workers with no or low exposure to CMME(BCME). The number of deaths (16) during this period was 2.7-fold greater than the number expected (5.9), based on a comparison with death rates for white males in the USA. All of the excess deaths (10) were attributable to lung cancer, 100% of which were small cell carcinomas that developed in individuals less than 55 years of age. The latency period for these cancers ranged from 10 to 24 years. Among individuals exposed to CMME(BCME) the "incidence" of pulmonary tumours was inversely related to their use of tobacco (Weiss, 1980). In a follow-up study of these workers, the number of deaths (13) due to lung cancer (which were attributable to either moderate or heavy exposure to CMME[BCME]) was 19.5-fold greater than the number (0.66) expected, based on lung cancer mortality rates in the surrounding municipality (Philadelphia) (Weiss,

1982). The standardized mortality ratio for deaths due to lung cancer which peaked 15 to 19 years from the onset of exposure, declined during the subsequent 20- to 29-year period. Subsequently, Weiss (1989) indicated that over-representation of workers with moderate to high exposure within the cohort led to some over-estimation of the risk of lung cancer. However, even when such selection bias was accounted for, an increased risk of lung cancer remained associated with exposure to CMME(BCME).

Maher & DeFonso (1987) examined mortality in a group of workers exposed to CMME(BCME). [This report represented an update and extension of a previous investigation on death due to lung cancer performed by these authors (DeFonso & Kelton, 1976)]. The study population consisted of a group of 737 "exposed" and 2120 "unexposed" white male workers (who comprised 97% of the labour force) employed for any length of time at a chemical plant in the USA between 1948 and 1971. The vital status of 90% of the group was determined up to 1982. No quantitative information on exposure was provided, but an exposure rating (from 0-6) was developed based on the type of work, proximity of exposure to CMME(BCME) and production methods. Cumulative exposure was calculated based on the exposure rating and duration of employment at a particular job. The expected number of deaths for each type of cancer was calculated using cause-specific death rates for white males residing in the surrounding municipality (Philadelphia). Information on smoking habits was incomplete but "no marked differences between smoking habits of exposed and unexposed workers were noted" (Maher & DeFonso, 1987). Among the workers exposed to CMME(BCME), the number of deaths (32) due to cancer of the "respiratory tract" was significantly ($P < 0.01$) higher than the number expected (11.5). For individuals not exposed to CMME(BCME), the number of deaths (25) due to respiratory tract cancer was similar to those expected (23.8). In the CMME(BCME)-exposed group, the number of deaths due to cancer of the digestive, genito-urinary, haematopoietic, lymphatic and central nervous systems was not significantly greater than expected. The greatest increase in deaths due to cancer of the respiratory tract occurred approximately 10 to 20 years after the first exposure to CMME(BCME). Among workers exposed to CMME(BCME), the ratio of observed/expected number of deaths due to lung cancer was lower between 1975 and 1981 than for the period between 1960 and 1974, this being attributed to a reduction in the level of exposure to CMME(BCME) in 1971 as a result of the implementation of stringent

engineering controls on the use of this substance (Maher & DeFonso, 1987).

Collingwood et al. (1987) assessed mortality due to respiratory cancer in a group of workers employed at seven industrial facilities in which CMME(BCME) was produced or utilized. This report represented a follow-up and extension of a previous study by two of these authors (Pasternack et al., 1977). The study group (97% white, 96% male) comprised 2460 CMME(BCME)-exposed and 3692 unexposed workers employed between 1948 and 1980. Only limited information on smoking habits was available. No quantitative or qualitative information on exposure was provided, but an exposure index (taking into account type of job, frequency of work and potential exposure to CMME(BCME)) was developed. Cumulative exposure was calculated on the basis of the exposure index and duration of employment at a particular job. The number of expected deaths was calculated from death rates in the USA specific for age, cause, sex, race and calendar year. Among workers exposed to CMME(BCME), the standardized mortality ratio for death due to respiratory cancer was significantly increased (SMR = 3.01; 95% CI = 2.24-3.98); this was attributed to excess deaths at two companies (where the ratio of observed to expected deaths due to lung cancer among exposed workers was 32/7.4 and 9/1.5). In the entire study group, there were 90 deaths due to respiratory cancer, 52 and 38 in the CMME(BCME)-exposed and unexposed groups, respectively. In those cases with verifiable histology, 12/32 (38%) cases in the exposed group had small (oat) cell carcinomas while 6/20 (30%) cases in the unexposed group had adenocarcinomas. The relative risk of death due to lung cancer was found to be related to total cumulative exposure based on a regression model.

Gowers et al. (1993) examined the incidence of lung cancer among 1203 males employed at an ion-exchange resin manufacturing plant in France between 1958 and 1986; of the total study cohort, 258 were exposed to technical grade CMME (i.e., containing BCME), the remainder were considered to be unexposed. Data on the incidence of lung cancer among these workers was obtained from a local registry; the expected number of lung cancer cases was calculated, based upon incidence rates for males provided by a registry serving an area some 250 km distant from the plant (i.e., external population). There were 8 (one small cell carcinoma) and 11 (10 small cell carcinomas) cases of lung cancer among the unexposed and CMME(BCME)-exposed

workers, respectively. Reductions in occupational exposure to CMME(BCME) were instituted in 1972 and 1984. Potential exposure to CMME(BCME) was rated according to employment experience; cumulative exposure was based upon the job exposure rating and length of employment at a particular job. Based upon limited monitoring studies, conducted between 1979 and 1984, the average level of BCME in the plant ranged from 3.3 to 20.7 $\mu g/m^3$ (0.7 to 4.4 ppb); after 1984 the average level in the plant was reportedly < 2.4 $\mu g/m^3$ (0.5 ppb). The rate ratio for lung cancer among the CMME(BCME)-exposed workers, compared to the rate for the unexposed workers or external population, was 5.5 (95% CI = 2.0-12.3) and 7.6 (95% CI = 4.3-13.5), respectively. The rate ratio for lung cancer among the unexposed workers, compared to the rate for the external population, was 1.6 (95% CI = 0.8-3.12). Linear regression analysis revealed an increased rate of lung cancer with increasing cumulative exposure. The ratio of observed/expected cases of lung cancer for the CMME(BCME)-exposed workers (based upon comparison with the external population) generally increased with increasing cumulative exposure. The mean age at diagnosis for the unexposed and CMME(BCME)-exposed workers was 56.5 and 46 years, respectively; the mean induction period for lung cancer among the CMME(BCME)-exposed workers was approximately 13 years.

