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 bromomethane 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 bromomethane.

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

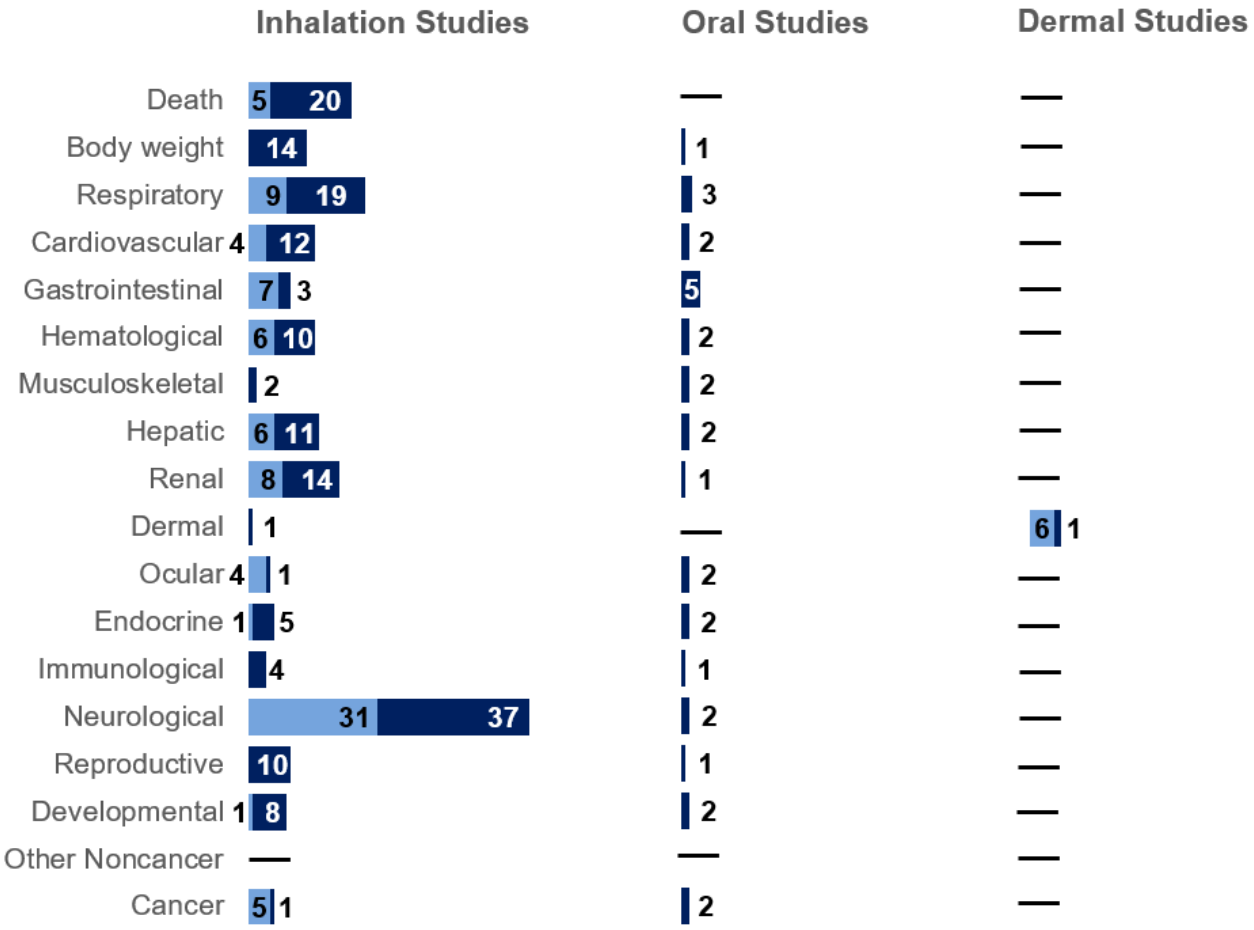
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to bromomethane that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of bromomethane. The number of human 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.

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

Potential 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. Studies may have examined multiple health effects. No dermal studies in humans or animals were located.

Acute-Duration MRLs. The acute-duration inhalation database was not considered suitable for derivation of an MRL for bromomethane. Acute inhalation studies identify the neurological and respiratory systems as the primary targets of acute inhalation of bromomethane in humans; however, information on these effects was obtained from case reports and, therefore, is not adequate for the basis of an acute MRL. Several targets for acute exposure to bromomethane have been identified in animal studies, including respiratory system, neurological system, liver, kidneys, heart, reproductive system, and the developing fetus. The most sensitive endpoint identified is a duration-adjusted LOAEL of 2.14 ppm; however, there is considerable uncertainty associated with classifying this concentration as a LOAEL. NTP (1992) reported that "neurological signs including trembling, jumpiness, and paralysis were observed in all groups but were most pronounced in the three highest dose groups (50, 100, 200 ppm)." However, the NTP report did not include incidence data for these effects and it is unclear whether any or all of the effects were observed at the lowest concentration tested (12 ppm). Additional acute-duration inhalation studies using low exposure levels (duration adjusted concentrations ≤5 ppm) are need to reliably define NOAEL and LOAEL values for neurological effects.

