TOXICOLOGICAL PROFILE FOR BIS(2-CHLOROETHYL)ETHER

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

In collaboration with:

U.S. Environmental Protection Agency

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Mention of company name or product does not constitute endorsement by the Agency for Toxic Substances and Disease Registry.

FOREWORD

The Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law (also known as SARA) directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the most significant hazardous substances were published in the Federal Register on April 17, 1987, and on October 20, 1988.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

> (A) An examination, summary and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,
>
> (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, or chronic health effects, and
>
> (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every 3 years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that

describes a hazardous substance's toxicological properties. Other literature is presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the statement is material that presents levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the front of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public. We plan to revise these documents as additional data become available.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS BIS(2-CHLOROETHYL) ETHER?

Bis(2-chloroethyl) ether (BCEE) is a colorless non-flammable liquid with a strong, unpleasant odor. It does not occur naturally, but is manufactured by humans for use in the production of pesticides and other chemicals. Limited amounts of BCEE will dissolve in water, and it also will slowly evaporate into air. In the environment, BCEE is broken down by bacteria in soil and water and by chemical reactions in the air, so it does not tend to persist for long periods. Further information on the properties and uses of BCEE, and how it behaves in the environment, is presented in Chapters 3, 4 and 5.

1.2 HOW MIGHT I BE EXPOSED TO BCEE?

Exposure to BCEE is most likely to occur in or near chemical plants where it is made or used, or near waste sites where it has been improperly disposed of. One way exposure might occur is through consumption of drinking water that contains BCEE. Low levels (0.01 to 0.5 parts per billion (ppb)) of BCEE have been detected in the drinking water supplies of several cities, and higher levels (840 ppb) have been detected in underground water near some chemical waste sites. Although BCEE evaporates relatively slowly, exposure might also occur through breathing BCEE vapors near areas where it is used or stored. However, no information exists on the levels of BCEE in outdoor air. Further discussion of how people may be exposed to BCEE is presented in Chapter 5.

1.3 HOW CAN BCEE ENTER AND LEAVE MY BODY?

BCEE enters the body easily after being swallowed in food or water, or after being inhaled in air. It may also enter by crossing the skin when dermal contact occurs. Once inside the body, BCEE is broken down to a number of different chemicals, and these are eliminated in the urine or the breath. Most BCEE which enters the body is removed in this way within two to three days, so BCEE does not tend to accumulate in the body. Further information on how BCEE enters and leaves the body is presented in Chapter 2.

1.4 HOW CAN BCEE AFFECT MY HEALTH?

People exposed to BCEE vapors report that it is highly irritating to the eyes and the nose. Animal studies show that BCEE vapors can cause severe injury to the lungs, and may lead to death. Mice given repeated doses of BCEE through the mouth developed liver tumors. This

suggests that BCEE might cause cancer in humans, although no cases of cancer due to BCEE have been reported in people and BCEE was also not found to induce excess cancer after feeding to rats. Effects of BCEE on other organs and body functions have not been well studied, and it is not known if BCEE impairs reproduction or the development of fetuses. Further information on the possible health effects of BCEE is presented in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE IF I HAVE BEEN EXPOSED TO BCEE?

Although there are chemical tests that can identify and measure BCEE, these have not been developed for measuring BCEE in humans. Further information on the methods used to measure BCEE is presented in Chapter 6.

1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Tables 1-l through l-4 show the relationship between exposure to BCEE and known health effects. A Minimal Risk Level (MRL) is also included in Table l-l. This MRL was derived from animal data for longterm exposure, as described in Chapter 2 and in Table 2-1. This MRL provides a basis for comparison with levels that people might encounter in air. If a person is exposed to BCEE at an amount below the long-term MRL, it is not expected that harmful noncancer health effects will occur. Because this level is based only on information currently available, some uncertainty is always associated with it. Also, because the method for deriving MRLs does not use any information about cancer, a MRL does not imply anything about the presence, absence, or level of risk of cancer.

Based on studies in animals, if an amount of BCEE equal to 1 to 2 fluid ounces entered the body across the skin, death could result. Skin contact with even small amounts (less than a drop) of liquid BCEE will cause irritation to the skin.

Further information on the amounts of BCEE that cause health effects in humans and animals is presented in Chapter 2.

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TABLE 1-1. Human Health Effects from Breathing BCEE*

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects**
35	Several hours***	Minimal eye and nose irritation.
100	Several minutes***	Moderate eye and nose irritation.
260	One minute***	Severe eye and nose irritation.
550	One minute***	Nauseating; intolerable.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects
0.02		Estimated Minimal Risk Level (based on studies in animals; see Section 1.6 for discussion).

* See Section 1.2 for a discussion of exposures encountered in daily life.
** These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.
*** Available information is not precise; these are estimated values.

TABLE 1-2. Animal Health Effects from Breathing BCEE

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
35	10 minutes	Nose irritation in guinea pigs.
105	13 hours	Lung injury, death in guinea pigs.
250	4 hours	Death in rats.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
69	18 weeks	Decreased weight in guinea pig and rats.

* These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

TABLE 1-3. Human Health Effects from Eating or Drinking BCEE*

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from short-term human exposure to food containing specific levels of BCEE are not known.
Levels in Water (ppm)		The health effects resulting from short-term human exposure to water containing specific levels of BCEE are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from long-term human exposure to food containing specific levels of BCEE are not known.
Levels in Water (ppm)		The health effects resulting from long-term human exposure to water containing specific levels of BCEE are not known.

* See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-4. Animal Health Effects from Eating or Drinking BCEE

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects*
		The health effects resulting from short-term animal exposure to food containing specific levels of BCEE are not known.
Levels in Water (ppm)		
530	1 day	Death in rats.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects*
		The health effects resulting from long-term animal exposure to food containing specific levels of BCEE are not known.
Levels in Water (ppm)		
180	18 months	Weight loss in rats.
360	18 months	Increased death rate in rats.

* These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

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1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH ?

The Federal government has taken a number of steps to reduce the possibility of human exposure to BCEE. The U.S. Environmental Protection Agency (EPA) has developed rules and regulations that limit the amount of BCEE that can be discharged into water or air from industrial sources as well as how it is to be disposed of at waste sites. Levels of BCEE exposure in the workplace are strictly regulated by the Occupational Safety and Health Administration (OSHA), since BCEE is considered a probable human carcinogen. Further information on regulations which apply to BCEE is presented in Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have further questions or concerns, please contact your State Health or Environmental Department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to BCEE. Its purpose is to present levels of significant exposure for BCEE based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with .(l) an overall perspective of the toxicology of BCEE and (2) a depiction of significant exposure levels associated with various adverse health effects.

Bis(chloroethy1) ether (BCEE) occurs in two isomeric forms: bis(l-chloroethyl) ether, or alpha BCEE, and bis(2-chloroethyl) ether, or beta BCEE. The alpha isomer is chemically more reactive than the beta isomer, but it has had little industrial use and there are very few data on the toxicological effects of this isomer. The beta form is more stable and has been widely produced and used by industry. It is the beta isomer (bis(2-chloroethyl) ether) that is referred to as BCEE in the remainder of this document.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELS) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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The significance of the exposure levels shown on the tables and graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (minimal risk levels, MRLs) are of interest to health professionals and citizens alike.

For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited. Because cancer effects could occur at lower exposure levels, the figures also show estimated excess risks, ranging from a risk of one in 10,000 to one in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1980c), uncertainties are associated with the techniques.

2.2.1 Inhalation Exposure

Table 2-1 and Figure 2-1 summarize the available toxicity data for inhalation exposure to BCEE, and these data are discussed below.

2.2.1.1 Death

One case of a human fatality attributed to inhalation of BCEE vapors in a fulling mill was reported by Elkins (1959), but no details were provided. In animals, acute inhalation lethality depends on the level and duration of exposure to BCEE. Exposure of animals (rats, mice guinea pigs, rabbits) to concentrations of 500-1,000 ppm caused death within 1 to 2 hours (Schrenk et al. 1933; Smyth and Carpenter 1948;

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TABLE 2-1. Levels of Significant Exposure to BCEE - Inhalation

Graph Key	Species	Exposure Duration/ Frequency	Syst. Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	rat	45 min				1000	Smyth and Carpenter 1948
2	rat	4 hr				250	Carpenter et al. 1949
3	gn pig	13 hr		35		105	Schrenk et al. 1933
Systemic							
4	human	NR[a]	Derm/Oc	35	100 eye, nose irritation	260 eye, nose irritation	Schrenk et al. 1933
5	gn pig	1-15 hr	Derm/Oc	35	100 eye irritation		Schrenk et al. 1933
6	gn pig	1-15 hr	Resp	35		105 congest., edema	Schrenk et al. 1933
7	gn pig	1-15 hr	Derm/Oc		35 nasal irritation		Schrenk et al. 1933
Neurological							
8	gn pig	1-15 hr		35		105 CNS depression	Schrenk et al. 1933
INTERMEDIATE EXPOSURE							
Death							
9	rat	130 d 5d/wk 7hr/d		69			Dow Chemical 1958
10	gn pig	130 d 5d/wk 7hr/d		69			Dow Chemical 1958
Systemic							
11	rat	130 d 5d/wk 7hr/d	Cardio Renal Hepatic Hemato Resp Other	69 69 69 69 69	69[b] decr. body wt.		Dow Chemical 1958

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TABLE 2-1. continued

Graph Key	Species	Exposure Duration/ Frequency	Syst. Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
12	gn pig	130 d 5d/wk 7hr/d	Renal Cardio Other Resp Hepatic	69 69 69 69	69 decr. body wt.		Dow Chemical 1958
Neurological							
13	rat	130 d 5d/wk 7hr/d		69			Dow Chemical 1958
14	gn pig	130 d 5d/wk 7hr/d		69			Dow Chemical 1958
Reproductive							
15	rat	130 d 5d/wk 7hr/d		69			Dow Chemical 1958
16	gn pig	130 d 5d/wk 7hr/d		69			Dow Chemical 1958

(a) Not reported in detail, but described as "brief."
(b) Used to derive intermediate MRL: dose adjusted for intermittent exposure, converted to an equivalent concentration in humans, and divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for human variability), resulting in an MRL of 0.02 ppm. This value is presented in Table 1-1.