Excess deaths due to lung cancer have also been reported for Chinese (Xue et al., 1988) chemical workers exposed to "chloromethylether"; latency as low as 2 years was reported. In a follow-up study of one of the cohorts examined by Xue et al. (1988), exposed to both CMME and BCME, there was an increased rate of lung markings similar to asbestosis as well as evidence of reduced pulmonary function (Xue et al., 1996). The magnitude of these changes was higher among workers exposed before 1975 to CMME levels of 0.096 $\mu g/m^3$ than to those exposed after 1981 to approximately 0.013 $\mu g/m^3$. Sram et al. (1983, 1985) reported the increased frequency of chromosomal aberrations in peripheral lymphocytes of workers (1.64 to 3.75% in controls, and 5.06 to 5.49% in subjects employed from 1-10 years) exposed in the production of ion exchange resins to levels of 0.01 to 0.1 μg BCME/m^3 and 20 to > 200 μg CMME/m^3.

No relevant studies are available concerning the neurological, immunological, developmental or reproductive effects of BCME or CMME in humans.

9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

For aquatic species, the 7-day LC_{50} for exposure of the guppy (*Poecilia reticulata*) to BCEE was 56.9 mg/litre (Konemann, 1981). Buccafusco et al. (1981) reported a 96-h LC_{50} of 600 mg BCEE/litre for the bluegill sunfish (*Lepomis macrochirus*). LeBlanc (1980) reported a 48-h LC_{50} of 240 mg BCEE/litre for *Daphnia magna*. In all three of the above studies, organisms were exposed to nominal concentrations of BCEE in closed containers, under static or static-with-renewal conditions.

Anaerobic activity was not inhibited when microorganisms were exposed to BCEE at concentrations up to 100 mg/litre in a nutrient buffer solution (Johnson & Young, 1983). Cho et al. (1989) reported an LC_{50} and an LC_{10} of 2160 and 600 µg BCEE/litre, respectively, for microbes indigenous to industrial waste stabilization ponds and that required a supply of organic material for food.

No relevant data are available to assess toxicity of BCEE to species of wildlife, and no studies have been identified in which the toxicity of either BCME or CMME to aquatic or terrestrial organisms was investigated.

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation of human health risks

10.1.1 BCEE

The lack of available information on concentrations of BCEE in several environmental media to which humans are exposed precludes quantitative estimation of the total daily intake of this substance from the general environment. Based upon extremely limited data, the estimated intake of BCEE from drinking-water for adults would be approximately 0.01 μg/kg body weight per day. Quantitative information on the extent of potential workplace exposure to this substance was not identified.

Available data on the toxicity of BCEE in humans are extremely limited. Irritation to the eyes, nasal passages and respiratory tract could result from acute inhalation exposure to moderate levels of BCEE. Data were considered inadequate to assess the human health risks of non-neoplastic effects arising from longer-term exposure to this substance.

Studies on the toxicological effects produced by the long-term exposure of laboratory animals to BCEE have focused on its carcinogenic potential. Some very limited evidence of carcinogenicity in hybrid F_1 mice was reported in one study (Innes et al., 1969). However, none of the long-term (subchronic or chronic/ carcinogenicity) studies in laboratory animals is considered to be of sufficient quality to provide useful quantitative information on the carcinogenic potential of BCEE or the toxicological effects produced by long-term exposure to this substance. Moreover, studies of developmental and reproductive effects of BCEE in laboratory animals have not been identified. Available data were, therefore, considered inadequate to assess the risks to human health associated with exposure to BCEE in the general or occupational environments.

10.1.2 BCME and CMME

Information on the concentrations of BCME and CMME in air, drinking-water, soil or foodstuffs were not identified, and therefore it

was not possible to estimate the intake of these substances by the general population. However, owing to the extremely rapid hydrolysis of these compounds in aqueous media, exposure of non-occupationally exposed individuals is likely to be negligible. However, in some countries exposure of the general population to chloromethyl ethers may occur through the use of mosquito coils. Information on occupational exposure to BCME and CMME is also limited, although a recent study of a resin manufacturing plant reported lower levels of BCME than had been observed in previous, older investigations of plastics, textile and chemical manufacturing plants.

Based upon the results of studies conducted with animals, inhalation of BCME or CMME may produce severe irritation of the eyes and respiratory tract as well as necrotizing bronchitis. Dermal exposure to BCME and CMME can result in erythema and necrosis.

In all of the cohort studies of occupationally exposed workers conducted to date, an association between lung cancer and exposure to either BCME or CMME has been observed. The type of lung cancer, the standardized mortality ratios, the latency periods and average age of appearance of lung cancer in groups of workers exposed to either BCME or CMME have been remarkably consistent. The type and incidence of lung cancer in individuals exposed to BCME or CMME, predominantly small (oat) cell carcinomas, occurring in relatively young individuals after short latency periods (as low as 2 years), is distinct from that caused by tobacco, one of the potential confounders in such studies, where lung tumours are predominantly squamous cell carcinomas, occurring after long latency periods in individuals greater than 60 years of age. The association between exposure to either BCME or CMME and lung cancer is strong, with standardized mortality ratios ranging up to 21.

For CMME, there is also evidence of a positive relationship between a qualitative measure of exposure and mortality due to lung cancer. In two studies of occupationally exposed individuals, the standardized mortality ratios for deaths due to lung cancer peaked 10 to 20 years following the onset of exposure. Furthermore, observation of an association between occupational exposure to BCME or CMME and the development of lung cancer is plausible. This observation is based on the results of early, rather limited carcinogenesis bioassays in exposed animal species, in which increases in the incidence of

tumours, predominantly of the respiratory tract, have been observed, as well as on available data on the genotoxicity of BCME and CMME.

