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.

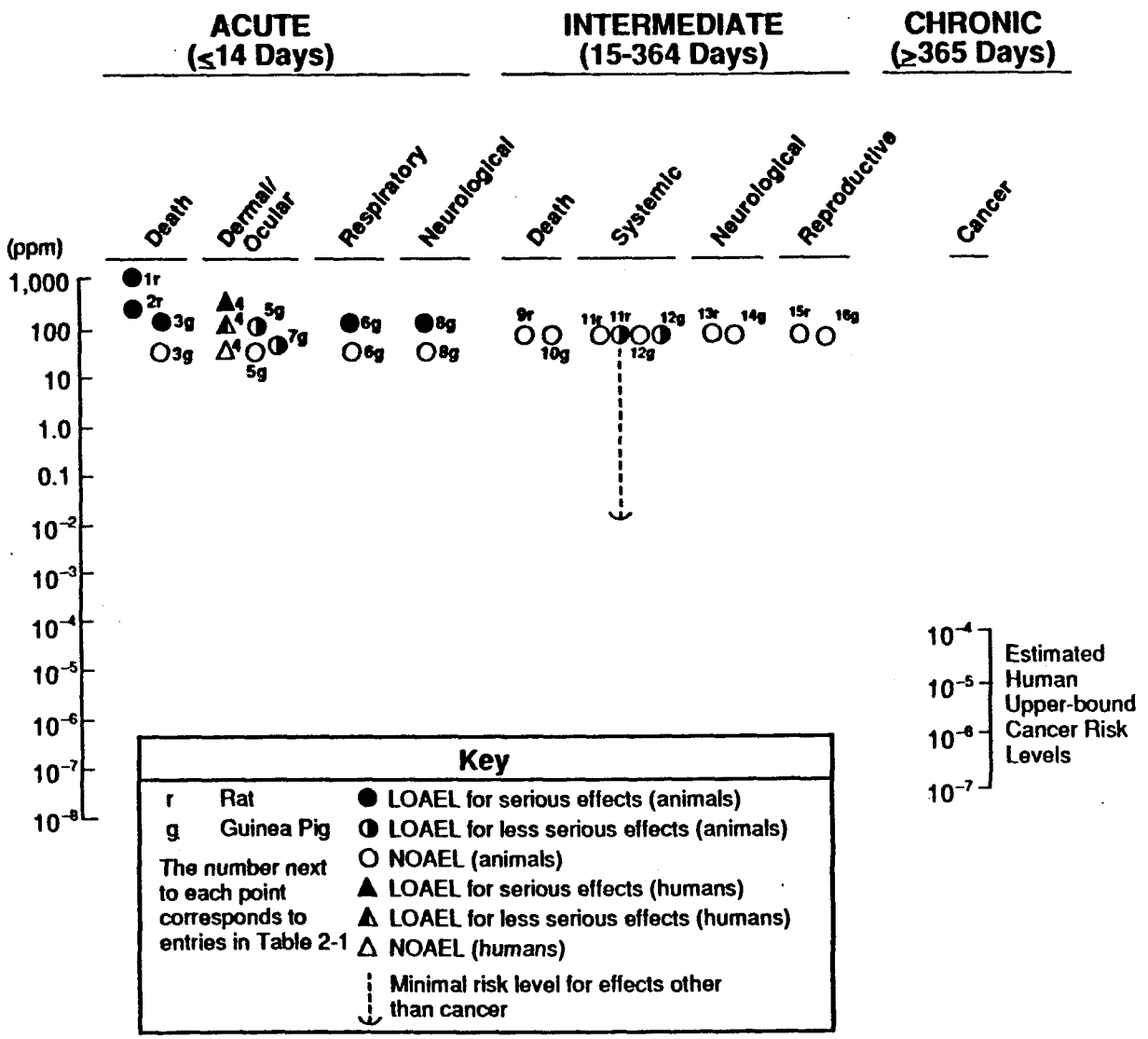

FIGURE 2-1. Levels of Significant Exposure to BCEE – Inhalation

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.

