

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 chloromethane 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 chloromethane.

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 EXISTING INFORMATION ON HEALTH EFFECTS

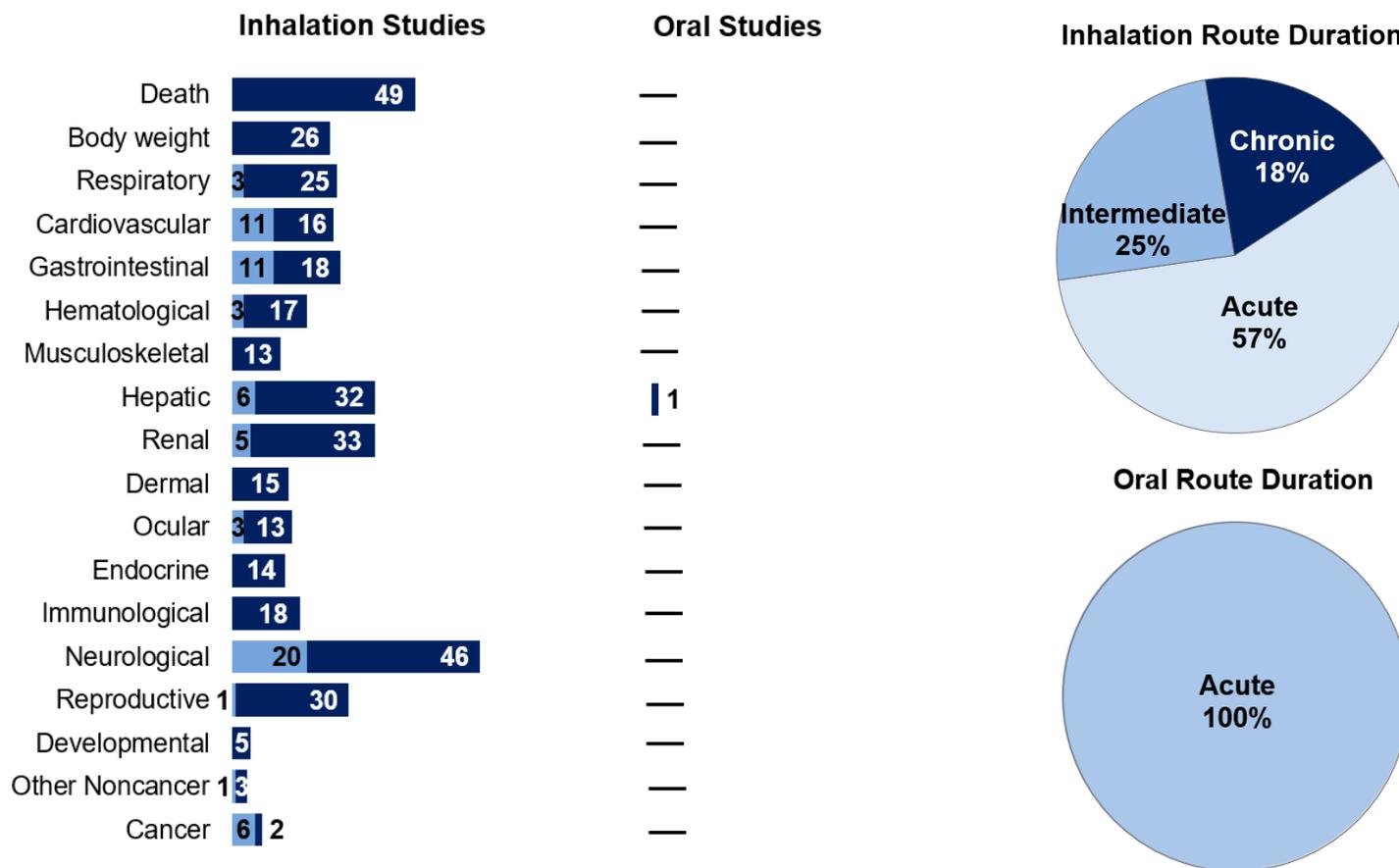
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to chloromethane that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of chloromethane. The number of 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 shown in Figure 6-1, information on the health effects in humans exposed to chloromethane is available only for exposure via inhalation. Accidental leaks of chloromethane from refrigeration units primarily involves the inhalation exposure route. The organs or systems adversely affected in humans after exposure to chloromethane include the liver, kidney, neurological system (including behavioral alterations) and potentially the cardiovascular system. Death may occur at sufficiently high doses. Information on the adverse health effects of chloromethane has been presented for occupational exposures of acute, intermediate, and chronic durations. The evidence on chloromethane's carcinogenicity is mixed in epidemiological studies (Barry et al. 2011; Dosemeci et al. 1999; Holmes et al. 1986; Kernan et al. 1999; Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014). One found an association with increased risk of death from renal cancer (Rafnsson and Kristbjornsdottir 2014), while another found an increased risk with non-Hodgkin's lymphoma for those individuals with one genetic phenotype whose functional significance is unclear (Barry et al. 2011). Other studies either did not find