The observed association of lung cancer and occupational exposure to either BCME or CMME fulfil traditional criteria for assessment of causality in epidemiological studies, i.e. consistency, strength, specificity, temporal relationship, exposure-response relationship, plausibility and supporting data on chromosomal effects in workers exposed to 0.01 μg BCME/m^3 and 20 μg CMME/m^3. Clearly, BCME and technical grade CMME are carcinogenic to humans, and, therefore, exposure to these substances should be eliminated.

10.1.3 Guidance values

Available data on BCEE were considered inadequate to derive a meaningful guidance value for this substance.

Inhalation is the principal route of exposure to these substances. Data available in epidemiological studies of workers exposed to BCME and CMME are inadequate to characterize quantitatively the exposure-response relationship for carcinogenicity. There is evidence that the general population may be exposed to BCME and CMME through the use of mosquito coils, but there are no quantitative exposure data available. However, in humans there is an increase in cancer incidence (latency period as short as 2 years) with cumulative exposure to BCME and an increase in chromosomal aberrations in workers at levels as low as 0.01 μg BCME/m^3 and 20 μg CMME/m^3. Based on multistage modelling of the incidence of esthesioneuroepitheliomas in rats exposed to BCME (Leong et al., 1981), the estimated concentration of this substance associated with a 5% increase in tumour incidence (TD_{05}), corrected for intermittent (6 of 24 h, 5 days/week) versus continuous exposure, is 6 μg/m^3. Data on CMME were insufficient to derive a TD_{50}. Limitations of the critical study including the relatively short period of exposure (6 months followed by 22-month observation period) and sharp increase in the incidence of these tumours between the mid- and high-concentration groups, should, however, be borne in mind in the interpretation of this value.

The above analysis of data further strengthens the recommendation to eliminate human exposure to BCME and CMME.

10.2 Evaluation of effects on the environment

10.2.1 BCEE

BCEE is highly soluble in water and tends to remain there, although some volatilization from soil and water to the atmosphere occurs. Owing to lack of adsorption, BCEE is mobile in soils, especially those with low organic carbon content, and therefore it has the potential to reach groundwater. BCEE does not bioaccumulate or biomagnify to any significant extent.

Exposure of terrestrial organisms to BCEE is considered to be negligible because of its extremely low rate of release and short persistence in the atmosphere. For aquatic biota, a 7-day LC_{50} of 56.9 mg/litre (nominal concentration) for the guppy (*Poecilia reticulata*) has been reported. The lowest LC_{50} reported for acute toxicity (48-h) is 240 mg/litre (nominal concentration) for *Daphnia magna*. The highest concentration of BCEE reported for surface water in the USA (1.4 µg/litre) is approximately 40 000 times lower than the reported 7-day LC_{50} for the guppy (*Poecilia reticulata*).

Although it is relatively persistent in water, the highest reported concentration of BCEE in surface water is approximately five orders of magnitude lower than the concentration found to induce adverse effects in the guppy, the most sensitive aquatic species identified among existing toxicity studies. Therefore, BCEE is not expected to pose a significant risk to environmental organisms.

10.2.2 BCME and CMME

Both substances are readily hydrolysed in aqueous media or photo-oxidized in the atmosphere and, therefore, are not likely to accumulate. Because of their extremely short residence times, levels in the environment (if any) are likely to be extremely low. Thus, despite the lack of data concerning the environmental toxicity of BCME and CMME, there is no reason to suspect that adverse effects could occur to organisms living in the ambient environment.

11. RECOMMENDATIONS FOR PROTECTION OF HUMAN HEALTH AND THE ENVIRONMENT

a) Exposure to BCME and technical CMME should be eliminated.

b) Levels of BCEE in environmental media to which humans are exposed should be determined.

12. FURTHER RESEARCH

a) Workers previously exposed to BCME and technical grade CMME should be followed using all available methods, including markers of biological effect for the detection of lung cancer at an early stage.

b) The degree of exposure of the general public to BCME and CMME through the use of mosquito coils containing the S-2 synergist octachlorodipropyl ether should be measured. In this study the degree of possible contamination of the S-2 synergist by BCME and CMME should also be taken into account.

c) If it is still used, the toxicological profile for BCEE should be determined in well-designed toxicological studies.

13. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

BCEE has been evaluated by the International Agency for Research on Cancer (IARC) and placed in Group 3 - "not classifiable as to its carcinogenicity in humans" (IARC, 1987). BCME and CMME are considered by IARC to be carcinogenic to humans (Group 1) (IARC, 1987).

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RÉSUMÉ ET CONCLUSIONS

1. Identité, propriétés physiques et chimiques, méthodes d'analyse

Le bis (2-chloroéthyl) éther (BCEE), le bis (chlorométhyl) éther (BCME) et le chlorométhylméthyléther (CMME) sont des composés chimiques qui appartiennent à un vaste groupe de produits connus sous le nom de chloroalkyléthers. A la température ambiante, ces trois éthers se présentent sous la forme de liquides volatils incolores à l'odeur caractéristique. Ils sont dotés d'une forte tension de vapeur. La solubilité dans l'eau du BCEE est de 1,7% et son coefficient de partage entre l'octanol et l'eau est égal à 1,46. Le BCME et le CMME, qui sont des α-chloroalkyléthers, sont des composés réactifs. Ils subissent une hydrolyse rapide en milieu aqueux (avec une demi-vie ou temps de demi-hydrolyse respectivement égale à 38 secondes et < 0,007 secondes); le BCEE, qui est un β-chloroéthyléther, s'hydrolyse plus lentement (demi-vie dans l'eau approximativement égale à 20 ans).

Les méthodes d'échantillonnage et d'analyse applicables au BCEE dans l'eau et au CMME dans l'air sont décrites dans la littérature. On peut citer comme exemples caractéristiques la chromatographie en phase gazeuse (détection par capture d'électrons) ou le couplage chromatographie en phase gazeuse-spectrométrie de masse.