LOAEL = lowest-observed-adverse-effect level; NOAEL = No-observed-adverse-effect level; ppm = parts per million; min = minutes; hr = hour; gn = guinea; NR = not reported; Derm/oc = dermal/ocular; Resp = Respiratory; congest. = congestion; CNS = central nervous system; d = day; wk = week; Cardio = cardiovascular; Hemato = hematological; decr. = decreased; wt. = weight.

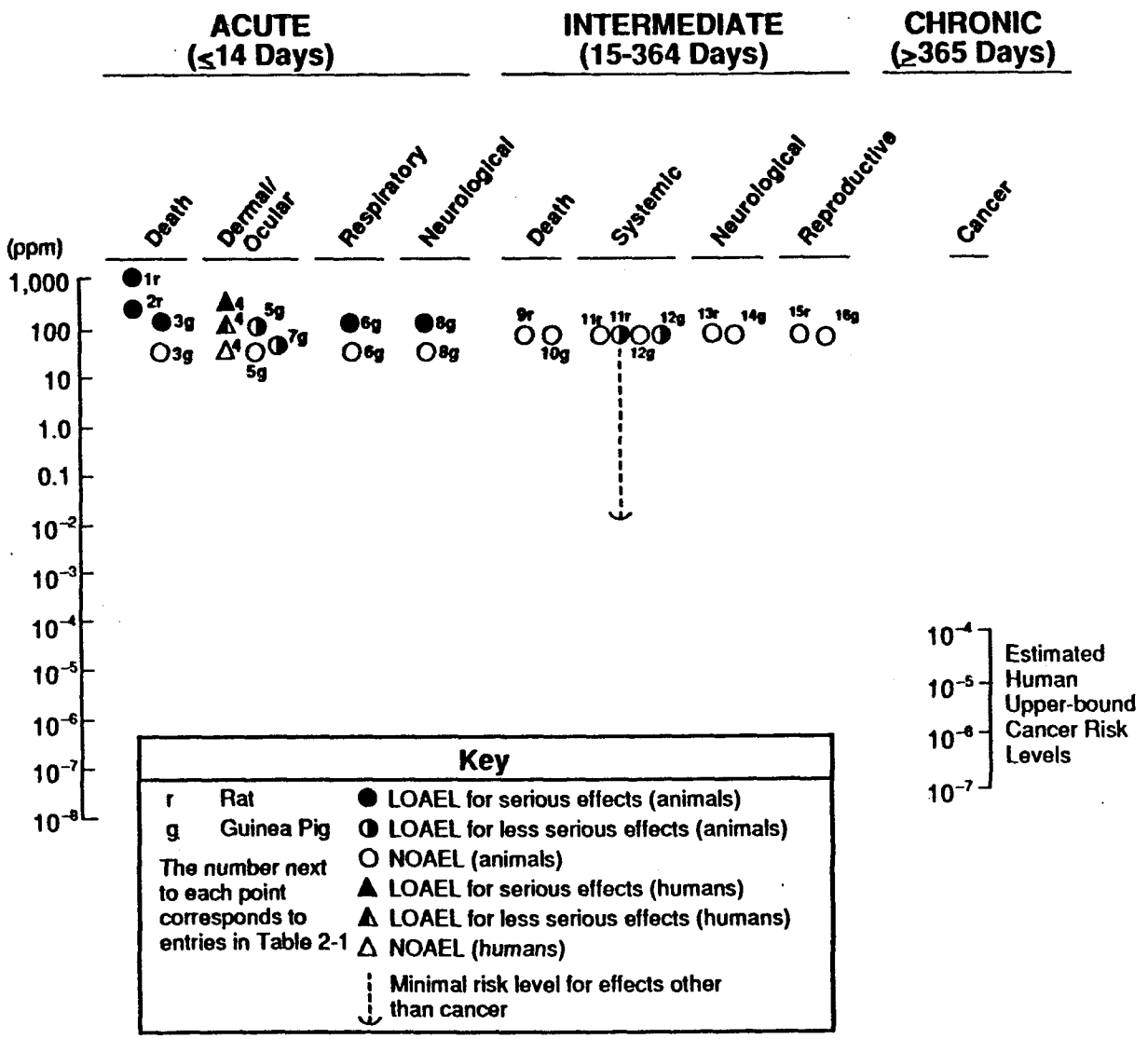


FIGURE 2-1. Levels of Significant Exposure to BCEE – Inhalation

Union Carbide 1948). Exposure of rats to 250 ppm for 4 hours caused death in about half the animals (Carpenter et al. 1949), while exposure of mice, rats, and rabbits to 200 ppm for 1 hour did not cause any deaths (Union Carbide 1948). Four of six guinea pigs exposed to 105 ppm for 13 hours died within four hours after the exposure, while no deaths occurred in animals exposed to 35 ppm for 13.5 hours (Schrenk et al. 1933). Animals exposed to BCEE vapors display marked signs of respiratory distress, and acute lung injury appears to be the principal cause of death (Carpenter et al. 1949). The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1. The values of 105 ppm (Schrenk et al. 1933) and 250 ppm (Carpenter et al. 1949) are presented in Table 1-2.

2.2.1.2 Systemic Effects

Respiratory Effects. The principal acute effect of inhalation exposure to BCEE vapor is irritation and injury to the cells of the respiratory epithelium. In humans, exposure to concentrations of 550 ppm or higher produces extreme irritation and cannot be tolerated for more than a few moments (Schrenk et al. 1933). Exposure to 260 ppm is highly irritating, but is tolerable for brief periods. Irritation is mild at 100 ppm, and minimal at 35 ppm (Schrenk et al. 1933). These values have been presented in Table 1-1.

Studies in guinea pigs provide similar findings, with 35 ppm producing mild nasal irritation within minutes, and higher concentrations producing proportionately greater and more rapid signs of irritation to nose and eyes (Schrenk et al. 1933). Histological examination of animals exposed to concentrations of 100 ppm or higher revealed marked congestion, edema and hemorrhage of the lung. Moderate congestion of brain, liver and kidneys was also noted in some animals, but this was judged to be secondary to the marked lung injury (Schrenk et al. 1933). Animals that survived the exposures recovered fully within 4 to 8 days, and had no histological signs of residual injury. Exposure of rats or guinea pigs to 69 ppm BCEE for 130 days did not result in significant changes in lung/body weight ratios, and did not lead to histological changes in lung (Dow Chemical 1958).

Other Systemic Effects. As noted above, short-term exposure of guinea pigs to 100 ppm resulted in moderate congestion of brain, liver, and kidneys, but this was judged to be secondary to lung injury (Schrenk et al. 1933). Longer-term exposure (130 days) of rats and guinea pigs to 69 ppm of BCEE did not result in hematological effects or gross or

histological signs of injury to liver, kidney, heart, spleen, adrenal or pancreas, but did result in a significant decrease in body weight gain in both rats and guinea pigs (Dow Chemical 1958). Based on this, an intermediate inhalation MRL of 0.02 ppm has been calculated, as described in the footnote on Table 2-1. This value is also presented in Table 1-1.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following inhalation exposure to BCEE.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects of BCEE inhalation in humans. However, data from animal studies indicate that BCEE is a central nervous system depressant, Schrenk et al. (1933) observed that guinea pigs exposed to concentrations of 100 ppm or higher began to become lethargic and uncoordinated within several hours, and that unconsciousness and death could follow. No effects on behavior were noted in guinea pigs or rats exposed to 69 ppm for 130 days (Dow Chemical 1958), but no details were provided on how behavior was evaluated.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Developmental Effects

No studies were located regarding the developmental effects in humans or animals following inhalation exposure to BCEE.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to BCEE. In animals, no gross or histological effects were observed in reproductive tissues of rats and guinea pigs exposed to 69 ppm of BCEE for 18 weeks (Dow Chemical 1958), but no tests of reproductive function or success were performed.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following inhalation exposure to BCEE.

2.2.1.8 Cancer

Although no studies have been performed on the carcinogenic potential of BCEE following inhalation exposure, studies by the oral route (see Section 2.2.2.8, below) indicate that BCEE is carcinogenic in animals. Based on the oral data, EPA has calculated an inhalation unit risk of 3.3×10^{-4}, $(\mu g/m^3)^{-1}$ (EPA 1988). Based on this, the concentrations of BCEE in air corresponding to estimated upper-bound excess lifetime cancer risk levels of 10^{-4}, 10^{-5} and 10^{-6} are 0.05, 0.005 and 0.0005 ppb, respectively. These values are shown in Figure 2-1.

2.2.2 Oral Exposure

No studies were located regarding health effects in humans following oral exposure to BCEE. Table 2-2 and Figure 2-2 summarize available toxicity data for oral exposure of animals to BCEE, and these data are discussed below.

