CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, 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 conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of BCEE.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

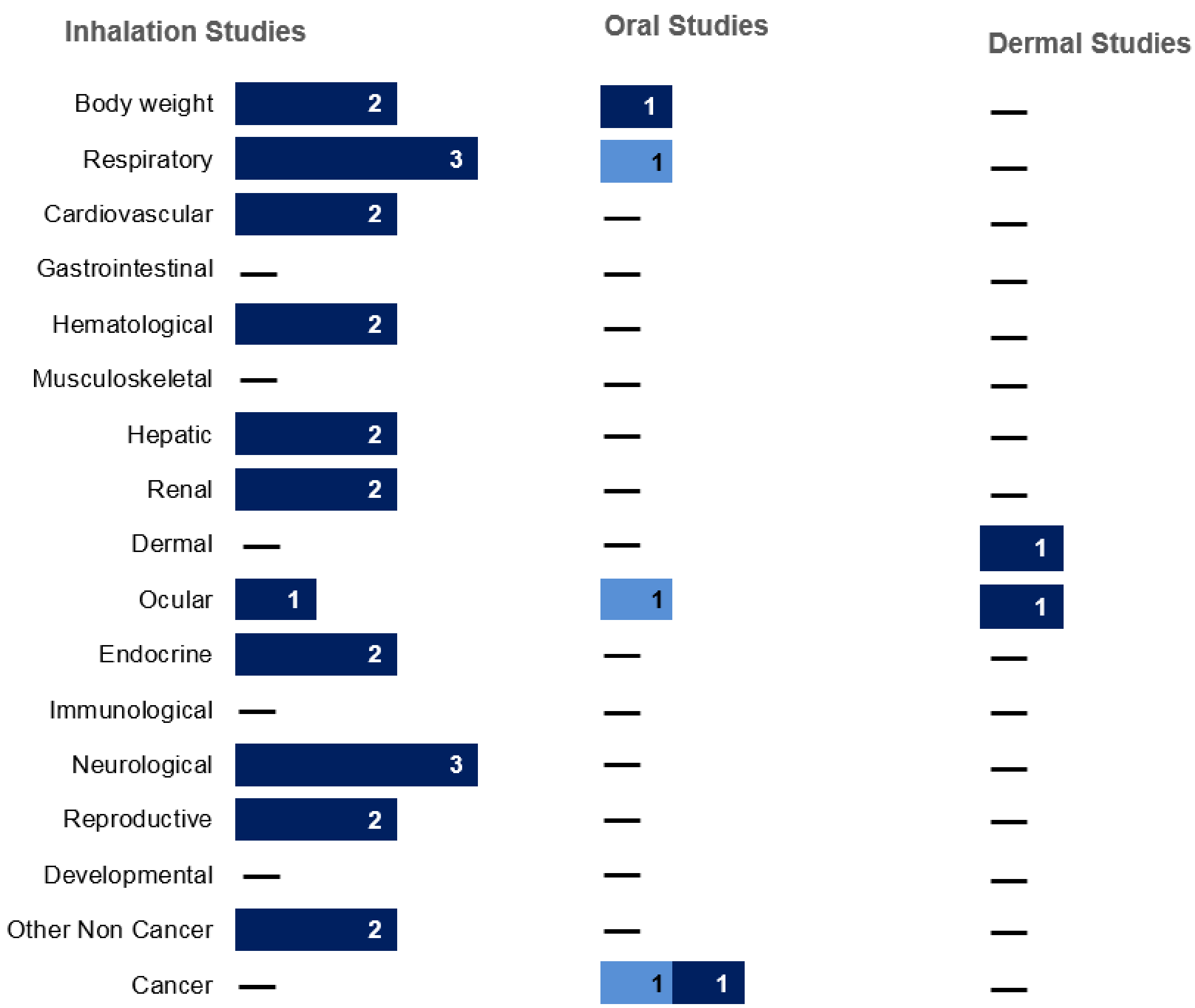
6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to BCEE that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of BCEE. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As illustrated in Figure 6-1, a small number of studies have evaluated the toxicity of BCEE. Half of these studies involved inhalation exposure in laboratory animals. The most commonly examined endpoints were body weight, respiratory, and neurological. In addition, six studies examined the acute lethality of BCEE following inhalation, oral, or dermal exposure. An inhalation study in rats and guinea pigs was the only study examined a wide range of potential endpoints (Dow Chemical 1958).