2. Sources d'exposition humaine

On n'a pas trouvé dans l'environnement de BCEE, de BCME ou de CMME qui soient d'origine naturelle. Les données de production récentes se limitent aux Etats-Unis et au Canada. On a produit environ 10 000 tonnes de BCEE aux Etats-Unis en 1986 en vue d'une utilisation comme solvant, pour la production de polymères ou encore dans un certain nombre de processus industriels. Dans ce même pays, l'usage du BCME est actuellement limité à certaines réactions chimiques intermédiaires bien déterminées. On produit également du BCME en vue de la fabrication de résines échangeuses d'ions ou autres types de polymères ou encore comme solvant dans les réactions de polymérisation. En Chine, on produit chaque année, environ 200 tonnes de BCME comme intermédiaire dans la préparation d'un synergisant d'insecticide, l'octachlorodipropyléther. Le CMME de qualité technique contient de 1 à 8% de BCME.

3. Transport, distribution et transformation dans l'environnement

La mobilité et la distribution de ces chloroalkyléthers sont, dans le cas du BCME et du CMME, déterminées par la grande réactivité de ces composés et, dans le cas du BCEE, par la grande solubilité et stabilité dans l'eau de cet éther. Le BCME et le CMME, des éthers α-chloroalkylés, subissent une hydrolyse rapide en milieu aqueux et sont rapidement décomposés par photolyse. En milieu aqueux, les produits d'hydrolyse du BCME et du CMME sont constitués de formaldéhyde et d'acide chlorhydrique dans le cas du premier et de méthanol, de formaldéhyde et d'acide chlorhydrique dans le cas du second. Parmi les produits de décomposition du BCME et du CMME, figurent le chlorure d'hydrogène, le formaldéhyde et le chlorométhylformiate, pour le premier, et le chlorométhyl- ainsi que le méthylformiate, pour le second. Le BCEE est soluble dans l'eau; les précipitations l'éliminent de l'atmosphère et il a tendance à rester dans l'eau où il subit une très lente hydrolyse. En l'espace d'une semaine, il s'évapore de la surface et se décompose en un peu moins d'une journée sous l'action de processus abiotiques.

En raison du caractère extrêmement réactif des α-chloroalkyléthers dans l'eau et dans l'air, on ne peut guère s'attendre à trouver du CMME et du BCME dans l'environnement. Toutefois, le BCEE peut présenter une plus grande persistance en raison de la meilleure stabilité relative des β-chloroalkyléthers.

4. Niveaux d'exposition dans l'environnement et exposition humaine

On ne dispose que de données limitées sur la concentration du BCEE dans les divers compartiments de l'environnement. On l'a mis en évidence dans l'air, mais sans procéder à un dosage; aux Etats-Unis, on en a trouvé jusqu'à 42 µg/litre dans de l'eau de boisson. Les concentrations rapportées dans la littérature en ce qui concerne les eaux de surface vont de 0,001 µg/litre dans une décharge industrielle de gypse en Belgique, à 840 µg/litre dans une autre décharge située aux Etats-Unis. On a mesuré des concentrations encore plus élevées dans les eaux de lessivage d'une décharge contrôlée. On n'a pas connaissance de la teneur des denrées alimentaires en BCEE, mais on ne pense pas qu'il puisse y avoir bioaccumulation.

On ne dispose d'aucune donnée sur la concentration du BCME et du CMME dans les divers compartiments de l'environnement.

Si l'on se base sur la concentration maximale de BCEE rapportée pour l'eau de boisson, soit 42 µg/litre, un être humain moyen pesant 64 kg et consommant 1,4 litres d'eau par jour ingérerait quotidiennement environ 0,01 µg de ce produit par kg de poids corporel, plus une quantité indéterminée provenant de sources inconnues. Il est impossible d'évaluer la dose quotidienne de BCME et de CMME ingérée à partir de sources environnementales. Toutefois, comme ces deux composés ne persistent pas dans l'environnement, il est probable que l'exposition humaine à ces produits est très faible.

En s'appuyant sur des données limitées et assez anciennes, on pense que les ouvriers travaillant à la production de plastiques et de fibres textiles ont pu être exposés, dans l'air des lieux de travail, à des concentrations de BCME comprises entre 1,2 et 72,9 µg/m^3. Cependant, une récente étude, effectuée dans une usine de production de résines plastiques, fait état d'une exposition professionnelle moyenne allant de 2,4 à 20,6 µg/m^3. Selon d'autres travaux, la concentration de BCME ne dépasserait pas 0,01 µg/m^3.En Chine, l'exposition au BCME a été plus élevée que ces chiffres jusqu'en 1975 et elle persiste encore, quoiqu'à un niveau moindre, dans les usines qui produisent de l'octachlorodipropyléther. Il y exposition de la population générale au BCME et au CMME là où l'on fait beaucoup brûler de serpentins anti-moustiques qui en contiennent comme synergisants.

La concentration la plus élevée de BCEE signalée aux Etats-Unis dans les effluents industriels se situe entre 8 et 170 µg/litre; dans le cas d'eaux provenant du lessivage de décharges contrôlées industrielles et municipales, la concentration était de 12 400 µg/litre.

5. Cinétique et métabolisme

On ne dispose pas de données quantitatives sur la cinétique et le métabolisme du BCEE, du BCME et du CMME chez l'homme. On estime toutefois que, même si le BCME et le CMME doivent, en principe, être rapidement hydrolysés *in vivo*, pour donner, le premier, du formaldéhyde et de l'acide chlorhydrique et le second, du

formaldéhyde, du méthanol et de l'acide chlorhydrique, il se produit sans doute une alkylation.

D'après des données limitées, du BCEE radiomarqué administré à des rats par inhalation ou gavage subit une résorption rapide. Après administration par gavage, on a constaté que l'organisme des rats n'avait retenu que moins de 3% de la dose initiale au bout de 24 heures.

Chez le rat, le BCEE est rapidement métabolisé. Son principal métabolite est l'acide thiodiglycolique (TDGA). Chez des rats qui avaient reçu par gavage une dose unique de ^{14}C- BCEE, on a constaté que 12% environ de la radioactivité absorbée se trouvait sous la forme de $^{14}CO_2$.