An acute-duration oral MRL was not derived. The only effect observed in acute-duration oral studies is damage to the glandular stomach (Kaneda et al. 1998). As noted earlier in Sections 1.2 and 2.1, there is some question as to whether the forestomach effects in rats are due to the bolus administration of a very reactive chemical and whether gavage administration is an appropriate model for human exposure to bromomethane. Longer duration exposure studies using dietary exposure did not observe damage to the gastrointestinal tract (Wilson et al. 2000). Additional acute-duration dietary oral exposures studies are important to determine if gastrointestinal tract damage is only observed when bromomethane is administered by gavage.

Intermediate-Duration MRLs. The database for intermediate-duration inhalation exposure to bromomethane was considered adequate for derivation of an MRL. The intermediate-duration oral database was not sufficient to derive an MRL. The most sensitive effect observed from oral gavage exposure was hyperplasia and focal hyperemia of the forestomach (Danse et al. 1984). As discussed above under Acute-Duration MRLs and in Sections 1.2 and 2.1, in this study, bromomethane was administered by gavage; therefore, there is uncertainty regarding the relevance of gastrointestinal damage to human health. Additional acute-duration dietary exposures studies are important to determine if gastrointestinal tract damage is only observed when bromomethane is administered by gavage.

Chronic-Duration MRLs. The database for chronic-duration inhalation exposure to bromomethane was considered adequate for derivation of an MRL. The chronic-duration oral database was not sufficient to derive an MRL. The two chronic-duration oral studies did not identify targets for bromomethane (EPA 1999; Wilson et al. 2000). Additional studies examining the effects of chronic-duration dietary bromomethane over a wide range of doses may provide information on potential targets of exposure.

Health Effects.

Neurotoxicity. There is clear evidence from studies in humans and animals that the nervous system is adversely affected by inhalation exposure to bromomethane. This includes evidence of clinical neurological signs and behavioral changes (Akca et al. 2009; Alexeeff et al. 1985; Anger et al. 1986; Balagopal et al. 2011; Behrens and Dukes 1986; Bishop 1992; Breslin et al. 1990; Clarke et al. 1945; Deschamps and Turpin 1996; Eustis et al. 1988; Greenberg 1971; Herzstein and Cullen 1990; Hine 1969; Hustinx et al. 1993; Irish et al. 1940; Kantarjian and Shaheen 1963; Longley and Jones 1965; Marraccini et al. 1983; O'Neal 1987; Prain and Smith 1952; Prockop and Smith 1986; Rathus and Landy 1961; Viner 1945; Wyers 1945; Yamano and Nakadate 2006; Yamano et al. 2001), as well as biochemical changes and histological lesions in the brain (Alexeeff et al. 1985; Eustis et al. 1988; Honma 1987; Honma et al. 1982; Hurtt et al. 1987; Kato et al. 1986; NTP 1992). Although quantitative exposure information from humans is limited, the thresholds for acute, intermediate, and chronic inhalation exposures are known with reasonable precision. No information is available on humans exposed by the oral route, but two oral studies in rats (Boorman et al. 1986; Danse et al. 1984) did not produce any visible neurological signs. It is not known if this apparent route specificity is due simply to differences in dose, or to differences in absorption, distribution, or metabolism between routes. For this reason, additional oral dose-response studies in animals that focus specifically on histological, biochemical, or functional tests of nervous system injury would be valuable. If these tests indicate that the nervous system is not injured following oral exposure, additional toxicokinetic studies would be helpful in understanding the basis for the distinction between inhalation and oral effects.

Reproductive Toxicity. No information was located regarding reproductive effects in humans. Intermediate-duration inhalation studies in animals (Eustis et al. 1988; Kato et al. 1986) indicate that the testes may undergo degeneration and atrophy at high exposure levels, but the dose-response curve is not well defined. Further studies in animals to identify the threshold for this endpoint would be helpful. Two studies in female animals (Hardin et al. 1981; NIOSH 1980)

have not detected reproductive effects even at doses that produced maternal toxicity. Additional studies to confirm this in several different animal species would be helpful.

No information exists on reproductive effects in humans or animals after oral exposure. Based on the inhalation studies in animals that indicate that the testes are a target tissue, it would be valuable to include histological examination of the testes in any intermediate- or chronic-duration oral studies in animals. In addition, tests of male reproductive success would be valuable in assessing the functional significance of any testicular lesions.