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

Potential reproductive, neurological, renal, hepatic, gastrointestinal and cardiovascular effects were the most studied endpoints
 The majority of studies examined inhalation exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2. The number of studies includes those finding no effect; most inhalation studies examined multiple endpoints. No dermal studies in humans or animals were located.

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an association with death from renal, lung, bladder, lymphatic, or other types of cancer (Dosemeci et al. 1999; Holmes et al. 1986), or the association was not dose, race, or gender related (Kernan et al. 1999).

No information was available regarding immunological, developmental, or genotoxic effects in humans exposed to chloromethane by inhalation, oral, or dermal exposure routes. There are *in vivo* and *in vitro* studies on human tissues. Reproductive effects were limited to one case study that did not provide exposure data.

Several studies have evaluated the health effects of chloromethane exposure in animals for the inhalation route, although only a single comprehensive chronic-duration study in rats and mice has been performed (CIIT 1981). Health effects of acute-, intermediate-, and chronic-duration inhalation exposures in animals include increased mortality, liver damage, kidney damage and tumors, neurological damage; and adverse reproductive, genotoxic, and possibly developmental effects. In the only oral study in animals, an attempt was made to compare the hepatotoxicity of chloromethane with that of carbon tetrachloride and chloroform. The administered dose of chloromethane, however, was too low to produce hepatic effects, and the use of a higher dose was precluded due to neurotoxicity.

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 inhalation database is adequate to derive an acute-duration inhalation MRL. The oral database is inadequate to derive an acute-duration oral MRL. Available oral data are limited to a single acute-duration gavage study reporting no adverse hepatic effects. Additional acute-duration oral studies examining a wide range of potential effects are needed to identify the most sensitive targets of toxicity and establish dose-response relationships. However, since the predominant route expected for human exposure is via inhalation, oral data may be less relevant to ongoing exposure scenarios in humans.

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Intermediate-Duration MRLs. The inhalation database is adequate to derive an intermediate-duration inhalation MRL. The oral database is inadequate to derive an intermediate-duration oral MRL due to a complete lack of data. Intermediate-duration oral studies examining a wide range of potential effects are needed to identify the most sensitive targets of toxicity and establish dose-response relationships. However, since the predominant route expected for human exposure is via inhalation, oral data may be less relevant to ongoing exposure scenarios in humans.

Chronic-Duration MRLs. The inhalation database is adequate to derive a chronic-duration inhalation MRL. No chronic-duration studies were located for other routes. Additional low-concentration studies designed to identify a NOAEL for the critical effect (neurotoxicity) could decrease uncertainty in the chronic-duration inhalation MRL. The oral database is inadequate to derive a chronic-duration oral MRL due to a complete lack of data. Chronic-duration oral studies examining a wide range of potential effects are needed to identify the most sensitive targets of toxicity and establish dose-response relationships. However, since the predominant route expected for human exposure is via inhalation, oral data may be less relevant to ongoing exposure scenarios in humans.

Health Effects. Chloromethane is a volatile chemical. Subsequently, the primary concern regarding toxicity relates to exposure via inhalation. However, chloromethane is ubiquitous in the environment. No studies evaluated dermal exposure to chloromethane and only one animal study looked at oral exposure and hepatic effects. Therefore, a data need for all endpoints includes information on health effects resulting from oral and dermal exposure. For inhalation studies, identification of data needs for health effects in animal studies is limited to targets included in the systematic review.

Cardiovascular. While human case studies and one (presumably) highly exposed occupational cohort indicate that the cardiovascular system may be a target of chloromethane toxicity, supporting animal data are inconsistent or lacking. Human epidemiological studies and/or additional animal studies designed to evaluate cardiovascular toxicity following exposure, particularly cardiovascular function, may be useful. Data showing mechanisms of cardiovascular toxicity distinct from CNS depression would also be useful.