Chez le rhésus comme chez le rat, le BCEE est rapidement éliminé. Chez des rhésus auxquels on avait administré du ^{14}C-BCEE par la voie orale, on a retrouvé moins de 2% de la radioactivité initiale dans les matières fécales 72 h après l'administration. Chez des rats, c'est approximativement 2,3% de la radioactivité initiale qui ont été retrouvés dans les tissus et les matières fécales, 48 h après l'administration. Après avoir administré par gavage du ^{14}C-BCEE à des rats, on a retrouvé plus de 50% de la radioactivité dans les urines et dans l'air expiré 12 heures après l'administration. Moins de 2% de la radioactivité présente dans l'air expiré correspondaient au composé initial.

6. Effets sur les animaux de laboratoire et les systèmes d'épreuve *in vitro*

Absorbé par la voie orale, par inhalation ou par voie transcutanée, le BCEE peut provoquer des intoxications aiguës. Les valeurs de la DL_{50} dont il est fait état dans la littérature en cas d'exposition d'animaux par la voie orale, vont de 75 à 215 mg/kg de poids corporel. Le BCME et le CMME provoquent également des intoxications aiguës lorsqu'ils sont absorbés par voie orale ou par inhalation. Les valeurs de la CL_{50} pour des animaux de laboratoire exposés par la voie respiratoire à du BCME ou à du CMME, vont de 25 à 48 mg/m^3 dans le cas du premier composé et de 182 à 215 mg/m^3 dans le cas du second.

L'exposition d'animaux de laboratoire par la voie respiratoire à une seule mais forte concentration de BCEE (>320 mg/m^3), a provoqué une irritation oculaire ainsi qu'une congestion, un oedème et des hémorragies pulmonaires. Pendant l'inhalation de BCME, on a noté une irritation des yeux et des voies respiratoires ainsi qu'une bronchite nécrosante. L'application du produit sur la peau a donné lieu à un érythème et à une nécrose. L'instillation dans les yeux provoque une nécrose cornéenne. On a observé des effets analogues après exposition au CMME.

On a constaté un accroissement de la mortalité et une hyperplasie trachéenne chez des rats et des hamsters exposés par la voie respiratoire à du BCME à la dose de 4,7 mg/m^3. Des résultats analogues ont été obtenus à plusieurs reprises chez des rats exposés à du CMME par la voie respiratoire à raison de 3,3 ou de 33 mg de composé par m^3.

En général, les épreuves de mutagénicité *in vitro* ont donné des résultats positifs avec le BCEE, le BCME et le CMME. Toutefois, les résultats sont difficiles à interpréter en raison de l'absence de détails dans les comptes rendus de ces expériences. Selon la littérature, le BCME et le CMME provoquent *in vitro* un accroissement de la synthèse non programmée de l'ADN et le BCME augmente la proportion de cellules transformées, également *in* vitro. Dans de petits groupes de souris mâles appartenant à deux souches de souris hybrides F_1 (de même que chez les femelles d'une des souches F_1), qui avaient reçu du BCEE par voie orale (dose pondérée par rapport au temps égale à 41,3 mg/kg p.c. sur une période de 18 mois), on a observé une augmentation significative de l'incidence des tumeurs hépatiques (bénignes et malignes) par rapport aux animaux témoins non exposés. Quatre autres études de portée plus limitée effectuées sur des rats et des souris qui recevaient le composé par gavage, en injections sous-cutanées ou intrapéritonéales ou par badigeonnage cutané, n'ont pas permis de confirmer ces résultats.

Les études de cancérogénicité effectuées sur des animaux de laboratoire (souris ou rats) exposés à du BCME, ont révélé un accroissement significatif de l'incidence des adénomes pulmonaires et autres tumeurs des voies respiratoires. Chez la souris, on a également obtenu des indices d'une élévation de l'incidence des tumeurs pulmonaires.

Les études effectuées sur le CMME ont révélé, chez le rat, un accroissement de l'incidence des métaplasies trachéennes et des hyperplasies bronchiques qui dépendait de la dose. Toutefois, les résultats des épreuves de cancérogénicité menées sur l'animal n'ont pas donné de résultats concluants.

On ne dispose d'aucun renseignement concernant les effets toxiques éventuels du BCEE, du BCME et du CMME sur la fonction de reproduction, le développement, le système immunitaire et le système nerveux.

7. Effets sur l'homme

On a constaté que le BCEE avait un effet irritant sur l'oeil et les fosses nasales aux concentrations supérieures à 150 mg/m^3 après exposition de courte durée.

On n'a pas trace d'études épidémiologiques sur les effets à long terme d'une exposition au BCEE.

Une association entre l'exposition d'ouvriers à du BCME ou du CMME et un risque accru de cancer du poumon a été mise en évidence dans 8 études épidémiologiques. Les travailleurs exposés à du CMME de qualité technique l'étaient probablement aussi à du BCME. Les tumeurs prédominantes observées chez les ouvriers exposés étaient des carcinomes à petites cellules, tout à fait distincts des carcinomes essentiellement spinocellulaires qui s'observent. chez les fumeurs. Il s'agissait d'une forte association, avec des rapports comparatifs de mortalité qui allaient jusqu'à 2,1. Le type de cancer pulmonaire, la période de latence et l'âge moyen d'apparition de la tumeur chez les ouvriers exposés au BCME ou au CMME présentaient une cohérence remarquable. Dans le cas du CMME, on est également fondé à penser qu'il y a une relation positive entre l'expression qualitative de l'exposition et la mortalité par cancer du poumon.

Lors d'une exposition professionnelle, et même à des concentrations de 0,01 µg/m^3 de BCME ou de 20 µg/m ^{3}de CMME, on a constaté une augmentation de la fréquence des aberrations chromosomiques dans les lymphocytes du sang périphérique des ouvriers exposés.

On ne dispose d'aucun renseignement concernant les effets du BCME ou du CMME sur la fonction de reproduction, le développement, le système nerveux et le système immunitaire chez l'homme.