2.2.2.1 Death

The acute oral LD_{50} for BCEE in rats is 75 mg/kg (Smyth and Carpenter 1948). This value has been converted to a corresponding concentration of 530 ppm in water for presentation in Table 1-4. Similar acute oral LD_{50} values (105 to 136 mg/kg) were reported for mice, rabbits, and rats by Union Carbide (1948). Little information exists regarding lethality following chronic exposure. Decreased survival was reported in female rats dosed twice a week with 50 mg/kg for 18 months (Weisburger et al. 1981). The cause of the increased mortality was not determined. The dose of 50 mg/kg/day has been converted to an equivalent concentration of 360 ppm in water for presentation in Table 1-4.

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

TABLE 2-2. Levels of Significant Exposure to BCEE - Oral

Graph Key	Species (Route)	Exposure Duration/ Frequency	Syst. Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE							
Death							
1	rat (G)	1 dose				75 LD50	Smyth and Carpenter 1948
CHRONIC EXPOSURE							
Death							
2	rat (G)	78 wk 2x/wk		25		50	Weisburger et al. 1981
Systemic							
3	rat (G)	78 wk 2x/wk	Other		25 body weight		Weisburger et al. 1981
Cancer							
4	mouse (F)	18 mo				41 CEL (hepatomas)	Innes et al. 1969

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; mg/kg = milligram/kilogram; G = Gavage; LD_{50} = lethal dose, 50% mortality; wk = week; x = time; F = Feed; mo = month; CEL = Cancer Effect Level.

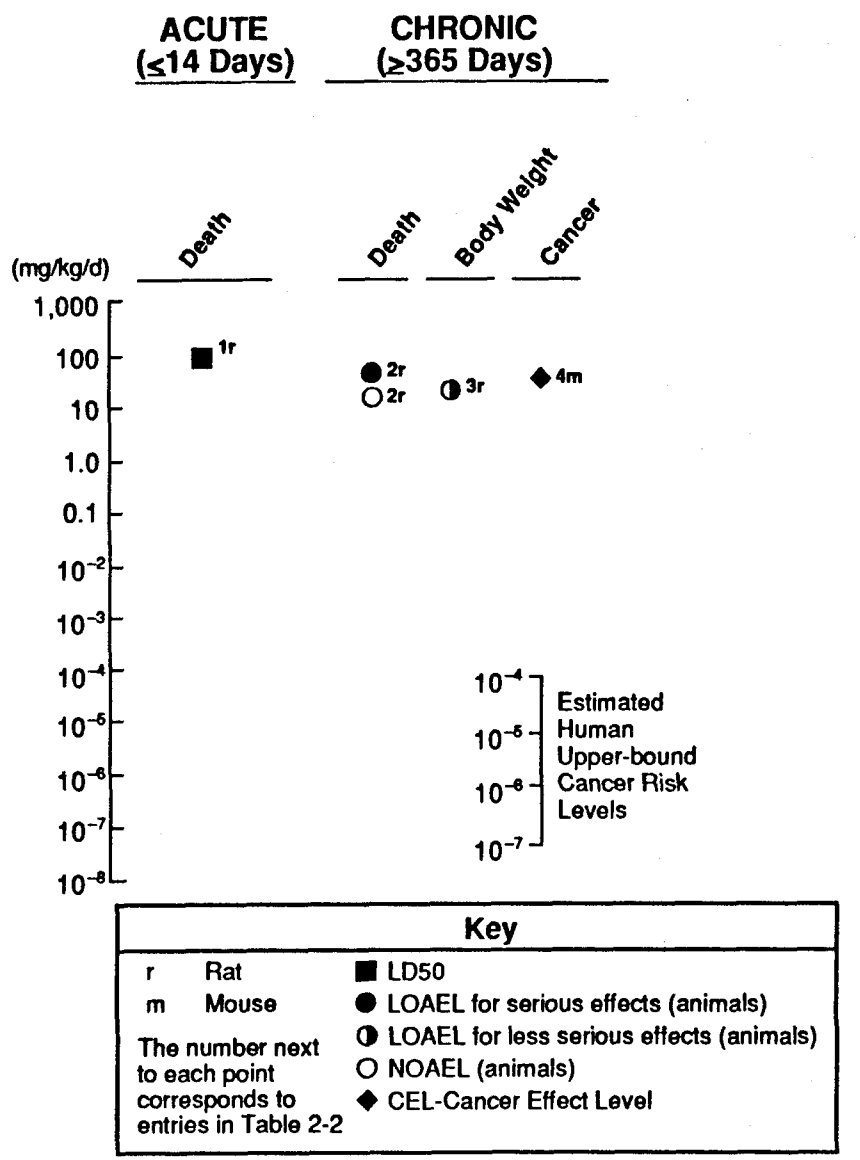


FIGURE 2-2. Levels of Significant Exposure to BCEE – Oral

2.2.2.2 Systemic Effects

No studies were located regarding systemic effects in humans following oral exposure to BCEE. Weisburger et al. (1981) reported that oral exposure to doses of 25 or 50 mg/kg (twice a week for 78 weeks) resulted in decreased body weights in rats, but the magnitude of this effect was not described. The dose of 25 mg/kg/day has been converted to an equivalent concentration of 180 ppm in water for presentation in Table 1-4.

No studies were located on the following effects in humans or animals following oral exposure to BCEE:

2.2.2.3 Immunological Effects

2.2.2.4 Neurological Effects

2.2.2.5 Developmental Effects

2.2.2.6 Reproductive Effects

2.2.2.7 Genotoxic Effects

Jorgenson et al. (1978) dosed male mice for eight weeks with BCEE and observed no evidence of heritable reciprocal translocation of chromosomes. Since dose levels were not reported, the significance of these findings is difficult to judge.

2.2.2.8 Cancer

Innes et al. (1969) reported an increased incidence of hepatomas in two strains of mice exposed to an average dose of 41 mg/kg/day for 80 weeks. The effect was most marked in the males, with liver tumors occurring in 53% and 88% of the exposed males of the two strains, compared with 10% and 6% in unexposed controls, respectively. A smaller effect (22% vs. 0%) was observed in females from one strain, but no effect was seen in females of the other strain. The authors of the study emphasized that although the tumors were described as hepatomas, the majority of tumors might have had malignant potential. No increased incidence of tumors was observed in male or female rats exposed twice a week to doses of 25 or 50 mg/kg (Weisburger et al. 1981).

Based on the results of the study by Innes et al. (1969), and supported by positive mutagenicity studies (see below), EPA (1988) has

ranked BCEE as a probable human carcinogen (Group B2). This category is for chemicals with adequate evidence of carcinogenicity in animals but inadequate evidence in humans. The slope of the linear portion of the cancer dose-response curve at low doses (the ql*) was calculated to be 1.1 $(mg/kg/day)^{-1}$. Based on this, daily intake of 9.1×10^{-7} mg/kg/day of BCEE for a lifetime corresponds to an excess cancer risk of no more than 1×10^{-6}. If exposure occurred by ingestion of water, this would correspond to a concentration of 3×10^{-5} mg/L for a 70-kg adult consuming 2 L/day. If exposure occurred via food, this would correspond to a concentration of 3.2×10^{-5} ppm, assuming consumption of 0.028 kg of food per kg of body weight per day.

2.2.3 Dermal Exposure

Table 2-3 summarizes available quantitative animal data on the toxic effects of BCEE following dermal or ocular exposure.

2.2.3.1 Death

BCEE has moderate dermal toxicity, with an estimated LD_{50} in rabbits of 870 mg/kg (Union Carbide 1948). Smyth and Carpenter (1948) and Union Carbide (1948) estimated that the amount absorbed through the skin of guinea pigs leading to death in 50% of the animals was about 370-390 mg/kg.

2.2.3.2 Systemic Effects

Direct Dermal and Ocular Irritation. Smyth and Carpenter (1948) found that 10 mg of BCEE applied to the skin of rabbits caused irritation, and Carpenter and Smyth (1946) reported that 25 mg of BCEE (0.02 mL of undiluted liquid) instilled in the eye of rabbits caused moderate irritation (a grade of 4 out of 10 was assigned).

Other Systemic Effects. No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic or renal effects in humans or animals following dermal exposure to BCEE.

No studies were located regarding the following effects in humans or animals following dermal exposure to BCEE:

2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

TABLE 2-3. Levels of Significant Exposure to BCEE - Dermal

Species	Exposure Duration/ Frequency	Syst. Effect	NOAEL	LOAEL (Effect) Less Serious	LOAEL (Effect) Serious	Reference
ACUTE EXPOSURE						
Death						
gn pig	24 hr				366 mg/kg LD50	Smyth and Carpenter 1948
rabbit	NR[a]				870 mg/kg LD50	Union Carbide 1948
Systemic						
rabbit	1 dose	Derm/Oc		10 mg skin irrit.		Smyth and Carpenter 1948
rabbit	1 dose	Derm/Oc			25 mg eye irritation	Carpenter and Smyth 1946

[a]Not reported.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; gn = guinea; hr = hour; LD_{50} = lethal dose, 50% mortality; mg/kg = milligram/kilogram; Derm/oc = dermal/ocular; irrit. = irritation.

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

Van Duuren et al. (1972) performed a two-stage initiation-promotion test for tumor production in mouse skin, using a single dose of BCEE (as the initiator) followed by repeated doses of phorbol myristate acetate (as promotor) for two years. The frequency of skin papillomas in the BCEE-treated mice (3/20) was not significantly different from the control group (2/20). Tests were not performed to investigate whether BCEE had any promotor activity, or if it was carcinogenic if applied repeatedly itself.

2.3 RELEVANCE TO PUBLIC HEALTH

Death. Death in animals can occur from an exposure to high levels of BCEE by either inhalation (Carpenter et al. 1949; Schrenk et al. 1933), ingestion (Smyth and Carpenter 1948), or dermal contact (Smyth and Carpenter 1948; Union Carbide 1948). However, only one instance of human death thought to be due to BCEE exposure has been reported (Elkins 1959). This was in a textile factory where exposure was probably quite high. In the environment, exposure to acutely lethal concentrations of BCEE is believed to be very unlikely.

