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 bromodichloromethane 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 bromodichloromethane.

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/ocular exposure of humans and animals to bromodichloromethane 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 bromodichloromethane. 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.

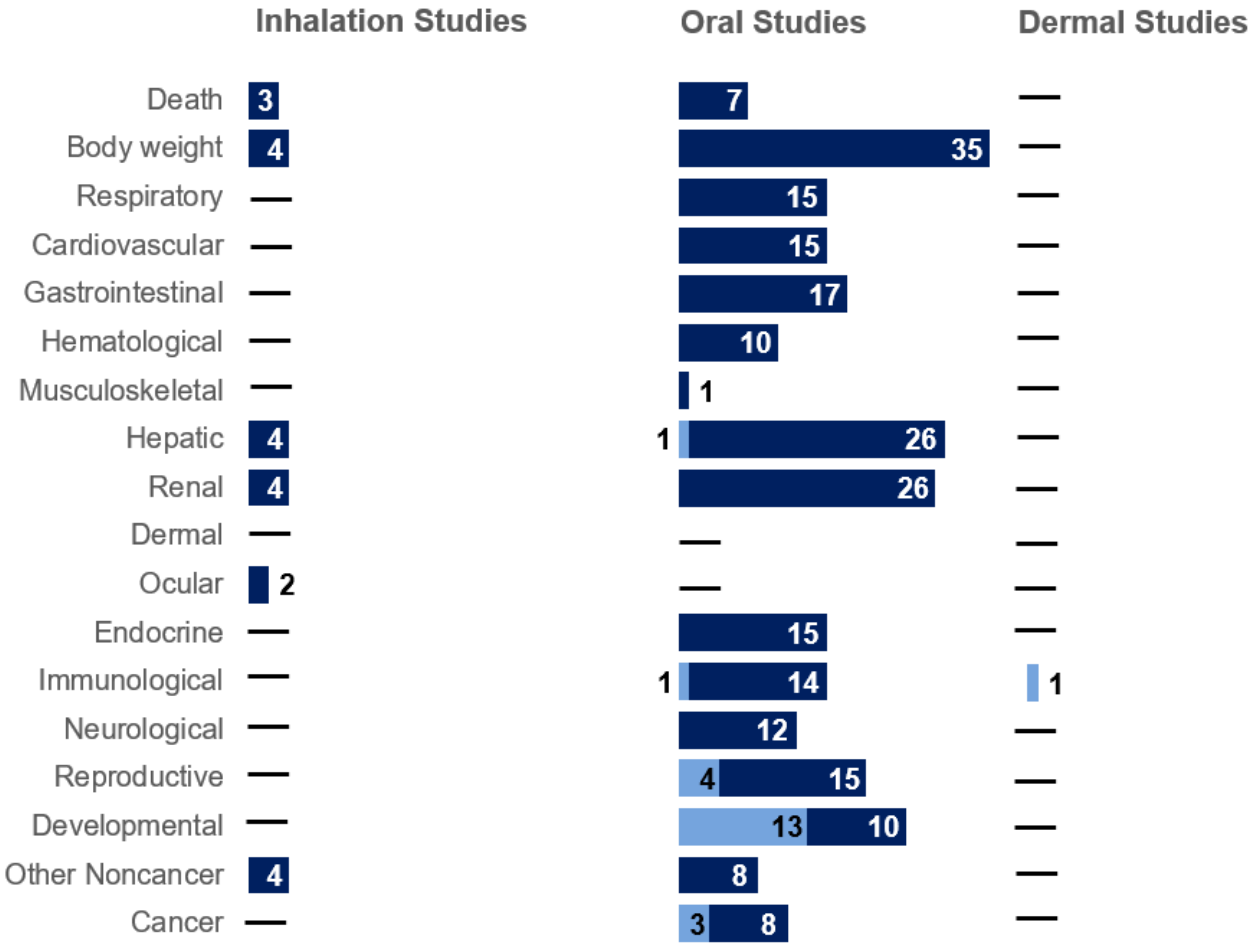
As illustrated in Figure 6-1, most of the data on the toxicity of bromodichloromethane come from oral studies in laboratory animals. The most commonly examined endpoints were body weight, liver, and kidneys. A small number of studies involving exposure to bromodichloromethane in tap water primarily examined developmental toxicity endpoints. The laboratory animal toxicity database consists of a small number of inhalation studies examining a couple of potential endpoints and no dermal exposure 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

Figure 6-1. Summary of Existing Health Effects Studies on Bromodichloromethane By Route and Endpoint*

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



*Includes studies discussed in Chapter 2; a total of 84 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

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, including the lack of examination of the respiratory tract, lack of reporting incidence data for the liver and kidney lesions, and lack of developmental toxicity studies, particularly since developmental toxicity is a sensitive endpoint following oral exposure. Additional inhalation toxicity studies are needed; these studies should include examination of suspected sensitive targets including the respiratory tract, kidney, and liver. Developmental toxicity studies are also needed to determine whether this is a more sensitive endpoint than liver or kidney toxicity.