8. Effets sur les autres êtres vivants au laboratoire et dans leur milieu naturel

Peu d'études ont été consacrées aux effets du BCEE sur les êtres vivants dans leur milieu naturel; la plupart des travaux se limitent aux espèces aquatiques. Ainsi la CL_{50} à 7 jours pour le guppy est égale à 56,9 mg/litre; pour d'autres poissons on a trouvé une CL_{50} à 96 h de 600 mg/litre et en ce qui concerne les invertébrés, on a fait état d'une CL_{50} à 48 h égale à 240 mg/litre pour *Daphnia magna*.

Il n'y a pas eu d'inhibition de l'activité microbienne anaérobie en présence de BCEE à des concentrations allant jusqu'à 100 mg/litre et on a trouvé une CL_{10} de 600 µg/litre pour des microorganismes colonisant des bassins de stabilisation.

On ne dispose d'aucune donnée concernant les effets toxiques que le BCME ou le CMME pourraient exercer sur les êtres vivants dans leur milieu naturel.

9. Conclusions

9.1 BCEE

- L'exposition des organismes terrestres au BCEE est jugée négligeable du fait que ce composé n'est que lentement libéré dans l'environnement et qu'il ne subsiste que peu de temps dans l'atmosphère.

- Le BCEE persiste davantage dans l'eau, mais la concentration la plus élevée mesurée dans les eaux de surface est beaucoup plus faible (environ cinq ordres de grandeur) que celle qui se révèle toxique pour le guppy, l'espèce la plus sensible selon les études toxicologiques.

- En raison de l'absence de données concernant la concentration du BCEE dans un certain nombre de compartiments de l'environne-

ment auxquels l'homme est exposé, il n'est pas possible de donner une estimation quantitative de la dose totale de ce composé absorbée au cours d'une journée.

- On ne dispose que de données limitées sur la toxicité du BCEE pour l'homme. On ne trouve pas de relation des effets sur la reproduction et le développement qui auraient pu être observés chez des animaux de laboratoire. Par ailleurs, aucune des études à long terme effectuées sur les animaux de laboratoire n'est d'une qualité suffisante pour que l'on puisse en tirer des données quantitatives sur la cancérogénicité du BCEE ou sur les effets toxiques à longue échéance que ce composé pourrait produire.

- Faute de données toxicologiques et cancérogénétiques suffisantes, la prudence commande de faire en sorte que l'exposition humaine soit réduite au minimum.

9.2 BCME et CMME

- Au cas ou ces composés pénétreraient dans l'environnement, ils subiraient rapidement une hydrolyse et une photo-oxydation. On ne possède pas de données sur la concentration du BCME et du CMME dans l'environnement.

- Le BCME et le CMME de qualité technique (qui contient du BCME) sont des substances dont la cancérogénicité pour l'homme est prouvée. Ils se sont d'ailleurs tous les deux révélés cancérogènes pour les animaux de laboratoire. Ces deux composés provoquent des aberrations chromosomiques chez les travailleurs qui leur sont exposés de par leur profession. Il faut éviter toute exposition professionnelle et toute exposition de la population générale à ces composés.

- Compte tenu de la destinée de ces composés dans l'environnement et de l'absence d'exposition, il n'y aucune raison de craindre des effets nocifs sur les organismes terrestres ou aquatiques.

RESUMEN Y CONCLUSIONES

1. Identidad, propiedades físicas y químicas y métodos analíticos

El bis(2-cloroetil)éter (BCEE), el bis(clorometil)éter (BCME) y el clorometilmetiléter (CMME) son sustancias químicas de una clase amplia conocida como cloroalquiléteres. Los tres éteres son líquidos volátiles incoloros a temperatura ambiente con olores característicos. La presión de vapor de estos tres compuestos es alta. La solubilidad del BCEE es del 1,7% en agua, y su coeficiente de reparto octanol/agua es de 1,46. Los α-cloroalquiléteres BCME y CMME son compuestos reactivos, que se hidrolizan con rapidez en medios acuosos (con semividas de alrededor de 38 segundos y <0,007 segundos, respectivamente); la hidrólisis del β-cloroéter BCEE, más estable, es más lenta (con una semivida en agua de unos 20 años).

Se han descrito métodos de muestreo y analíticos para el BCEE en el agua y para el BCME y el CMME en el aire. Normalmente la determinación se efectúa por cromatografía de gases (CG-captura de electrones) o CG-espectrometría de masas.

2. Fuentes de exposición humana

No se han identificado fuentes naturales de BCEE, BCME o CMME en el medio ambiente. Los datos recientes de producción disponible son limitados y corresponden solamente a los Estados Unidos y el Canadá. En 1986 se produjeron en los Estados Unidos alrededor de 10^4 toneladas de BCEE para utilizarlo como disolvente y en la producción de polímeros y en varios procesos industriales. Las aplicaciones industriales del BCME están actualmente limitadas en los Estados Unidos a reacciones químicas intermedias específicas. También se ha producido BCME para utilizarlo en la obtención de resinas de intercambio iónico, en la fabricación de otros polímeros y como disolvente en reacciones de polimerización. En China se producen unas 200 toneladas al año de BCME como producto intermedio en la fabricación de octaclorodipropiléter, un insecticida sinérgico. El CMME de calidad técnica contiene del 1% al 8% de BCME.

3. Transporte, distribución y transformación en el medio ambiente

En la movilidad y distribución de los cloroalquiléteres seleccionados influyen tanto la elevada radiactividad del BCME y del CMME como la solubilidad en agua y la estabilidad del BCEE. Los α-cloroalquiléteres BCME y CMME se hidrolizan con rapidez en medios acuosos y se degradan en poco tiempo por fotolisis. En medios acuosos, los productos hidrolíticos del BCME y del CMME son formaldehído y ácido clorhídrico, y metanol, formaldehído y ácido clorhídrico, respectivamente. Los productos de descomposición del BCME y el CMME en el aire son ácido clorhídrico, formaldehído y formato de clorometilo, y formato de clorometilo y de metilo, respectivamente. El BCEE es soluble en agua; la lluvia lo elimina de la atmósfera y tiende a mantenerse en el agua, con una hidrólisis muy lenta. El BCEE se evapora del agua superficial en una semana y se degrada en poco más de un día en la atmósfera mediante procesos abióticos.