Systemic Effects. The chief systemic health effect following inhalation exposure to BCEE is irritation to the respiratory tract (Schrenk et al. 1933). Because BCEE is so irritating, inhalation exposure conditions that are likely to cause significant injury to lung are easily detectable, and most people would presumably avoid such exposures. BCEE is similarly irritating to the skin following dermal contact (Smyth and Carpenter 1948), but no information was located on SystemicToxicity following dermal exposure. Oral exposure has been noted to result in decreased weight gain in animals (Weisburger et al. 1981), but no information exists on toxicity to specific organ systems following oral exposure.

Neurological Effects. Inhalation exposure to BCEE has been observed to cause central nervous system depression (lethargy, ataxia, sedation) in animals (Schrenk et al. 1933). Presumably this occurs by a

nonspecific mechanism similar to other volatile halocarbon anesthetics, and such effects are likely to be reversible once exposure ceases.

Other Noncarcinogenic Effects. Studies have not been performed to determine whether BCEE exposure leads to immunologic, reproductive, developmental, or genotoxic effects in animals or humans. In the absence of more information on the toxicity and metabolism of this compound, it is difficult to predict whether such effects are likely to be of concern in exposed humans or not.

Cancer. The principal reason for concern with BCEE is its apparent carcinogenic potential. The most direct evidence indicating that BCEE is carcinogenic is the increased incidence of hepatomas in two strains of mice dosed orally for 80 weeks (Innes et al. 1969). This is supported by limited data indicating that BCEE is mutagenic in some bacterial test systems, although several studies have yielded negative results (Table 2-4). On the other hand, increased incidence of mouse liver hepatomas has been questioned as a reliable indication of true carcinogenic potential (Maronpot et al. 1987), and BCEE was not observed to cause a significant increase in tumors in a chronic feeding study in rats (Weisburger et al. 1981) or in parenteral exposure studies in mice (Theiss et al. 1977; Van Duuren et al. 1972) and rats (Norpoth et al. 1986). Also, no binding of BCEE to DNA and no foci of ATPase-deficient cells (a sign of pre-neoplastic effects) were detected in liver of rats exposed to BCEE (Gwinner et al. 1983), and no evidence of heritable chromosome damage was detected in a preliminary study in mice (Jorgenson et al. 1978). Consequently, while the positive carcinogenicity findings in mice are adequate to conclude that BCEE may be a human carcinogen, the evidence on this point is limited.

2.4 LEVELS IN HUMAN TISSUES AND FLUIDS ASSOCIATED WITH HEALTH EFFECTS

No studies were located regarding levels of BCEE or its metabolites in human tissues or fluids.

2.5 LEVELS IN THE ENVIRONMENT ASSOCIATED WITH LEVELS IN HUMAN TISSUES AND/OR HEALTH EFFECTS

No studies were located regarding the relationship between exposure levels in air, food or water and resulting fluid levels or health effects in humans.

TABLE 2-4. Mutagenicity of BCEE in Vitro

Test Organism	Mutagenicity[a] With Activation	Mutagenicity[a] Without Activation	Reference
S. typhimurium (TA 100)	-	ND	Norpoth et al. 1986
S. typhimurium (TA 100)	ND	+	Simmon 1977
E. coli (MT 103, MT 119, MT 126)	ND	-	Quinto and Radman 1987

[a]ND = No data.

- = negative; + = positive.

2. HEALTH EFFECTS

2.6 TOXICOKINETICS

2.6.1 Absorption

2.6.1.1 Inhalation Exposure

Quantitative data on BCEE absorption across the lung are limited. Gwinner et al. (1983) reported that rats placed in a chamber containing BCEE vapor absorbed over 95% of the compound within 18 hours. This indicates that BCEE is well absorbed following inhalation exposure, but it is not possible to estimate the inhalation absorption fraction from this observation.

2.6.1.2 Oral Exposure

Lingg et al. (1982) reported that only 2% of a single oral dose of BCEE administered to rats was excreted in the feces, indicating that absorption across the gastrointestinal tract was essentially complete.

2.6.1.3 Dermal Exposure

No studies were located regarding the rate or the extent of absorption by the dermal route. However, acute dermal toxicity studies (Smyth and Carpenter 1948) suggest that BCEE is well absorbed across the skin.

2.6.2 Distribution

2.6.2.1 Inhalation Exposure

No studies were located regarding the distribution of BCEE in human or animal tissues following inhalation exposure.

2.6.2.2 Oral Exposure

Lingg et al. (1982) administered a single oral dose of ^{14}C-labelled BCEE to rats, and measured the radioactive content of tissues 48 hours later. Only a small fraction of the dose (2.3%) was found in organs and tissues, with 0.96% in muscle, 0.56% in kidney, 0.49% in blood, 0.19% in liver, and 0.1% in other tissues. These findings suggest that BCEE is not preferentially accumulated or retained in any one tissue or organ of the body.

2.6.2.3 Dermal Exposure

No studies were located regarding the distribution of BCEE in human or animal tissues following dermal exposure.

2.6.3 Metabolism

Studies in animals indicate that BCEE is extensively metabolized, with thiodiglycolic acid (TDGA) being the principal endproduct (Lingg et al. 1979; Norpoth et al. 1986). The pathway leading to TDGA formation is not certain, but probably involves oxidative cleavage of the ether bond to yield chloroacetaldehyde and 2-chloroethanol, as shown in Figure 2-3 (Bolt 1984; Gwinner et al. 1983; Norpoth et al. 1986; Lingg et al. 1979, 1982; Muller and Norpoth 1979). TDGA recovered in urine usually accounts for 50% to 80% of a dose of BCEE (Lingg et al. 1979, 1982). Smaller amounts of BCEE (3% to 5%) are metabolized by oxidation or substitution at a chlorine without ether cleavage (see Figure 2-3), and about 12% is degraded to CO_2 (Lingg et al. 1982). Only about 2% of the dose is excreted via the lungs as unchanged BCEE (Lingg et al. 1979).

Gwinner et al. (1983) exposed rats to ^{14}C-labelled BCEE vapor, and measured the amount of radioactivity irreversibly bound to tissue proteins 24 hours later. Distribution of unbound parent or metabolites was not measured. Highest levels were found in liver, kidney and small intestine, with much lower levels in lung, spleen and muscle. The presence of protein-bound label in these tissues suggested to the authors that reactive intermediates were formed that led to covalent adducts, but incorporation of label into protein might also have occurred through normal synthetic pathways involving non-toxic breakdown products from BCEE. No label was detectable in liver DNA or RNA.

2.6.4 Excretion

Lingg et al. (1979, 1982) found that approximately 80% of an oral dose of BCEE administered to rats was excreted within 48 hours. Most of the dose (65%) was excreted as urinary metabolites (mostly thiodiglycolic acid), with smaller amounts excreted in feces (3%) or expired air (11% as CO_2 and less than 2% as parent BCEE). Only 2% of the dose remained in the body. This indicates that BCEE is effectively excreted, and that it has a low tendency to accumulate in tissues.