Developmental Toxicity. There is no information on developmental effects in humans exposed to bromomethane. One study in rabbits found minor fetal malformations and variations at maternally toxic concentrations (Breslin et al. 1990). In contrast, no developmental effects were observed in a study in rats and rabbits (Hardin et al. 1981; NIOSH 1980). A summary of a neurodevelopmental study in rats reported neurological effects (decreased total and ambulatory activities) in high-dose male and mid-dose female offspring on postnatal day 21 (Beck 1994 [MRID46665001], as cited in EPA 2018a). Unfortunately, the study report is not available for review. Neurological effects have been well characterized in multiple species (rat, mouse, rabbit, and dog) and there is indication that protection factors for adults will be sufficient for infants and children. Therefore, it is considered that additional neurodevelopmental studies are not needed in determining the potential for adverse neurodevelopmental effects associated with gestational exposure to bromomethane. An oral exposure in rats and rabbits did not find developmental effects (Kaneda et al. 1998).

Gastrointestinal Toxicity. Gastrointestinal toxicity has not been reported in inhalation studies in animals. In oral toxicity studies, damage to the stomach has been observed in rats exposed for acute (Kaneda et al. 1998) and intermediate durations (Danse et al. 1984); however, in these studies, bromomethane was administered by gavage. In a chronic-duration oral study of dietary bromomethane, no gastrointestinal effects were observed (Wilson et al. 2000). Although oral exposure to bromomethane to humans is unlikely, if it occurs, exposure would be to small amounts in food or water. Therefore, there is uncertainty regarding the relevance of gastrointestinal damage of gavage administration to human health. Additional acute- and intermediate-duration dietary studies could provide information to determine if dietary exposure to bromomethane is relevant to human health.

Epidemiology and Human Dosimetry Studies. As noted previously, there are many reports on the adverse effects of bromomethane in humans. Most studies involve people with accidental acute high-level exposures in air, but there are also several studies of workers with repeated low-level exposures (Calvert et al. 1998a; Kishi et al. 1988; Verberk et al. 1979). These studies are sufficient to identify the main health effects of concern and to estimate the exposure levels that lead to effects. However, further studies of workers who are exposed to low levels during manufacture or use of bromomethane would be helpful, if reliable current and past exposure data are available. These additional quantitative human data would be valuable in increasing the confidence in the estimated safe exposure levels in the workplace and the environment. This would improve the ability to evaluate potential risk to humans exposed to low levels of bromomethane in air near waste sites.

Biomarkers of Exposure and Effect. The most common biomarker of exposure to bromomethane is serum bromide concentration. Studies in humans have established an association between bromide levels and severity of effect (Alexeeff and Kilgore 1983), although the quantitative relation between exposure level and bromide concentration has not been established. Since bromide is cleared from the blood with a half-life of 3–15 days, this test is best suited for detecting relatively recent exposures. Because bromide is a normal component of blood, and because bromide levels may be increased by other chemicals or drugs, increased serum bromide is not specific for bromomethane. Other possible biomarkers available include direct measurement of parent bromomethane or methanol in expired air or blood (Honma et al. 1985; Jaskot et al. 1988), and measurement of methylated adducts such as S-methylcysteine in hemoglobin (Iwasaki 1988a). Measurement of parent bromomethane or methanol is not likely to be helpful except in the interval immediately following an acute exposure, while measurement of stable methylated adducts, although not specific for bromomethane, could be useful for longer periods. Further studies in humans or animals would be helpful in determining the sensitivity of these biomarkers and evaluating their usefulness in monitoring people exposed to low levels of bromomethane near waste sites.

The most sensitive biomarkers of bromomethane effects appear to be changes in the nervous system. These can be detected in groups of exposed people by measuring the incidence of signs and symptoms such as weakness, nausea, ataxia, and vision problems. However, it is obvious that these are not specific for bromomethane-induced effects, and because of the large variation between people, these tests are not reliable for identifying preclinical effects in potentially exposed individuals. Studies to develop more specific and more objective biomarkers of bromomethane-induced effects would be useful in assessing the potential health significance of low-level bromomethane exposure near waste sites.

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of bromomethane have not been thoroughly investigated in humans, but there is good information from studies in animals on uptake, distribution, and excretion following inhalation exposure (Bond et al. 1985; Gargas and Andersen 1982; Honma et al. 1985; Jaskot et al. 1988; Medinsky et al. 1985), and there is one study on toxicokinetics following oral exposure (Medinsky et al. 1984). Available data indicate that the toxicokinetics of bromomethane absorption are mainly first-order except at very high doses. While the metabolism of related compounds such as chloromethane has been studied in detail (Kornbrust and Bus 1983), the metabolism of bromomethane has not been thoroughly investigated. Additional studies on the rate and extent of bromomethane hydrolysis and alkylation reactions *in vivo* would be valuable in understanding the basis of bromomethane toxicity, and in assessing the utility of various biomarkers of exposure (e.g., parent compound, bromide, methanol, adducts).