Intermediate-Duration MRLs. The available intermediate inhalation database was not considered adequate for derivation of an MRL. The lowest LOAEL identified in the 3-week study conducted by Torti et al. (2001) was for renal toxicity. As with acute inhalation exposure, a number of limitations were identified in the database, including the lack of incidence data for the kidney lesions, lack of examination of the respiratory tract, lack of developmental toxicity data, and relatively short duration of the only intermediate-duration study. Additional studies involving at least 13 weeks of exposure and examination of a wide array of tissues and systems are needed to derive an inhalation MRL.

The database for intermediate-duration oral exposure was considered inadequate for derivation of an MRL. Although the existing database includes a number of adequate studies examining relevant endpoints, an MRL based on the lowest LOAEL (6.1 mg/kg/day) was lower than the MRL derived for chronic-duration oral exposure. Additional studies testing lower doses and with a larger number of animals per group would provide valuable information for deriving an intermediate-duration oral MRL.

Chronic-Duration MRLs. The lack of chronic-duration inhalation studies precluded derivation of a chronic MRL. Chronic toxicity studies examining a wide range of endpoints are needed to identify the most sensitive target and establish concentration-response relationships.

Health Effects. Toxicokinetic studies (Backer et al. 2000; Kenyon et al. 2016; Nuckols et al. 2005) provide evidence that inhalation and dermal exposure to bromodichloromethane are significant contributors to the blood bromodichloromethane levels. However, Torti et al. (2001) is the only available inhalation study in laboratory animals and no dermal exposure studies were identified. Inhalation and

dermal exposure studies examining a wide range of potential endpoints are needed to identify whether the critical targets of toxicity for these routes differ from oral exposure targets and establish dose-response relationships. Oral toxicity studies in laboratory animals have administered bromodichloromethane via drinking water, gavage in oil, and feed. In humans, exposure via drinking water would be prominent oral exposure route. Studies are needed to investigate possible differences between various oral exposure subroutes; these data could provide insight into the applicability of dietary and gavage administration studies for assessing potential human toxicity of bromodichloromethane.

Hepatic. Oral exposure studies in laboratory animals have found considerable overlap in NOAEL and LOAEL values across studies, which are likely due to differences in oral route of exposure (i.e., gavage, drinking water, feed) and the vehicle used (Aida et al. 1989, 1992; Chu et al. 1982; Hooth et al. 2002; NTP 2006). Additional studies are needed to evaluate the relevance of each of these routes to humans exposed to bromodichloromethane in tap water.

Renal. Available oral exposure studies in laboratory animals suggest a higher toxicity associated with gavage administration than drinking water or feed exposure (Aida et al. 1989, 1992; Chu et al. 1982; Lipsky et al. 1993; Lock et al. 2004; NTP 1987, 2006). Additional studies are needed to explain these differences and evaluate whether the results of gavage studies are applicable to humans.

Reproductive. Human and animal studies provide suggestive evidence that the reproductive system of males and females are sensitive targets of bromodichloromethane toxicity (Bielmeier et al. 2001, 2004, 2007; Windham et al. 2003). However, the findings of many of the studies have not been confirmed and it is not known if the alterations would result in impaired reproductive function. Additional studies in animals examining reproductive endpoints in males and females would provide data useful for determining whether reproductive toxicity is an endpoint of concern for the general population.

Developmental. Studies in F344 rats (Bielmeier et al. 2001; Narotosky et al. 1997) have found increases in full-litter resorptions; however, this was not found when Sprague-Dawley rats were similarly exposed to the same or higher doses (Bielmeier et al. 2001) and was not observed in another developmental toxicity study (Christian et al. 2001a) or a 2-generation study (Christian et al. 2001b). Although this endpoint was used as the basis of the acute-duration oral MRL, additional research is needed to explain the strain difference and assess whether it is a relevant endpoint in humans.