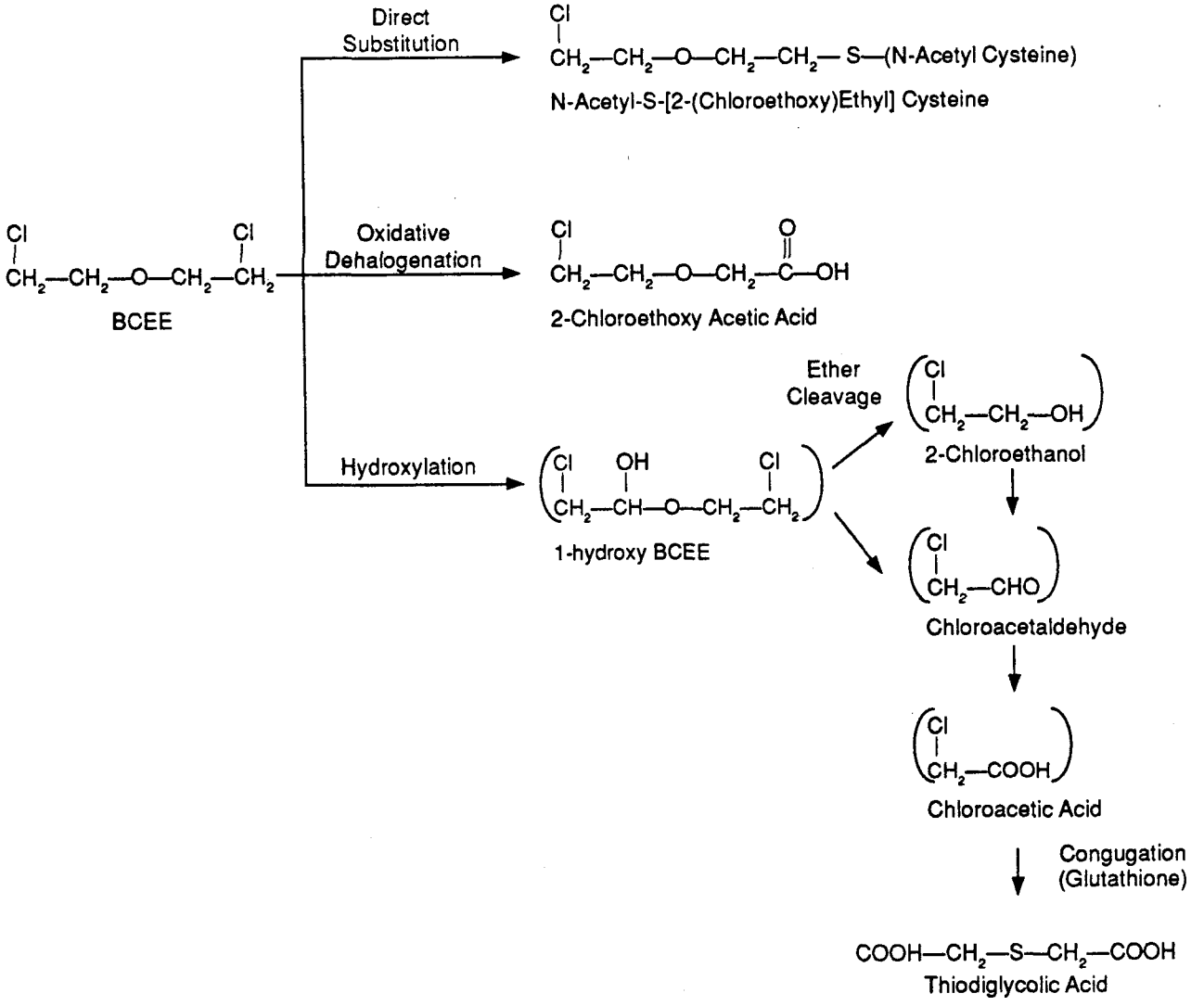


FIGURE 2-3. Summary of BCEE Metabolism in Rats

Adapted from Bolt 1984; Gwinner et al. 1983; Lingg et al. 1982; Norpoth et al. 1986.

Structures shown in parentheses have not been isolated in urine.

2. HEALTH EFFECTS

2.7 INTERACTIONS WITH OTHER CHEMICALS

No information was located on the interaction of BCEE with other chemicals.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No information was located to indicate that any human population might be especially susceptible to the toxic effects of BCEE. Based on the observation that BCEE is a powerful irritant of the respiratory tract, it may be expected that individuals with lung disease or other forms of respiratory distress might be particularly vulnerable to the effects of BCEE vapors.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of BCEE is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled,

2.9.1 Existing Information on Health Effects of BCEE

As shown in Figure 2-4, there is very little information on the health effects of BCEE in humans. In animals, limited data exist on acute lethality and direct irritant effects, and there is some information on systemic effects following inhalation exposure. Several studies have investigated carcinogenicity following oral or dermal exposure, but carcinogenicity following inhalation exposure has not been examined.

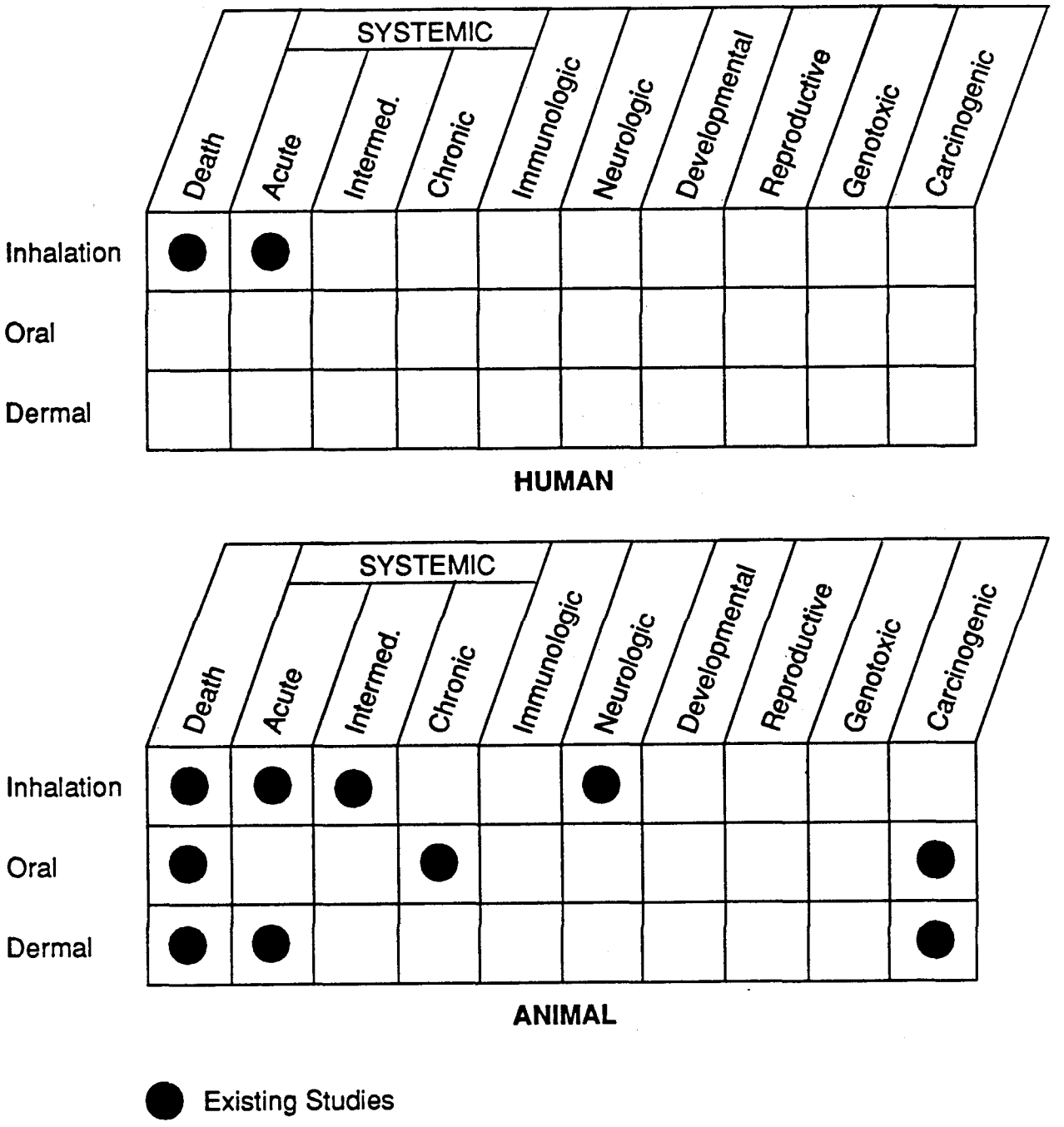


FIGURE 2-4. Existing Information on Health Effects of BCEE

2.9.2 Data Needs

Single Dose Exposure. The effects of single exposures to BCEE have not been thoroughly investigated. Estimates of acute inhalation exposures that cause death in animals are available, but only one study (Schrenk et al. 1933) provides dose-response data for more sensitive endpoints of toxicity (lung irritation and edema). Further inhalation studies using modern analytical and histological techniques would be valuable in confirming and refining the limited data available on lung injury, and in determining whether other tissues are injured as well. Essentially no acute oral toxicity data exist except for one estimate of the LD_{50} (Smyth and Carpenter 1948). For this reason, a thorough investigation of the toxic effects following oral exposure in animals would be useful.

Repeated Dose Exposure. Only limited data (Dow Chemical 1958) are available on the effects of repeated inhalation exposure to BCEE. This study employed only one exposure level (69 ppm), so thresholds were not established for any adverse effects following repeated exposures. For this reason, further studies using modern histological and biochemical tests would be useful in determining the NOAEL and LOAEL values for injury to lung and other tissues. Although several chronic oral studies have been performed (Innes et al. 1969, Weisburger et al. 1981), very little information has been obtained on noncarcinogenic endpoints. Consequently, studies to determine thresholds for systemic injury following oral exposure would be valuable. Since residents near industrial sources or waste sites that discharge BCEE are probably most likely to be exposed through drinking water, studies using BCEE in water would be especially helpful.

Chronic Exposure and Carcinogenicity. Oral studies in mice are adequate to establish that BCEE causes liver tumors in this species, but there is debate over the relevance of this to other species, including humans. For this reason further studies on the oral and inhalation carcinogenicity of BCEE in several different species would be valuable.

Genotoxicity. Several studies have been performed on the genotoxicity of BCEE, and the results have been mixed (e.g., see Table 2-4). Further studies to clarify the mutagenic and genotoxic potential of BCEE would be valuable, especially if information could be gained on the role of metabolic activation and on the identity of genotoxic intermediates.

2. HEALTH EFFECTS

Reproductive Toxicity. No studies were located on reproductive effects of BCEE. Single generation tests of reproductive toxicity following BCEE exposure (both oral and inhalation) would be valuable in determining whether this may be an effect of concern for humans.

Developmental Toxicity. No studies were located on the developmental effects of BCEE. Studies of teratogenic and fetotoxic potential would be valuable.

Immunotoxicity. No studies were located on the immunotoxicity of BCEE. Since the immune system is sometimes found to be sensitive to chemical agents, studies of the effects of BCEE on this system could be helpful.

Neurotoxicity. Inhalation exposure to high doses of BCEE appears to cause CNS depression and sedation (Schrenk et al. 1933), but the dose-response curve for this effect is not well defined. Further studies to identify the threshold for CNS depression and other effects on behavior following both oral and inhalation exposure would be helpful. In addition, studies employing modern histological and electrophysiological techniques would be valuable in determining if cells of the CNS are structurally injured by exposure to BCEE.

Epidemiological and Human Dosimetry Studies. No epidemiological studies were located in humans exposed to BCEE. Performance of such studies could be helpful in evaluating the chronic human health risk from BCEE exposure, especially cancer.

Biomarkers of Disease. No biomarkers of BCEE-induced disease in humans are known. Since the principal effect associated. with inhalation exposure is nonspecific lung irritation, it may be difficult to develop preclinical indices of potential lung injury that are specific for BCEE.