Comparative Toxicokinetics. Available studies indicate that bromomethane affects the same target tissues in humans and animals, although there are apparent differences in sensitivity between species, with rabbits being more sensitive than rats or mice (Irish et al. 1940). However, quantitative toxicokinetic data on absorption, distribution, and excretion are primarily available for rats (Bond et al. 1985; Gargas and Andersen 1982; Honma et al. 1985; Jaskot et al. 1988; Medinsky et al. 1984, 1985). Additional toxicokinetic studies would be helpful in understanding the basis of the differences in species sensitivity, and in determining which animal species is the most appropriate model for human exposure.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above. There are limited data on the toxicity of bromomethane in children; a report of an accidental exposure suggests that infants and adults would have similar toxic effects (Langard et al. 1996).

Physical and Chemical Properties. The physical and chemical properties of bromomethane are sufficiently well known to allow estimation of environmental fate. Although there is some disparity in reported values for the solubility in water and Henry's law constant for bromomethane (see Table 4-1), further studies to define these parameters more precisely are not essential, since volatilization from water is so rapid.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit

substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2014, became available in October of 2016. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The fate of bromomethane in the environment is dominated by rapid evaporation into air, where it is quite stable (EPA 1986b). The rates of volatilization from soil and water have been studied and are known with reasonable precision (although such rates are typically site-specific) (Anderson et al. 1996; Gan et al. 1996, 1997). The rates of breakdown by hydrolysis, reaction with hydroxyl radical, and direct photolysis in the stratosphere have also been estimated (Atkinson 1989; Castro and Belser 1981; Davis et al. 1976; Robbins 1976; WMO 2011; UNEP 2015). Further studies to improve the accuracy of available rate constants for these processes would be helpful, but are not essential to understanding the basic behavior of bromomethane in the environment.

Bioavailability from Environmental Media. Bromomethane is known to be well absorbed following inhalation and oral contact (Gargas and Andersen 1982; Medinsky et al. 1984). Small amounts may also be absorbed across the skin, but this has not been quantified. No information was located regarding the relative bioavailability of bromomethane from media such as food or soil. However, since bromomethane has a low K_{oc} value (EPA 1982), it is not likely that bioavailability would be much reduced by these media. Moreover, since bromomethane is rarely found in these media, research on this subject does not appear essential.

Food Chain Bioaccumulation. Although the bioconcentration, bioaccumulation, and biomagnification of bromomethane have not been formally investigated, it seems clear that these are not of significant concern. This is the result of several factors, including the high volatility and high water solubility of the compound, its low K_{ow}, and its relatively rapid metabolism by reaction with organic materials (EPA 1982; Medinsky et al. 1985). On this basis, it does not appear that research in this area is essential.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of bromomethane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of bromomethane in the environment can be used in combination with the known body burden of bromomethane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Bromomethane levels in ambient air are decreasing since the phase out of this substance in 2005 (EPA 2019a; WMO 2011; UNEP 2015). Detections of bromomethane in water are rare. Bromomethane has been analyzed for, but rarely detected, in foods (Daft 1987, 1988, 1989). The EPA RED (EPA 2008b) for bromomethane provides estimates of human exposure levels to handlers, workers, and bystanders associated with its use as a soil fumigant. An exposure assessment for the general population would be helpful.

Exposure Levels in Humans. Bromomethane is not normally measured in human tissues such as blood or urine, even in people exposed to high levels. This is because bromomethane is removed from the body very quickly after exposure ceases. Consequently, this is not likely to be a useful means of monitoring exposure of humans to low levels of bromomethane. Increased levels of bromide have been detected in blood of persons exposed to bromomethane in accidents or in the workplace, but no studies were located regarding bromide levels in persons potentially exposed to bromomethane near waste sites. Since bromide is a normal component of serum, and since the serum bromide level is quite variable, it does not seem that broad surveys of blood bromide levels in persons living near waste sites would be useful. However, site-specific studies at locations where bromomethane exposure is likely might prove helpful.

Exposures of Children. Data on the exposures of children to bromomethane were not located. Because humans are most likely to be exposed to bromomethane in air, studies that are tailored to assessing exposure of children to bromomethane in ambient air would be useful given the tendency for children to spend more time outdoors than many adults.

6.3 ONGOING STUDIES

No ongoing studies of bromomethane were identified by NIH RePORTER (2019).