Hepatic. The liver has been identified as a sensitive target following acute-, intermediate-, and chronic-duration inhalation exposure in animals, particularly in mice. Studies designed to determine the mechanism of hepatotoxicity could be useful for evaluating the apparent species sensitivity and determining potential human relevance of these findings.

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Neurological. The nervous system, particularly the motor areas of the cerebellum and spinal cord, have been identified as sensitive targets of chloromethane exposure in animals. Additionally, neurotoxic effects in humans from inhalation exposure to chloromethane are described in numerous case studies and one (presumably) highly exposed occupational cohort study. The acute-duration inhalation database is considered adequate. However, additional animal studies evaluating neurological function following intermediate-duration inhalation exposure at low exposure concentrations would be useful to strengthen the confidence and provide dose-response data. Additional repeat-exposure, low-concentration studies designed to identify a NOAEL for neurological effects following chronic-duration exposure, particularly neurological function, are needed. Studies designed to determine the mechanism of neurotoxicity may also be useful.

Male Reproductive. One case study described potential reproductive effects (i.e., impotence) in an occupationally exposed individual; however, no data on exposure levels were provided. The male reproductive tract has been identified as a target of toxicity following acute-, intermediate-, and chronic-duration inhalation exposure in animals, particularly rats. Human epidemiological studies and/or additional animal studies designed to evaluate male reproductive toxicity, particularly reproductive function, following inhalation exposure may be useful. Evaluation of male reproductive function in a second species (e.g., mice) and studies designed to determine the mechanism of male reproductive toxicity may be useful.

Developmental. Developmental toxicity data from inhalation studies in animals report species differences in fetal toxicity as well as questions regarding the validity of reported heart defects in mice. Additional studies evaluating specialized developmental effects (e.g., cardiotoxicity, neurotoxicity) following developmental exposure, including immediate effects in neonates as well as potential adverse effects at later life stages (delayed effects from developmental exposure) may be useful. Studies designed to determine the mechanism(s) of developmental toxicity could be useful for evaluating the apparent species differences and determining potential human relevance of these findings.

Epidemiology and Human Dosimetry Studies. A small number of epidemiology studies evaluated the toxicity of chloromethane in populations exposed to chloromethane most often due to occupational or accidental releases. One study evaluated the impact of chloromethane exposure in high

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traffic areas in subsets of the general population and found no association between asthma symptoms and chloromethane exposure (Delfino et al. 2003); however, the exposures were very low and were not expected to cause health effects. A common limitation of occupational studies is the lack of exposure information (Rafnsson and Kristbjornsdottir 2014) and the need to use job-exposure matrices to either estimate the exposure or assess whether exposure is or is not likely to have occurred in the populations with unknown or no direct individual exposure data (Barry et al. 2011; Dosemeci et al. 1999; Kernan et al. 1999). Several human controlled trials were conducted with chloromethane; however, in several studies, the protocols used were confusing and limited the interpretation of the results. Further, some human controlled trials had trouble with volunteer attrition. Therefore, additional studies in occupational populations that include individual exposure data across a range of industries and a range of exposure levels relevant to community exposure would be useful.

Biomarkers of Exposure and Effect.

Exposure. No biomarker that can be associated quantitatively with exposure to chloromethane has been identified (see Section 3.3.1). While methods are available for the analysis of chloromethane in blood, expired air, and breast milk and the metabolite S-methylcysteine in urine, quantitative relationships have not been established between exposure and measurement of chloromethane or S-methylcysteine in these biological media. Several studies have unsuccessfully tried to relate blood and alveolar air levels of chloromethane and urinary levels of S-methylcysteine with exposure (DeKok and Anthenius 1981; Nolan et al. 1985; Stewart et al. 1980; van Doorn et al. 1980). However, the blood and alveolar air levels of chloromethane and the urinary levels of S-methylcysteine are highly variable. The observed variability of metabolism (see the discussion of the metabolism of chloromethane in Section 3.1.3) suggests that a correlation of chloromethane levels in tissues with levels of chloromethane exposure is not likely to be found. It may be possible to use levels of yet unidentified metabolites in blood or urine as biomarkers of exposure. If reliable biomarkers of exposure were available, it would allow both investigators and reviewers to assess the accuracy and uncertainty of the methods used in toxicological studies. Furthermore, the ready availability of tested analytical methods for biomarkers, including sample preservation, would permit a standardized approach to the analysis of biological materials to assist in measuring human exposure and monitoring effects in humans.

