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 BCME 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 BCME.

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 BCME 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 BCME. 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.

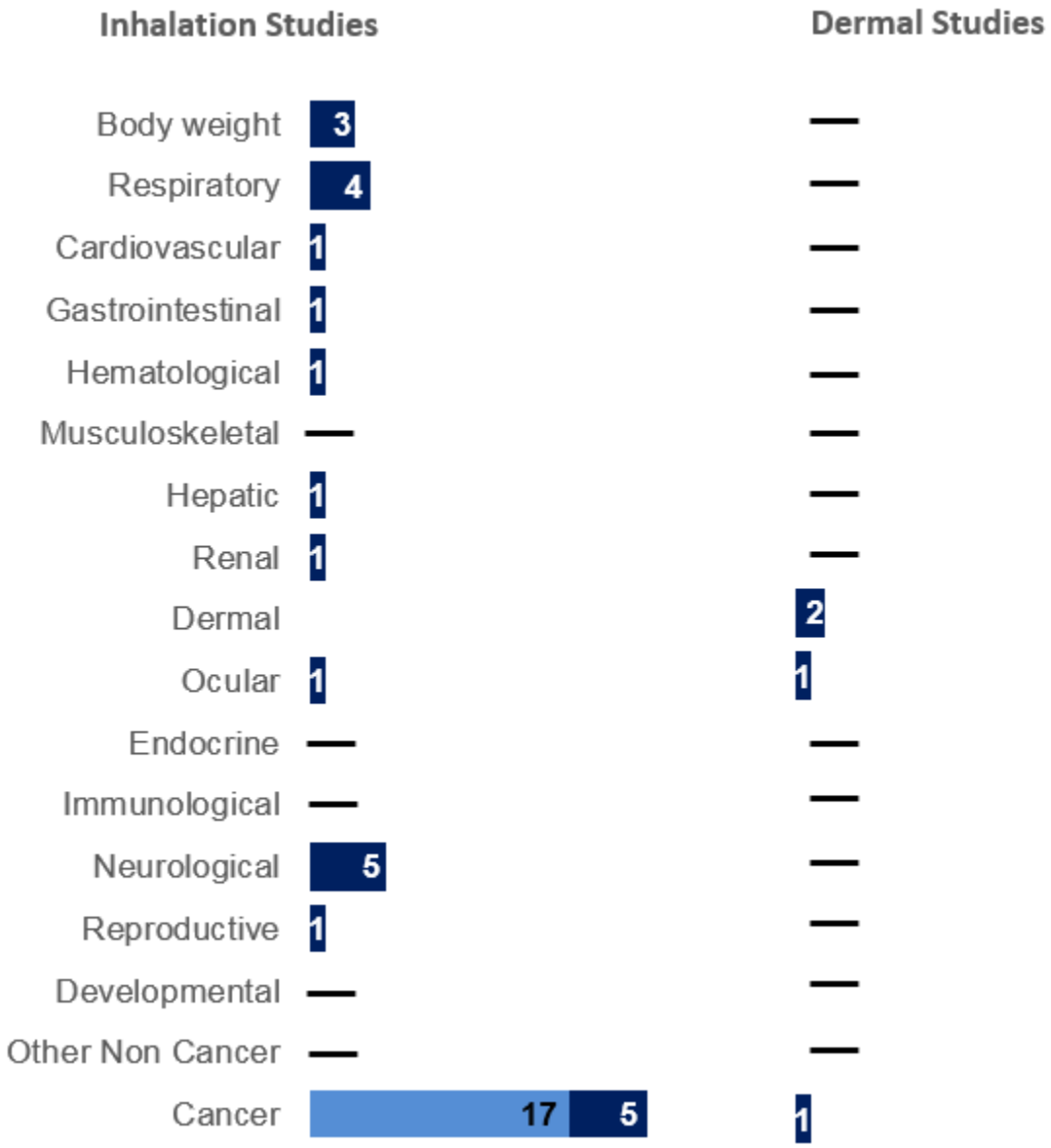
6.2 Identification of Data Needs

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. Several studies have been performed in animals on the effects of single inhalation exposures to BCME, and exposure conditions leading to acute lethality are reasonably well defined. However, the acute concentration-response curve for nonlethal effects on the respiratory has not been determined, and further studies to identify the acute NOAEL would be valuable for derivation of an

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

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



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. No oral studies in humans or animals examining nonlethal endpoints were located.