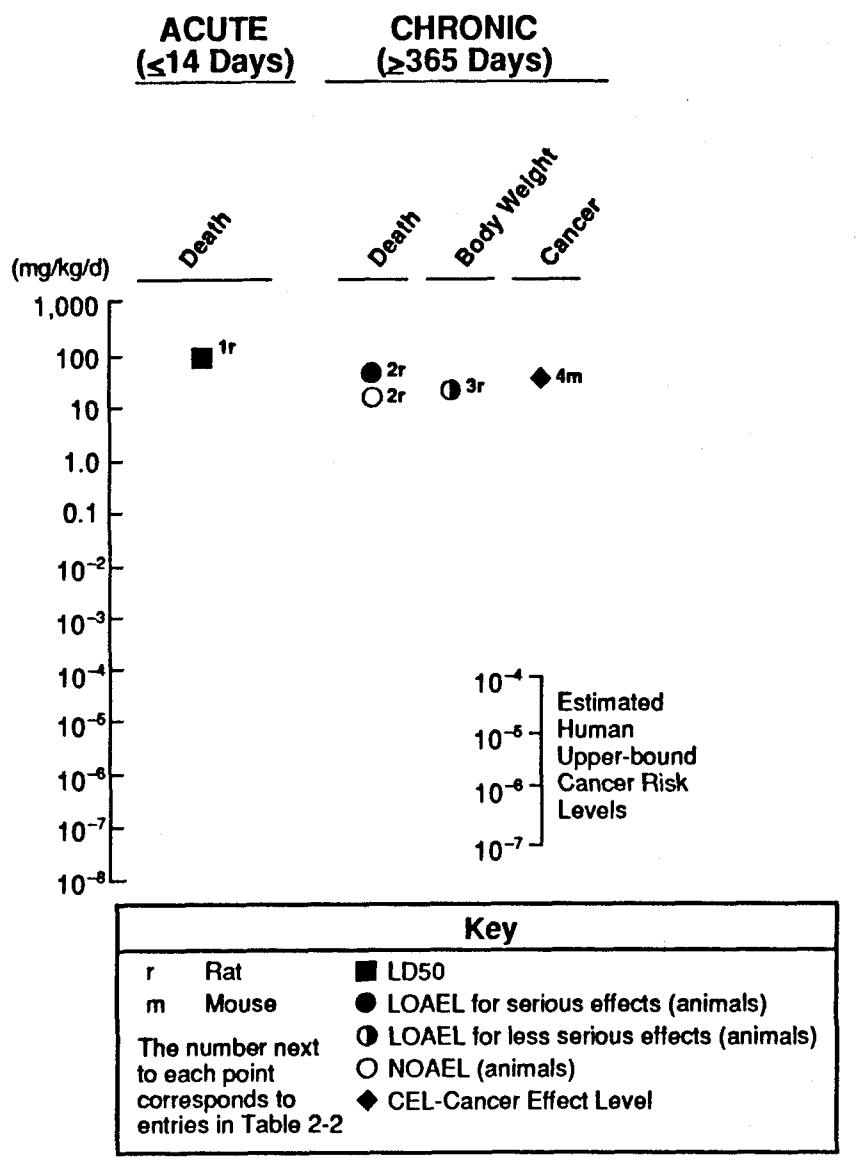

FIGURE 2-2. Levels of Significant Exposure to BCEE – Oral

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.

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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.