Figure 6-1. Summary of Existing Health Effects Studies on Bis(2-Chloroethyl)Ether By Route and Endpoint*

The majority of the studies examined inhalation exposure in animals (versus **humans**)
Potential body weight, respiratory, and neurological effects were the most studied endpoints



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect.

6.2 Identification of Data Needs

Missing information in Figure 6-1 should not be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. The available acute inhalation database was not considered adequate for derivation of an MRL. Several limitations were identified in the only available study (Schrenk et al. 1933), including limited evaluation of the respiratory tract and other potential targets of toxicity, lack of reporting incidence data for the nasal lesions, and limited details on the study design. Additional inhalation toxicity studies are needed; these studies should include examination of a wide range of potential targets including the nose and lungs. Acute-duration oral studies are needed to identify sensitive targets of toxicity and establish dose-response relationships.

Intermediate-Duration MRLs. Although limited data are available on the effects of intermediate-duration inhalation exposure to BCEE, the database was considered adequate for derivation of an MRL. Further studies using modern histological and biochemical tests would be useful to support this MRL. No intermediate-duration oral studies were identified and are necessary for derivation of an MRL. These studies should evaluate a wide variety of potential endpoints and test a range of dose levels.

Chronic-Duration MRLs. The lack of chronic-duration inhalation studies precluded derivation of a chronic MRL. The only available chronic-duration oral study (Weisburger et al. 1981) was limited to an examination of body weight and carcinogenic endpoints and was not considered suitable for derivation of an MRL. Chronic toxicity studies utilizing inhalation and oral exposure and examining a wide range of endpoints are needed to identify the most sensitive target and establish dose-response relationships.

Health Effects. A small number of studies have evaluated the toxicity of BCEE. The available studies suggest that the most sensitive effect of BCEE is mucosal irritation; however, the data are not sufficient for establishing concentration-response relationships. Acute-, intermediate-, and chronic-duration inhalation and oral studies examining a wide range of potential targets of toxicity are needed to identify the critical targets and effect levels. Inhalation studies should also include examination of the nasal cavity

since the results of an acute study (Schrenk et al. 1933) suggest that this may be the most sensitive target. Dermal studies are also needed to examine the toxicity of repeated exposure to BCEE.

No studies were located on reproductive or developmental effects of BCEE. Single-generation tests of reproductive toxicity and developmental toxicity studies would be valuable in determining whether these may be effects of concern for humans. The results of an *in vitro* study (Sakazaki et al. 2001) provide suggestive evidence that the immune system may be a target of BCEE toxicity; inhalation and/or oral studies examining immune function would be useful for determining whether it is target of concern for humans. Inhalation exposure to high doses of BCEE appears to cause central nervous system depression and sedation (Schrenk et al. 1933), but the concentration-response curve for this effect is not well defined. Further studies to identify the threshold for central nervous system depression and other effects on behavior following both oral and inhalation exposure would be helpful.

Epidemiology 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 Exposure and Effect. No biomarkers of exposure to BCEE were located. Studies evaluating whether levels of BCEE or one of its metabolites in biological fluids are reflective of exposure levels would be useful. 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.

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 that 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.

Children's Susceptibility. No studies have evaluated the toxicity of BCEE in children or young animals. Studies in young animals and/or children would be useful to address potential concerns of that children may be more susceptible to the toxicity of BCEE than adults.

Physical and Chemical Properties. The physical and chemical properties of BCEE have been determined (Table 4-1), and further research on these properties does not appear to be essential.

Production, Import/Export, Use, Release, and Disposal. Data on current uses and disposal practices would be valuable in determining whether industrial activities pose an important source of human exposure to BCEE.

Environmental Fate. Although there is information that provides 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.

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.

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 groundwater) 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.

Food Chain Bioaccumulation. No studies were located on food chain bioaccumulation of BCEE; studies designed to evaluate potential BCEE accumulation in fish and plants would also be valuable.

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 groundwater) 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.

Exposures of Children. No studies are available to assess whether children are at a higher exposure risk than adults. Studies examining potential exposure sources for children would be useful.

Analytical Methods. 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. Although methods exist for the determination of BCEE in environmental samples, detection limits are not adequate to measure BCEE in water or air at low concentrations.

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 Ongoing Studies

No ongoing studies were identified for BCEE.