MRL. The oral database is limited to a lethality study and repeated exposure studies are needed for MRL derivation.

Intermediate-Duration MRLs. Available studies on the effects of repeated inhalation exposure of animals to BCME (Leong et al. 1971, 1981) indicate that an exposure level of 0.1 ppm is a NOAEL for most systemic effects in rats. The data was considered adequate for derivation of an MRL; however, additional studies are needed to define the NOAEL/LOAEL boundary for noncancerous respiratory effects. No intermediate-duration oral studies were identified and are needed to identify sensitive targets of toxicity and for derivation of an MRL.

Chronic-Duration MRLs. No chronic-duration studies in laboratory animals were identified; epidemiology studies have focused on the carcinogenicity of BCME in workers. Given the lethality and carcinogenicity of BCME, studies examining low concentrations are needed to identify critical targets of toxicity and establish concentration-response relationships.

Health Effects. A small number of studies have evaluated the toxicity of BCME. The available studies suggest that the most sensitive effect of BCME is respiratory effects, neurotoxicity, and cancer; 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. Dermal studies are also needed to examine the toxicity of repeated exposure to BCME.

Cancer. A number of studies in animals indicate that inhalation of BCME is associated with risk of nasal or lung tumors. In order to assess the potential risks in the workplace, further studies in animals might be helpful in improving information on the dose- and time-dependency of BCME-induced tumorigenesis. In particular, studies would be valuable to investigate why BCME induces tumors with such a short latency, and why it results in nasal tumors in some species and lung tumors in others. Studies on the interaction of BCME with other chemicals such as CME (with which it is often associated in the workplace) would also be valuable.

Genotoxicity. The genotoxicity of BCME has been investigated in several strains of bacteria, but such systems may not be optimal for investigating the effects of such a rapidly hydrolyzed material. Specifically, if BCME acts as an alkylating agent to damage DNA, then tests that favor

hydrolysis before entry into the cell can occur may yield misleading results. Tests in prokaryotic and eukaryotic systems designed to minimize the degree of hydrolysis in the medium prior to cell penetration would be valuable in estimating the potential genotoxic effect of BCME on the respiratory epithelium.

Reproductive Toxicity. Only one study, Leong et al. (1981), was located that addressed the toxic effects of BCME on reproductive organs. This study examined the histological appearance of reproductive tissues in male rats only, and no test of reproductive function was performed. No studies were located on reproductive effects in females. On this basis, more extensive tests of BCME exposure on reproductive function in both male and female animals would be valuable in predicting the possible risk of reproductive effects in workers exposed to BCME.

Developmental Toxicity. No studies were located on the developmental toxicity of BCME. Although the rapid hydrolysis of BCME makes it unlikely that BCME could act on the fetus directly, effects might still occur as a consequence of maternal toxicity.

Immunotoxicity. No studies were located on the effects of BCME exposure on the immune system. Because the immune system is often observed to be especially sensitive to chemical toxicants, investigations in animals on the effects of BCME on the immune system would be valuable.

Neurotoxicity. Drew et al. (1975) reported that inhalation exposure of rats and hamsters led to subarachnoid hemorrhage, but the severity or significance of this finding was not discussed. These limited data suggest that a more thorough study of the effects of BCME on the nervous system would be useful, including tests both of functions (behavior, electrophysiological tests, etc.) and of structure (histopathology).