Bioavailability from Environmental Media. No studies were located on the relative bioavailability of BCEE in different environmental media. Based on the physical properties of BCEE, it would not be expected that bioavailability would vary widely between media, but studies to investigate this would be helpful in risk assessments involving exposure to BCEE in soil or food.

Food Chain Bioaccumulation. No studies were located on food chain bioaccwnulation of BCEE. Based on the observation that BCEE metabolism is rapid and essentially complete in rats, accumulation of BCEE in the tissues of mammals does not appear likely. Studies on BCEE retention in several species besides rat would be helpful to confirm this, however. The studies on BCEE accumulation in fish and plants would also be valuable.

Absorption, Distribution, Metabolism, and Excretion. Although there are limited toxicokinetic data on BCEE from studies of animals, there are several areas where additional information would be valuable. Since available information is derived from studies employing single exposures, studies of uptake, distribution and excretion patterns following repeated exposures would be useful. Quantitative studies of absorption rates across the lungs and the skin would be helpful is estimating absorbed doses and resultant health effects following inhalation and dermal exposure. Additional metabolism studies would be valuable in identifying intermediate metabolites which might be involved in the genotoxic or carcinogenic effects of BCEE. Finally, further studies of the kinetics of BCEE metabolism and clearance would be valuable in evaluating the potential for cumulative toxicity.

Comparative Toxicokinetics. Toxicokinetic studies of BCEE metabolism and excretion have been performed in rats (Gwinner et al. 1983; Lingg et al. 1979; Muller and Norpoth 1979; Norpoth et al. 1986). Consequently, studies of metabolism in other species would be valuable, especially in mice (since a carcinogenic response has been observed in mice but not in rats). In addition, studies of the pattern of BCEE degradation products in human urine would be helpful in evaluating whether BCEE is metabolized in humans as it is in rats.

2.9.3 Ongoing Studies

No information was located on any ongoing studies on the health effects or toxicokinetics of BCEE in humans or animals.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

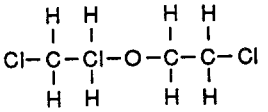
Table 3-1 lists common synonyms, trade names and other pertinent identification information for BCEE.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of BCEE.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of BCEE

Property	Value	References
Chemical Name	Bis(2-chloroethyl) ether	IARC 1975
Synonyms	1,1'-Oxybis(2-chloro) ethane; bis(chloroethyl) ether; bis(β-chloroethyl)ether; sym-dichloroethylether; 2,2'-dichloro-diethyl ether; 2-dichloroethyl ether; dichloroethyl ether; dichloroethyl oxide; DCEE	IARC 1975
Trade Name	Chlorex	IARC 1975
Chemical Formula	$C_4H_8Cl_2O$	Weast 1985
Chemical Structure		
Identification Numbers:		
CAS Registry	111-44-4	NLM 1988
NIOSH RTECS	KN0875000	HSDB 1988
EPA Hazardous Waste	U025	NLM 1988
OHM-TADS	7216672	HSDB 1988
DOT/UN/NA/IMCO Shipping	UN1916	NLM 1988
HSDB	502	NLM 1988
NCI	--[a]	

CAS - Chemical Abstracts Service
NIOSH - National Institute for Occupational Safety and Health
RTECS - Registry of Toxic Effects of Chemical Substances
OHM-TADS - Oil and Hazardous Materials/Technical Assistance Data System
DOT/UN/NA/IMCO - Department of Transportation/United Nations/North America/ International Maritime Dangerous Goods Code
HSDB - Hazardous Substances Data Bank
NCI - National Cancer Institute

[a]No data located.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Physical and Chemical Properties of BCEE

Property	Value	References
Molecular Weight	143.04	Weast 1985
Color	colorless, clear	Windholz 1983
Physical State	liquid	Windholz 1983
Melting Point, °C	-24.5	Weast 1985
Boiling Point, °C	178	Weast 1985
Density, 20°/4°	1.2199	Weast 1985
Odor	pungent	Windholz 1983
Odor Threshold		
Air, ppm	0.049	Amoore and Hautala 1983
Solubility		
Water, mg/L	10,700 10,200 17,200	Hake and Rowe 1963 Verschueren 1977 Veith et al. 1980
Organic Solvents	soluble	Weast 1985
Partition coefficients		
Log octanol/water	1.58 1.5 1.1	Callahan et al. 1979 Mabey et al. 1982 Veith et al. 1980
Log k_{oc}	1.1	Mabey et al. 1982
Vapor Pressure, mm Hg, 20 °C	0.71	Verschueren 1977
Henry's law constant, atm-m^3/mol	1.31E-05	Mabey et al. 1982
Autoignition temperature, °C	369	HSDB 1988
Flash point °C	55	HSDB 1988
Flammability limits	No Data	HSDB 1988
Conversion factors		Verschueren 1977
ppm (v/v) to mg/m^3 in air (25 °C)	1 ppm = 5.85 mg/m^3	
mg/m^3 to ppm (v/v) in air (25 °C)	1 mg/m^3 = 0.17 ppm	

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

All BCEE produced in the United States is made by direct chlorination of ethylene glycol (Buckman Laboratories 1988). BCEE can also be produced by the treatment of ethylene chlorohydrin or 2-chloroethanol with sulfuric acid, or by chlorination of ethylene chlorohydrin at 80°C. Production of BCEE in the United States in 1986 was estimated to be 1,200 kkg (Buckman Laboratories 1988).

4.2 IMPORT

Imports of BCEE in 1977 were estimated to be about 590 kkg (HSDB 1988). Imports of BCEE in 1986 were estimated to be about 60 kkg (Buckman Laboratories 1988).

4.3 USE

In the past, BCEE has been used as a solvent for fats, waxes, greases and esters (Schrenk et al. 1933). It has also been used as a constituent of paints and varnishes, as a cleaning fluid for textiles, in the purification of oils and gasoline, in the manufacture of medicines and pharmaceuticals, as an intermediate in the synthesis of other chemicals, and as an insecticide and a soil fumigant (Browning 1965; Hake and Rowe 1963; HSDB 1988; Verschueren 1977; Windholz 1983).

BCEE is currently used primarily as a chemical intermediate for the manufacture of pesticides. The two major pesticide products made from BCEE are WSCP, an isoprene polymer used primarily as an algicide, and CDQ, a diquaternary ammonium compound used as a microbicide and corrosion inhibitor in the petroleum industry. A small amount of BCEE (about 1%) is still used as a solvent.

4.4 DISPOSAL

No information was located on the amounts of BCEE disposed of to the environment or to waste sites. Because BCEE is classified as a hazardous waste under the Resource Conservation and Recovery Act (RCRA), all BCEE waste must be disposed of in an authorized RCRA facility. Permitted disposal methods include incineration and land disposal, although EPA is currently considering possible restrictions on land disposal methods (40 CFR 268.11).

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.5 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of BCEE is available. Where adequate information is not available, ATSDR, in cooperation with the National.Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

4.5.1 Data Needs

Production, Import, Use, and Disposal. Data are available on the production, import and general use patterns, but more complete information on present disposal volumes and methods would be valuable in estimating the likelihood and possible magnitude of further environmental contamination with BCEE.

According to the Emergency Planning and Community Right to Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The Toxic Release Inventory (TRI), which contains release information for 1987, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and emission.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Relatively little information is available on human exposure to BCEE. In the workplace, the most likely exposure routes are inhalation or dermal contact. For the general public, the most likely route is ingestion of BCEE in drinking water. Low levels of BCEE have been detected in some drinking water systems, and BCEE has been detected in groundwater at about 2% of the waste sites being investigated under Superfund. The most likely means of exposure near these sites is consumption of contaminated water, but dermal contact and inhalation exposure might also occur.

5.2 RELEASES TO THE ENVIRONMENT

No studies were located regarding the amount of BCEE being released from industrial processes or waste sites into air, water or soil.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Little information was located on the transport or partitioning of BCEE in the environment. The vapor pressure of BCEE at 20°C is 0.7 mm Hg (Verschueren 1977), suggesting that volatilization from soil or water, while probably very slow, could be significant (Callahan et al. 1979). EPA (1987a) calculated a half-time for volatilization of BCEE from a river to be 3.4 days. Because BCEE is quite soluble in water (10,200 mg/L) (Verschueren 1977), it is expected that BCEE in air would tend to be removed by wet deposition, resulting in a cycle between water, soil and air (Callahan et al. 1979). The relative distribution between these phases, however, is not known.

Because BCEE has good solubility in water and a relatively low log octanol-water partition coefficient (measured to be 1.1 by Veith et al. 1980), BCEE in aqueous media is not expected to adsorb strongly to sediments, nor is it likely to be bioaccumulated by aquatic organisms (Callahan et al. 1979). Consistent with this, a bioconcentration factor of 11 has been measured in sunfish by Veith et al. (1980).

For the same reasons, BGEE is not expected to adsorb strongly to soils, and would be expected to migrate in soil water. Consistent with this, Wilson et al. (1981) reported a soil retardation factor of <1.5 for sandy soil with low organic content, while other contaminants (e.g., di- and trichlorobenzene) had retardation factors of 3.4 to 9.4.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Callahan et al. (1979) reviewed the potential fate of BCEE in the environment and suggested that BCEE in a smog-like atmosphere would probably undergo photooxidative destruction with a half-life of approximately four hours. The rate of atmospheric photooxidation under other conditions was not estimated. Direct photolysis was judged to be an unimportant process, since BCEE does not absorb visible or near ultraviolet light (Callahan et al. 1979).