Debido al carácter muy reactivo de los α-cloroalquiléteres en el agua y en el aire, no es previsible la presencia de CMME y BCME en el medio ambiente; sin embargo, el BCEE puede ser persistente, debido a la estabilidad relativa de los ß-cloroalquiléteres.

4. Niveles ambientales y exposición humana

Los datos disponibles sobre los niveles de BCEE en medios ambientales son limitados. Se ha identificado en el aire, pero sin determinación cuantitativa; se han encontrado niveles de hasta 0,42 µg/litro en el agua potable en los Estados Unidos. Los niveles notificados de BCEE en el agua fréatica han oscilado entre 0,001 µg/litro en un vertedero de yeso industrial en Bélgica y 840 µg/litro cerca de un vertedero en los Estados Unidos. Se han medido concentraciones más elevadas en productos de lixiviación de vertederos. No se dispone de información sobre los niveles de BCEE en los productos alimenticios, pero se supone que no se produce bioacumulación.

No se dispone de datos cuantitativos sobre los niveles de BCME o CMME en el medio ambiente.

Tomando como base el nivel máximo notificado de BCEE en el agua potable, es decir, 0,42 µg/litro, la persona de tipo medio (64 kg) que consuma 1,4 litros/día tendrá una ingesta aproximada de 0,01 µg/kg de peso corporal al día de esta procedencia, con cantidades desconocidas de otras fuentes del medio ambiente. No se puede hacer ninguna estimación de la ingesta diaria de BCME y CMME a partir de fuentes del medio ambiente. Sin embargo, considerando la falta de persistencia del BCME y del CMME en el medio ambiente es probable que la exposición humana media a estos compuestos sea muy baja.

En función de datos limitados más antiguos, los trabajadores de industrias relacionadas con los plásticos y la producción textil podrían haber estado expuestos a cantidades comprendidas entre 1,2 y 72,9 µg de BCME/m^3 en el aire del lugar de trabajo. Sin embargo, en un estudio reciente de una fábrica de resina se señalaron exposiciones medias en el trabajo comprendidas entre 2,4 y 20,6 µg/m^3. En los datos de otros estudios se indicaron niveles de BCME muy bajos de 0,01 µg/m^3. En China se producía hasta 1975 una exposición más alta en el trabajo al BCME, y sigue existiendo con un nivel menor en la fabricación de octaclorodipropiléter. La población general está expuesta al BCME y al CMME cuando se producen en la quema generalizada de este producto sinérgico en serpentines fumigantes de mosquitos.

Las concentraciones más elevadas notificadas de BCEE en los Estados Unidos en efluentes industriales son de 8 a 170 µg/litro, y en los productos de lixiviación de vertederos municipales e industriales de 12 400 µg/litro.

5. Cinética y metabolismo

No se dispone de información cuantitativa sobre la cinética y el metabolismo del BCEE, del BCME y del CMME en el ser humano. Sin embargo, se supone que, aunque el BCME y el CMME se hidrolicen con rapidez *in vivo* en los tejidos a formaldehído y ácido clorhídrico, y a metanol, formaldehído y ácido clorhídrico respectivamente, debe haber actividad de alquilación.

Los datos limitados que se conocen indican que el BCEE radiactivo administrado a ratas por inhalación o con sonda se absorbe

con rapidez. A las 48 horas de la administración por sonda se retenía menos del 3% de la radiactividad.

El BCEE se metaboliza fácilmente en ratas. El principal metabolito es el ácido tiodiglicólico. Después de administrar una dosis única por sonda de [^{14}C]-BCEE, alrededor del 12% de la radiactividad administrada estaba presente en forma de $^{14}CO_2$.

El BCEE se elimina con rapidez tanto en ratas como en monos resus. A las 72 horas de la administración oral de [^{14}C]-BCEE se recuperó menos del 2% de la radiactividad en las heces de los monos; a las 48 horas de la administración, se encontró alrededor del 2,3% de la radiactividad administrada en los tejidos o las heces de ratas; más del 50% de la radiactividad se recuperó en la orina y en el aire exhalado a las 12 horas de la administración a ratas con sonda de una dosis de [^{14}C]-BCEE. De la radiactividad expirada a través de los pulmones, correspondió al compuesto original menos del 2%.

6. Efectos en animales de laboratorio y en sistemas de prueba *in vitro*

El BCEE tiene toxicidad aguda por vías de exposición oral, inhalación o cutánea. Los valores notificados de la DL_{50} para la exposición oral de especies animales al BCEE oscilan entre 75 y 215 mg/kg de peso corporal. El BCME y el CMME tienen toxicidad aguda por inhalación o ingestión. Los valores de la CL_{50} notificados para la exposición de animales de laboratorio por inhalación al BCME o al CMME oscila entre 25 y 48 mg/m^3 y entre 182 y 215 mg/m^3, respectivamente.

La exposición de animales de laboratorio por inhalación a una dosis elevada única de BCEE (>320 mg/m^3) provocó irritación ocular, además de congestión, edema y hemorragia pulmonar. Durante la inhalación de BCME, se observó irritación ocular y de las vías respiratorias, así como bronquitis necrosante. La aplicación cutánea dio lugar a la aparición de eritema y necrosis, y la aplicación en el ojo indujo necrosis corneal. Tras la exposición al CMME se observaron efectos análogos.

En ratas y hámsteres se observó un aumento de la mortalidad y la hiperplasia traqueal después de la exposición por inhalación múltiple

a 4,7 mg de BCME/m^3. Se observaron efectos análogos en ratas expuestas repetidamente por inhalación a 3,3 o 33 mg de CMME/m^3.

En general, se obtuvieron resultados positivos en las pruebas de mutagenicidad del BCEE, del BCME y del CMME *in vitro*. Sin embargo, la interpretación de los resultados resulta difícil, debido a la falta de detalles en los informes disponibles. Se ha notificado que el BCME y el CMME aumentan la síntesis no programada de ADN *in vitro*, y el BCME elevó el nivel de células transformadas en pruebas *in vitro*.