Epidemiology and Human Dosimetry Studies. A number of epidemiological studies have been performed on workers exposed to BCME in the past. While these studies are limited by the absence of reliable dosimetry data and the presence of other risk factors (smoking, other chemicals), the data nevertheless constitute strong evidence that BCME increases risk of lung cancer in humans. Although prospective epidemiological studies may not be feasible since exposure to BCME in the workplace is now so limited, continued follow-up of populations exposed in the past will be helpful in refining estimates of the latency and the incidence of cancer in these cohorts.

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

Absorption, Distribution, Metabolism, and Excretion. No studies were located on the toxicokinetics of BCME in animals or humans. Although acquisition of such data is made difficult by the rapid hydrolysis of BCME, studies focusing on the rate of entry of BCME into epithelial cells, the half-time for hydrolysis in the tissue environment, the fate of the degradation products, and interaction with DNA, if any, would be valuable in understanding the toxicity of this compound.

Comparative Toxicokinetics. No studies were located on the toxicokinetics of BCME in different species. Such studies might be helpful in understanding the differences that have been observed between species with respect to carcinogenic potency and tissue specificity.

Children's Susceptibility. No studies have evaluated the toxicity of BCME 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 BCME than adults.

Physical and Chemical Properties. The physical and chemical properties most important in evaluating the environmental fate of BCME have been determined (see Table 4-2). Although some of these values (e.g., solubility in water) are calculated, this is not a significant limitation, and additional studies on the physical or chemical properties of BCME do not appear essential.

Production, Import/Export, Use, Release, and Disposal. Although BCME is not produced as a commercial product in the United States, available information indicates that small quantities are produced and used in captive processes within at least one chemical factory. Determination of the amounts involved and whether BCME is used at other locations would be useful in evaluating whether risk of BCME exposure from current industrial practices remains of concern. In addition, compilation of data on typical contaminant levels of BCME currently found in other products such as CME would be helpful in determining whether or not this is a source of concern.

Environmental Fate. Available data make it clear that BCME is not likely to endure in the environment. No further studies appear to be required on fate in water or other moist media (food, soil),

since the principal fate is rapid hydrolysis. Additional studies on the kinetics of BCME destruction in air by oxidation and hydrolysis would be valuable in refining mathematical models used to calculate levels of BCME in air around a point source.

Bioavailability from Environmental Media. No studies were located on bioavailability of BCME in environmental media. However, this is not a significant limitation, since BCME is not expected to occur in significant quantities in any medium except air.

Food Chain Bioaccumulation. No studies were located on food chain bioaccumulation of BCME. This is not a significant limitation, however, since it is expected that BCME is rapidly hydrolyzed in living organisms and will not bioaccumulate.

Exposure Levels in Environmental Media. Information on the occurrence of BCME in environmental media is very limited. No information was located on levels in ambient air, water, or soil. BCME has been reported to occur in water or soil near a few waste sites, but these findings may not be reliable. Because of the instability of BCME in water and soil, further efforts to measure BCME in these media are unlikely to produce useful information. However, the volatility and atmospheric lifetime of BCME are such that monitoring air for BCME in the vicinity of waste sites, industrial facilities, or other possible sources could provide valuable information on the occurrence of this chemical in the environment.

Exposure Levels in Humans. No data exist on present-day exposure levels of humans to BCME. Exposure is likely to be close to zero for the general public. However, because BCME is such a potent carcinogen, even low levels of exposure are of potential concern, and additional data on exposure levels in the workplace and in the environment near waste sites would be valuable.

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. No methods were located for determining BCME in biological samples. It does not appear that this is a significant limitation, however, since BCME is not expected to endure in tissues or fluids. Although there are adequate methods for the detection of formaldehyde and chloride, these are not likely to be useful for assessing exposure to BCME, since any change in the levels of these compounds would be well within normal biological variability.

Air is the only environmental medium susceptible to significant contamination by BCME and methods for the determination of this compound in air are straightforward. The greatest need for improvement in the analysis of BCME is the development of methodologies that enable its efficient collection from large volumes of air without hydrolysis during collection or storage. Since health concern might extend to concentrations well below 1 ppb, improvement in sensitivity would also be valuable.

6.3 Ongoing Studies

No ongoing studies were identified for BCME.