5.3.2.2 Water

Most ethers are very resistant to hydrolysis, and the rate of cleavage of the carbon-oxygen bond by abiotic processes is expected to be insignificant (Callahan et al. 1979). The carbon-chlorine bond is also quite stable to abiotic cleavage. Based on a measured hydrolysis rate constant of $1.5 \times 10^{-5} min^{-1}$ at 100°C, Mabey et al. (1982) estimated the half-life of the carbon-chlorine bond to be about 22 years at 20°C. This rate is somewhat slower than observed for simple alkyl halides (Callahan et al. 1979; Mabey et al. 1982), an effect which Mabey et al. (1982) attributed to the effect of the chloro-ethoxy group on the adjacent carbon.

Biodegradation may be an important fate process for BCEE in water. In laboratory studies, Tabak et al. (1981) found that in aqueous media inoculated with sewage, BCEE underwent 100% transformation within seven days, and there was a rapid adaptation of the degradative microorganisms. Similar results were reported by Ludzack and Ettinger (1963), although in this case there was a 25 day lag before adaption occurred, and 30 more days were required to convert 80% of the BCEE to CO_2. A second dose of BCEE added to the adapted medium was 80% oxidized in 15 days. Monsen (1986) reported that BCEE also underwent significant biodegradation (68%) in an anaerobic laboratory test pond designed to simulate an industrial primary lagoon. Losses via evaporation and sorption were minimal. In contrast to these findings, Dojlido (1979) did not observe significant biodegradation of BCEE in several laboratory

test systems. The reason for this discrepancy is not certain, but may be due to insufficient incubation time (two weeks) for the adaptation to occur. Biodegradation in surface waters would likely be slower than observed in the laboratory, but could lead to significant destruction of BCEE.

5.3.2.3 Soil

Wilson et al. (1981) observed no significant transformation of BCEE percolated through soil for 45 days, but Kincannon and Lin (1986) found that BCEE was significantly degraded in a 97-day laboratory soil column study. The initial rate constant for degradation was reported to be 0.042 day^{-1} (half-time of 16.7 days). After 48 days, the rate increased to 0.086 day^{-1} (half-time of 8.0 days), suggesting that there was an acclimation of soil microbes occurring.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

No studies were located with regard to concentrations of BCEE in ambient air. Based on the physical-chemical properties of BCEE, some release of BCEE into air from contaminated chemical waste sites or industrial settings is expected, but no quantitative data were located.

5.4.2 Water

In 1977, the EPA carried out an extensive study (the National Organics Monitoring Survey) of organic contaminants in finished drinking water supplies across the United States. BCEE was not detected in any samples in Phase I of the study, but the detection limit was only 5 μg/L. In phase II, the detection limit was lowered to 0.005 μg/L, and BCEE was detected in water from 13 of 113 cities sampled. The values ranged from 0.01 to 0.36 μg/L, with a mean concentration (for the 13 positive samples) of 0.1 μg/L (Dressman et al. 1977). In phase III of the Survey, BCEE was detected in drinking water from 8 of 110 cities, with a mean concentration of 0.024 μg/L. Trace quantities of BCEE have been reported in several rivers, including the Mississippi, the Delaware and the Kanawha (Staples et al. 1985; EPA 1987a). BCEE was detected in ground water at about 2% of waste disposal sites being investigated under Superfund, at a geometric mean concentration of around 840 μg/L (CLPSD 1988).

5. POTENTIAL FOR HUMAN EXPOSURE

5.4.3 Soil

BCEE was detected in soil at only 0.4% of waste sites monitored under Superfund, at geometric mean concentration of 140 ppb (CLPSD 1988).

5.4.4 Other Media

No studies were located regarding the occurrence of BCEE in food or other media.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The primary known source of exposure for the general population is via the water supply. The reports of quantities in several drinking water supplies provided a mean value of approximately 0.1 ppb. Ingestion of approximately 2 liters of water per day by an adult would provide a daily intake of 0.003 μg/kg/day of BCEE. Based on the slope factor of 1.1 $(mg/kg/day)^{-1}$ (see Section 2.2.2.8), this corresponds to an upperbound lifetime cancer risk from this source of about 3×10^{-6}.

No studies were located regarding exposure of workers to BCEE.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Even though there are no exposure data, those at greatest risk of exposure to BCEE are probably workers who are exposed to BCEE while on the job. Residents who live near waste sites or industrial facilities that permit escape of BCEE may also experience higher than average exposure to BCEE. Exposure would be most likely by ingestion of contaminated water, but inhalation exposure might also occur. The level and significance of such exposures can only be evaluated on a site-by site basis.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of BCEE is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following

discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

5.7.1 Data Needs

Physical and Chemical Properties. The physical and chemical properties of BCEE have been determined (Table 3-1), and further research on these properties does not appear to be essential.

Environmental Fate. Although there is information which provides a general prediction of the likely fate and transport of BCEE in the environment, quantitative data are not available for most fate processes. Reliable quantitative data on rates of volatilization from water and soil, atmospheric oxidation, hydrolysis in water, and biodegradation in soil and water would be useful in estimating likely concentrations of BCEE in air, soil and water around waste sites and other possible sources of BCEE emissions.

Exposure Levels in Environmental Media. Available data suggest that contamination of water may occur around chemical waste sites or industrial facilities where BCEE is present. For this reason, additional monitoring data on BCEE concentrations in water (both surface water and ground water) around such sites would be valuable. Monitoring of BCEE levels in air, soil, fish, and possibly other foods would be helpful in estimating the significance of exposures through these media.

Exposure Levels in Humans. Information on exposure of the general population to BCEE is limited. The compound has been reported in drinking water in some locations, but many water supplies have not been tested. It would appear that an increased monitoring of drinking water supplies for this compound would be beneficial. Similarly, data on typical occupational exposure levels and durations would be valuable in estimating doses to workers, and data on exposure levels around chemical waste sites would be valuable in determining whether nearby residents are likely to be subject to significant health risk.

5. POTENTIAL FOR HUMAN EXPOSURE

Exposure Registries. No registry exists for humans known to have been exposed to BCEE. Creation of such a registry would be valuable in collection of further information on the health effects of BCEE on humans, especially chronic effects (such as cancer) that do not become manifest at the time of exposure.

5.7.2 On-going Studies

No information was located regarding on-going studies on the environmental fate of BCEE, or on BCEE levels in the ambient environment. Remedial investigations being performed under Superfund at chemical waste sites will provide additional data on the occurrence of BCEE in water, soil and possibly in air at these locations, and on the levels of human exposure that result.

6. ANALYTICAL METHODS

6.1 BIOLOGICAL MATERIALS

No methods were located that are routinely used for the detection of BCEE in biological materials. Norpoth et al. (1986) reported a method for measuring thiodiglycolic acid (the principal animal metabolite of BCEE) in the urine of rats. This method employed an ion exchange isolation of TDGA followed by gas chromatographic analysis using a flame ionization detector. Sensitivity was not reported, but the method was able to detect a two-fold increase in thiodiglycolic acid (TDGA) excretion (from 0.37 to 0.72 μmo1/24 hours) resulting from an 8-hour exposure to 10 ppm BCEE.

6.2 ENVIRONMENTAL SAMPLES

BCEE in environmental samples is most commonly determined by gas chromatography with a halogen-specific detector (GC/HSD) (Dressman et al. 1977; EPA 1982a), gas chromatography/mass spectrometry (GC/MS) (EPA 1986a), or capillary column gas chromatography/Fourier transform infrared (GC/FT-IR) spectrometry (EPA 1986c).

The determination of BCEE in air requires passing the air samples through a sorbent, followed by elution of adsorbed BCEE from the sorbent and gas chromatographic measurement. Coconut shell charcoal is the favored sorbent, carbon disulfide is used for elution, and gas chromatography is employed for analysis (NIOSH 1984).

The EPA has developed a method of analysis specifically for haloethers in water (EPA 1982a). These compounds include bis(2-chloroethyl), bis(2-chloroisopropyl), 4-chlorophenol phenyl, and 4-bromophenol phenyl ethers, and bis(2-chloroethoxy) methane. The analysis involves an extraction into dichloromethane solvent, concentration by evaporation with exchange to hexane, and Florisil cleanup prior to gas chromatographic measurement. Other standard EPA methods are adapted to the determination of BCEE in wastes.

If BCEE is identified in a sample by a GC procedure other than GC-MS, it is important to confirm the identification by a second method. For example, in a survey of water samples from 113 cities, 44 samples were tentatively found to contain BCEE. Reanalysis of these samples (either by using a different GC column, or by separating interfering components with Florisil prior to GC analysis) indicated that only 13 of the 44 tentatively-identified samples actually contained BCEE (Dressman et al. 1977). Thus, false positive results are likely if confirmatory tests are not performed.

6. ANALYTICAL METHODS

Methods for the determination of BCEE in environmental samples are summarized in Table 6-1.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of BCEE is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

6.3.1 Data Needs

Methods for Determining Parent Compound and Metabolites in Biological Materials. Since there are no standard methods for analysis of BCEE in biological materials, development of such methods would be useful. The properties of this compound suggest that it should be amenable to determination in biological samples. It is a relatively high-boiling liquid (178°C) with a low log octanol/water partition coefficient, extractable from water into dichloromethane, relatively stable to hydrolysis, and easily measured by gas chromatography. The high boiling temperature suggests that purge-and-trap and headspace techniques may not be readily applicable to the determination of BCEE in biological samples, but techniques based upon solvent extraction should work well.

Norpoth et al. (1986) reported a method for measuring TDGA in urine. Although this is the principal animal metabolite of BCEE, it occurs naturally in the urine of control animals and is also formed by metabolism of other chemicals. For these reasons, it would be helpful to develop methods for the detection and quantification of urinary metabolites that are unique to BCEE, such as N-acetyl-S-[2-(chloroethoxy)ethyl] cysteine or 2-chloroethoxyacetic acid.