En pequeños grupos de machos pertenecientes a dos estirpes de ratones F_1 híbridos (y en hembras de una estirpe F_1) tratados por vía oral con BCEE (dosis media ponderada por el tiempo de 41,3 mg/kg de peso corporal durante 18 meses), se registró un aumento significativo de la incidencia de hepatomas (hepatomas benignos y tumores malignos combinados) en comparación con los testigos no tratados. En otros cuatro estudios limitados con ratas y ratones en los que se utilizó la administración oral con sonda, la inyección subcutánea o intraperitoneal y la aplicación sobre la piel no se confirmaron esos resultados.

Los estudios de carcinogenicidad en animales experimentales (ratones y ratas) expuestos a BCME pusieron de manifiesto una incidencia significativamente elevada de adenomas pulmonares y tumores de las vías respiratorias. En ratones, tras la exposición por inhalación también se observaron pruebas de una incidencia elevada de tumores pulmonares.

Los estudios realizados con CMME han puesto de manifiesto una mayor incidencia de metaplasia traqueal e hiperplasia bronquial dependiente de la dosis en ratas. Sin embargo, los resultados de las biovaloraciones de carcinogenicidad en estudios con animales no han sido concluyentes.

No hay información disponible relativa a la toxicidad reproductiva, en el desarrollo, inmunológica o neurológica del BCEE, del BCME o del CMME.

7. Efectos en el ser humano

Se ha comprobado que el BCEE irrita los ojos y los orificios nasales de las personas en concentraciones >150 mg/m^3 tras una exposición breve.

No se tienen noticias de estudios epidemiológicos sobre los efectos de la exposición prolongada al BCEE.

En ocho estudios epidemiológicos, la exposición de los trabajadores al BCME (CMME) se relacionó con un aumento del riesgo de cáncer de pulmón. Los trabajadores expuestos al CMME de calidad comercial probablemente también estuvieron expuestos al BCME. Los tumores predominantes en los trabajadores expuestos fueron carcinomas de células pequeñas, bastante distintos de los que son principalmente de células escamosas y que suelen aparecer en los fumadores. Hubo una relación clara entre la exposición al BCME (CMME) y el cáncer de pulmón, con unas razones de mortalidad normalizada que llegaban hasta 21. El tipo de cáncer de pulmón, el período de latencia y la edad media de aparición de los tumores de pulmón en los trabajadores expuestos al BCME (CMME) han sido básicamente invariables. Para el CMME hay también pruebas de una relación positiva entre una medida cualitativa de la exposición y la mortalidad debida a cáncer de pulmón.

En el curso de una exposición en el trabajo, incluso concentraciones de 0,01 µg de BCME/m^3 y de 20 µg de CMME/m^3 aumentaron la frecuencia de aberraciones cromosómicas en los linfocitos periféricos de los trabajadores expuestos.

No se dispone de información relativa a los efectos neurológicos, inmunológicos, en el desarrollo o reproductivos del BCME o del CMME en el ser humano.

8. Efectos en otros organismos en el laboratorio y en condiciones naturales

Son pocos los estudios que se han realizado sobre los efectos del BCEE en los organismos del medio ambiente; la mayoría se limitan a especies acuáticas. Para el BCEE, se ha notificado un valor de la CL_{50} en siete días en *Lebistes reticulatus* de 56,9 mg/litro, una CL_{50} en peces

en 96 horas de 600 mg/litro y una CL_{50} en 48 horas en *Daphnia magna* de 240 mg/litro.

La actividad microbiana anaerobia no se vio inhibida en concentraciones de BCEE de hasta 100 mg/litro, y se ha notificado una CL_{10} de 600 µg/litro en el caso de microorganismos indígenas en estanques de estabilización de desechos.

No hay información sobre los efectos toxicológicos del BCME y del CMME en los organismos del medio ambiente.

9. Conclusiones

9.1 BCEE

- Se considera que la exposición de los organismos terrestres al BCEE es insignificante, debido a la escasa tasa de liberación y su breve persistencia en la atmósfera.

- Aunque es más persistente en el agua, la concentración más elevada notificada de BCEE en agua superficial es aproximadamente cinco veces inferior a la concentración con la que se ha comprobado que induce efectos adversos en *Lebistes reticulatus*, que es la especie acuática más sensible identificada en los estudios de toxicidad realizados.

- Debido a la falta de información disponible sobre las concentraciones de BCEE en varios tipos de medios a los cuales está expuesto el ser humano, no es posible estimar cuantitativamente la ingesta diaria total de BCEE.

- Los datos disponibles sobre la toxicidad del BCEE en el ser humano son limitados. No se ha encontrado información sobre los efectos del BCEE en el desarrollo y la reproducción en animales de laboratorio, y ninguno de los estudios de larga duración en animales de laboratorio tiene suficiente calidad para proporcionar información cuantitativa acerca del potencial del BCEE para provocar cáncer o sobre los efectos toxicológicos producidos por la exposición prolongada a esta sustancia.

- En ausencia de datos toxicológicos y de carcinogenicidad adecuados, es conveniente reducir al mínimo la exposición humana al BCEE.

9.2 BCME y CMME

- En el caso de que estas sustancias se incorporaran al medio ambiente, se degradarían con rapidez por hidrólisis y fotooxidación. No se han identificado datos relativos a las concentraciones de BCME y CMME en el medio ambiente natural.

- Está demostrado que el BCME y el CMME de calidad técnica (que contiene BCME) son carcinógenos para el ser humano. Además, ambos productos químicos son carcinógenos en animales de laboratorio. Los dos provocan aberraciones cromosómicas en los trabajadores expuestos en el trabajo. Se debe eliminar la exposición en el trabajo y de la población general a estos compuestos.

- Tomando como base el destino de estas sustancias en el medio ambiente y la falta de exposición, no hay motivo para suponer que se produzcan efectos adversos en organismos acuáticos y terrestres.

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