Epidemiology and Human Dosimetry Studies. A small number of epidemiology studies have evaluated the toxicity of bromodichloromethane in populations exposed to the compound in tap water using either bromodichloromethane levels in blood or tap water as exposure metrics (Bove et al. 2007; Burch et al. 2015; Cao et al. 2016; Danileviciute et al. 2012; Dodd and King 2001; Grazuleviciene et al. 2013; Hoffman et al. 2008; Iszatt et al. 2011; King et al. 2000; MacLehose et al. 2008; Rivera-Núñez and Wright 2013; Summerhayes et al. 2012; Waller et al. 1998; Wright et al. 2004; Zeng et al. 2013). A common limitation of these studies is the lack of control for the presence of other trihalomethanes and disinfection byproducts, many of which have similar toxic endpoints as bromodichloromethane. Additionally, epidemiology studies controlling confounding exposures and examining endpoints that have been shown to occur at low doses in laboratory animals (hepatic, renal, immunological, reproductive, and developmental) would be useful. *In vitro* studies (Chen et al. 2003, 2004) suggest an effect on trophoblasts; *in vivo* studies in nonhuman primates would provide additional information for the interpretation of the human studies finding increases in spontaneous abortions.

Biomarkers of Exposure and Effect. Levels of bromodichloromethane in alveolar air, urine, and blood have been used as biomarkers of exposure. Although increases in these levels are associated with exposure, additional research is needed to extrapolate biomarker levels to external exposure doses.

Absorption, Distribution, Metabolism, and Excretion. There are limited data on the toxicokinetic properties of bromodichloromethane following inhalation or dermal exposure; since these routes are major contributors to blood levels in populations using tap water containing bromodichloromethane, additional toxicokinetic data would be useful. Studies would also be useful evaluating potential metabolic saturation; these data would be useful for assessing the applicability of high-dose studies in laboratory animals to low-dose human exposure scenarios. A PBPK model that would allow extrapolation from animals to humans would decrease the uncertainties in MRL derivations.

Comparative Toxicokinetics. There are limited data available that allow for a comparison of the toxicokinetic properties across species. Since metabolites are responsible for the toxicity of bromodichloromethane, studies comparing metabolism in different animal species and humans could provide valuable information in extrapolating animal toxicity data to humans.

Children's Susceptibility. No studies have evaluated the toxicity of bromodichloromethane in children or young animals. Bromodichloromethane is primarily metabolized by CYP2E1, which is fully developed in children; it is not known if there would be toxicodynamic differences between children and

adults that might influence susceptibility. Studies in young animals and/or children would be useful to address these concerns.

Physical and Chemical Properties. Further studies on these parameters do 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 bromodichloromethane.

Environmental Fate. Studies to obtain reliable quantitative rate values for the key fate processes of bromodichloromethane would be valuable. Of particular importance would be studies on the volatilization of bromodichloromethane from chlorinated drinking water, and on the atmospheric reactions of bromodichloromethane. Studies of chemical and biological transformation and degradation rates in soil and water under conditions comparable to those around waste sites would also be helpful.

Bioavailability from Environmental Media. Based on the physical properties of bromodichloromethane, it is not expected that bioavailability would vary widely between water, soil, food, and other media. Investigative studies on the relative bioavailability of bromodichloromethane in different environmental media would add to the understanding of this chemical's behavior.

Food Chain Bioaccumulation. Studies on bromodichloromethane uptake and retention by fish, plants, and other food sources would be helpful.

Exposure Levels in Environmental Media. Studies of bromodichloromethane levels in air (especially indoor air) in the vicinity of open bodies of chlorinated water, including water treatment plants, would be helpful. In view of the ready volatilization of bromodichloromethane from water, airborne levels in such locations might be significant.

Exposure Levels in Humans. Additional data on bromodichloromethane levels in air to estimate inhalation exposure in ambient air or the workplace would be beneficial. It would be helpful to know how rapidly bromodichloromethane would volatilize from a glass of water, a bathtub full of water, and a swimming pool, and what concentration would then be in the breathing zone of occupants of the house.

Exposures of Children. Based on the concentrations of bromodichloromethane measured in water used for drinking and bathing, studies are needed to assess the inhalation, dermal, ocular, and oral exposures of children during water-related activities. Data on inhalation and dermal doses would especially be useful for in and around both indoor and outdoor swimming pools.

Analytical Methods. Since bromodichloromethane may be toxic to humans, very low levels in water, air, or other media may be of concern, so improvements in detection sensitivity would be valuable, especially in environmental media such as water and air.

6.3 ONGOING STUDIES

No ongoing studies were identified for bromodichloromethane.