6. ANALYTICAL METHODS

TABLE 6-1. Analytical Methods for BCEE in Environmental Media

Sample type	Extraction/cleanup	Detection	Limit of Detection	References
Air	Absorb on charcoal, desorb with carbon disulfide	GC	1 $\mu g/m^3$	Berck 1965
Air	Absorb on coconut shell charcoal, elute with carbon disulfide	GC/FID	0.01 mg/ sample	NIOSH 1984
Soil/sediment	Extraction and cleanup	GC/MS	1 mg/kg	EPA 1986a
Solid wastes	Extraction and cleanup	GC/MS	1-200 mg/kg	EPA 1986a
Soil/sediment	Extraction and cleanup	CCGC/MS	1 mg/kg	EPA 1986b
Solid Wastes	Extraction and cleanup	CCGC/MS	1-200 mg/kg	EPA 1986b
Water	Extract with ethyl ether/hexane; concentrate by evaporation; separate interfering compounds using Florisil	GC/HSD	0.005 µg/L	Dressman et al. 1977
Water	Extract with dichloromethane, exchange to hexane, Florisil cleanup	GC/HSD	0.3 µg/L	EPA 1982a
Water	Extract with dichloromethane, concentrate by evaporation	GC/MS	5.7 µg/L	EPA 1982b
Water	Extract with dichloromethane, dry, concentrate by evaporation	GC/IDMS	10 µg/L	EPA 1984
Environmental samples, waste water	Extract with dichloromethane, concentrate by evaporation	GC/FT-IR	35 µg/L	EPA 1986c, Gurka et al. 1987

Abbreviations: GC, gas chromatography; FID, flame ionization detector; MS, mass spectrometry; CCGC, capillary column gas chromatography; HSD, halide specific detector; IDMS, isotope dilution mass spectrometry; FT-IR, fourier transform infrared spectrometry.

6. ANALYTICAL METHODS

Methods for Biomarkers of Exposure. No routine tests for biomarkers of exposure to BCEE were located. Using radioactively labeled BCEE, Gwinner et al. (1983) reported incorporation of label into cellular proteins of animals exposed to BCEE. Studies to determine if this is due to protein adduct formation would be valuable. If so, immunological assays might be developed to detect such adducts formed from reaction of unlabeled BCEE with proteins such as albumin or hemoglobin. Gwinner et al. (1983) did not detect label in DNA or RNA from animals exposed to BCEE, suggesting that adduct formation with these macromolecules might not be a sensitive biomarker of exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Although methods exist for the determination of BCEE in environmental samples, detection limits (see Table 6-1) are not adequate to measure BCEE in water or air at the concentrations estimated to correspond to the 10^{-6} risk level for cancer (0.03 ppb in water, 0.003 $\mu g/m^3$ in air). Consequently, improvements in sensitivity would be helpful. The problem of high humidity interfering with the collection of BCEE from air (lowered breakthrough volume) should also be addressed.

6.3.2 Ongoing Studies

Supercritical fluid extraction/chromatography and immunoassay are two areas of intense current activity from which substantial advances in the determination of BCEE and metabolites in biological samples can be anticipated. The two techniques are complementary in that supercritical fluid extraction is especially promising for the removal of analytes from sample material (Hawthorne 1988) while immunoassay is very selective and sensitive (Vanderlaan et al. 1988).

An especially promising approach to the determination of BCEE in biological samples is supercritical fluid extraction coupled with supercritical fluid chromatography. This combination has been described for the determination of sulfonylurea herbicides and their metabolites in complex matrices, including soil, plant materials, and cell culture medium (McNally and Wheeler 1988). The approach described in this work should be applicable to BCEE.

6. ANALYTICAL METHODS

Thermospray techniques interfaced with mass spectrometry, with or without high performance liquid chromatographic separation, are proving useful for the determination of thermally labile compounds (as are some toxicant metabolites), and should be applicable to the determination of BCEE and its metabolites in biological materials (Korfmacher et al. 1987; Betowski et al. 1987).

The EPA is funding an ongoing effort to develop a master analytical scheme for organic compounds in water (Michael et al. 1988). The overall goal is the development of a technology capable of detecting and quantifying organic compounds at 0.1 μg/L in drinking water, 1 μg/L in surface waters, and 10 μg/L in effluent waters. Analytes are to include numerous semivolatile compounds and some compounds that are only semisoluble in water, as well as volatile compounds. A comprehensive review of the literature leading to these efforts has been published (Pellizzari et al. 1985). It may be anticipated that improved methods for the determination of BCEE in environmental samples will be developed as part of this effort.

The current high level of activity in supercritical fluid extraction of solid and semisolid samples should yield improved recoveries and sensitivities for the determination of BCEE in solid wastes, and the compound should be amenable to supercritical fluid chromatographic analysis. Immunoassay analysis (Vanderlaan et al. 1988) is an area of intense current activity from which substantial advances in the determination of BCEE in environmental samples can be anticipated.

7. REGULATlONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, a number of regulations and advisory values have been established for BCEE by various international, national and state agencies. These values are summarized in Table 7-l.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to BCEE

Agency	Description	Value	References
	International		
IARC	Carcinogenic classification	Group 3	IARC 1987
	National		
Regulations			
a. Air			
OSHA	Permissible Exposure Limit (PEL) Ceiling	15 ppm (90 mg/m^3)	29 CFR 1910.1000
b. Water			
EPA OWRS	General permits under the National Pollutant Discharge Elimination System (NPDES)	NA[a]	40 CFR 122 Appendix D Table II
	General Pretreatment Regulations for Existing and New Sources of Pollution (chloroalkyl ethers)	NA	40 CFR 403
c. Non-specific media			
EPA OERR	Reportable Quantity	1 lb	40 CFR 302.4 EPA 1985
	Reportable Quantity (proposed)	10 lb	EPA 1987c
	Extremely Hazardous Substances Threshold Planning Quantity	10,000 lb	40 CFR 355 EPA 1987b
EPA OSW	Hazardous Waste Constituent (chloroalkyl ethers, N.O.S.) (Appendix VIII)	NA	40 CFR 261 EPA 1980b
	Ground-water Monitoring List (Appendix IX)	NA	40 CFR 264 EPA 1987d
Guidelines			
a. Air			
ACGIH	Threshold Limit Value (TLV) Time Weighted Average (TWA)	5 ppm (30 mg/m^3)	ACGIH 1986
	Short-term Exposure Limit (STEL)	10 ppm (60 mg/m^3)	
NIOSH	Immediately Dangerous to Life or Health Level (IDLH)	250 ppm	NIOSH 1985

7. REGULATIONS AND ADVISORIES

TABLE 7-1 - continued

Agency	Description	Value	References
b. Water			
EPA OWRS	Ambient Water Quality Criteria to Protect Human Health[b]		EPA 1980a
	Ingesting Water and Organisms		
	10^{-5}	0.30 µg/L	
	10^{-6}	0.03 µg/L	
	10^{-7}	0.003 µg/L	
	Ingesting Organisms Only		
	10^{-5}	13.6 µg/L	
	10^{-6}	1.36 µg/L	
	10^{-7}	0.14 µg/L	
c. Other			
EPA	Carcinogenic Classification	B2	EPA 1988
	Cancer slope factor	1.1 $(mg/kg/d)^{-1}$	
	10^{-6} Risk level (water)	$3x10^{-5}$ mg/L	
	10^{-6} Risk level (air)	$3x10^{-6}$ mg/m^3	
	State Regulations and Guidelines		
State Environmental Agencies	Drinking Water Standards and Guidelines		FSTRAC 1988
	Arizona	0.01 µg/L	
	Kansas	4.2 µg/L	
	Maine	8.3 µg/L	
	Minnesota	0.31 µg/L	
State Environmental Agencies	Acceptable Ambient Air Concentration Guidelines or Standards		NATICH 1987
	Kansas	71.429 µg/m^3 (annual)	
	Nevada	0.119 ppm (8 hr)	
	Pennsylvania, Philadelphia	120 ppb (1 yr)	
	Virginia	500 µg/m^3 (24 hr)	

[a] Not applicable.
[b] Because of its carcinogenic potential, the EPA-recommended concentration for BCEE in ambient water is zero. However, because attainment of this level may not be possible, levels which correspond to upper bound incremental lifetime cancer risks of 10^{-5}, 10^{-6}, and 10^{-7} are estimated.

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same time period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study or group of studies which produces significant increases in incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling value (CL) -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

9. GLOSSARY

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In vivo -- Occurring within the living organism.

Lethal Concentration(LO) (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration(50) (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose(LO) (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose(50) (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

9. GLOSSARY

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

LT50 (lethal time) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-h shift.

q_1* -- The upper-bound estimate of the low-dose slope of the doseresponse curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

9. GLOSSARY

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-h period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

TD50 (toxic dose) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

9. GLOSSARY

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect, The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-h workday or 40-h workweek.

Uncertainty Factor (UP) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of humans, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX: PEER REVIEW

A peer review panel was assembled for BCEE. The panel consisted of the following members: Dr. Mohammad G. Mustafa, Professor, UCLA School of Public Health; Dr. Charles Baxter, Associate Professor of Environmental Health, University of Cincinnati Medical Center; Dr. Martin Alexander, Professor, Department of Agronomy, Cornell University. Unpublished studies were also peer reviewed by Dr. Nancy Tooney, Associate Professor of Biochemistry, Polytechnic University, Brooklyn, NY. These experts collectively have knowledge of BCEE's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Superfund Amendments and Reauthorization Act of 1986, Section 110.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.

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