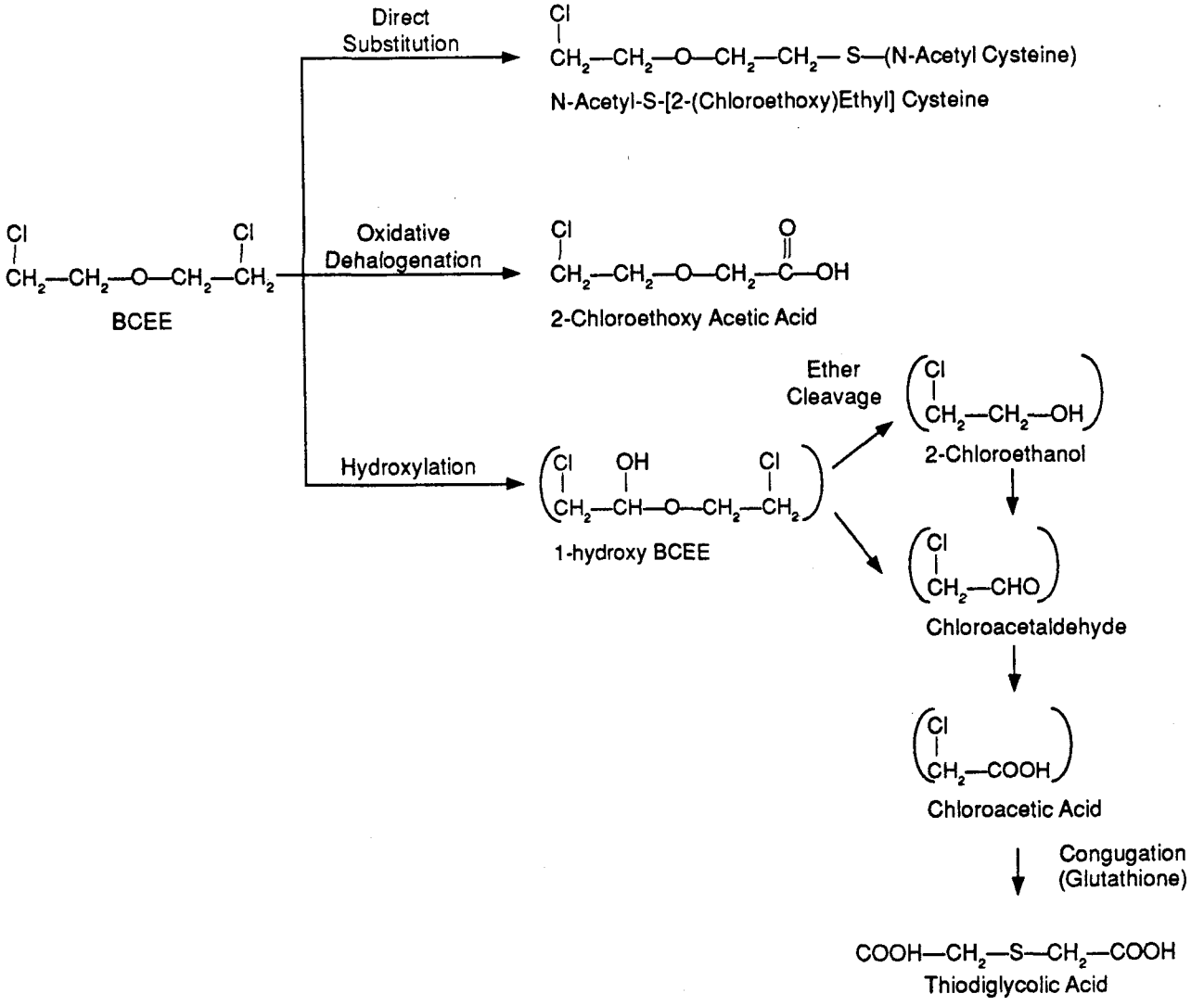

FIGURE 2-3. Summary of BCEE Metabolism in Rats

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.

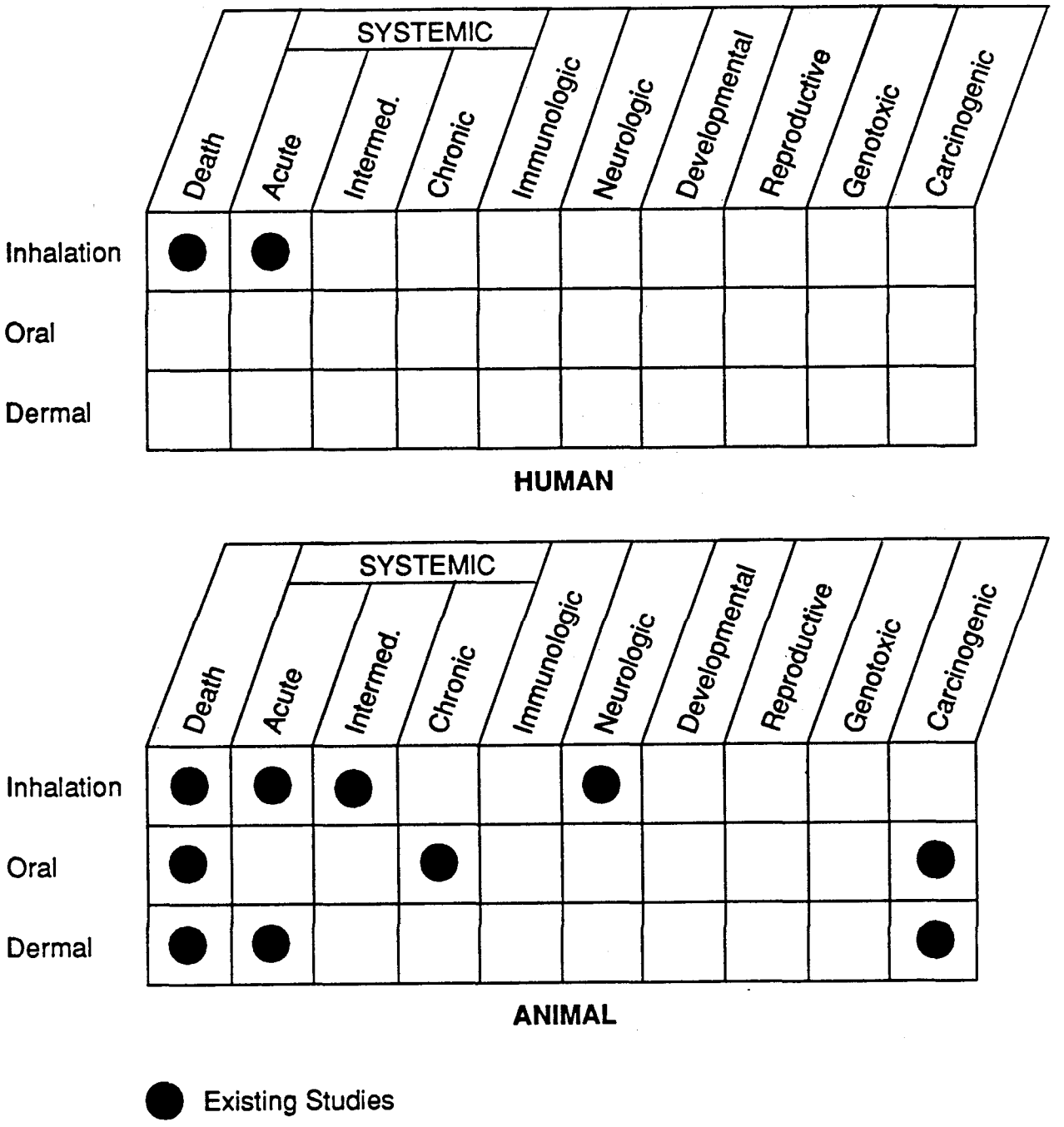

FIGURE 2-4. Existing Information on Health Effects of BCEE

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.