Although Xu et al. (1990) reported low chloromethane reactivity with hemoglobin, protein adducts may still hold promise as potential biomarkers for chloromethane exposure. In view of

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chloromethane's genotoxicity in short-term assays, an assay for a DNA adduct or indicator of oxidative damage to DNA from chloromethane exposure might also be pursued. Further studies are therefore needed to identify a metabolite or biomarker that can be used to monitor chloromethane exposure.

Effect. No biomarkers specific for the health effects of chloromethane are available. The predominant health effects associated with chloromethane exposure in humans are clinical signs of neurotoxicity; however, none of these signs are unique to chloromethane exposure. In the absence of reliable biomarkers or exposure to chloromethane, known or suspected exposure is needed to attribute signs and symptoms to chloromethane rather than another neurotoxicant.

Absorption, Distribution, Metabolism, and Excretion. Experimental inhalation studies in animals and humans indicate that chloromethane is rapidly taken up from the lungs into the blood, exhaled with rapid equilibrium, widely distributed throughout the body, extensively metabolized, incorporated into macromolecules, and either excreted as CO₂ or as metabolites in the urine (Dekant et al. 1995; Heck et al. 1982; Jager et al. 1988; Kornbrust and Bus 1983, 1984; Kornbrust et al. 1982; Landry et al. 1983a, 1983b; Putz-Anderson et al. 1981a, 1981b; Redford-Ellis and Gowenlock 1971a, 1971b; van Doorn et al. 1980; von Oettingen et al. 1949, 1950). Differences in the rate and extent of absorption, metabolic pathways, and disposition will have a profound effect on the toxicity of chloromethane. There are limited data on oral and dermal routes so it is unknown how chloromethane may distribute with these routes of exposure. However, the most likely exposure route for chloromethane is inhalation. Additional human and animal pharmacokinetic studies are needed to evaluate the potential for delivery of toxic levels of chloromethane to human target tissues from different routes of exposure and durations of exposure.

Comparative Toxicokinetics. Studies on the pharmacokinetics of chloromethane following inhalation exposure have been conducted in rats, mice, dogs, and humans (Dekant et al. 1995; Dodd et al. 1982; Heck et al. 1982; Jager et al. 1988; Kornbrust and Bus 1983, 1984; Kornbrust et al. 1982; Landry et al. 1983a, 1983b; NIOSH 1976; Putz-Anderson et al. 1981a, 1981b; Redford-Ellis and Gowenlock 1971a, 1971b; van Doorn et al. 1980; von Oettingen et al. 1949, 1950). The kinetics of chloromethane in humans were similar to those in rats and dogs, with data for each species consistent with a two-compartment model. Some species differences can be explained by differences in respiratory minute volumes and basal metabolic rates (rat > dog > human). Additional pharmacokinetic studies in different species and with different routes of exposure are needed to further evaluate the target tissues and the

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differences in potential toxic metabolites. Additional studies are especially needed to resolve the relative importance of GSH conjugation and P450 oxidation to the toxicity of chloromethane. These studies should be performed in different tissues, species, sexes, and life stages to resolve potential differences. Additional studies are needed to evaluate the importance of varying levels of human endogenous erythrocyte GSH transferase to the toxicity of chloromethane (Warholm et al. 1994), and to the identification of potentially susceptible populations.

Children's Susceptibility. Data needs related to both prenatal and childhood exposures, and developmental effects expressed whether (prenatally or during childhood), are discussed in the Developmental Toxicity subsection above.

There have been no studies on whether children are differentially susceptible than adults to adverse health effects from a given amount or duration of exposure to chloromethane, or how chloromethane may affect the developing human fetus or the development of young children.

Only limited information is available from rat and mouse studies on potential effects in the developing young (see above in Data Needs for Developmental Toxicity). In one rat study (Wolkowski-Tyl et al. 1983a), at levels that also produced maternal toxicity, fetal effects consisted of reduced fetal body weight (10.1% in males, 10.4% in females), reduced crown rump length (4% in females), and reduced ossification in the metatarsals and phalanges, the centra of thoracic vertebrae, the pubis of the pelvic girdle, and the metatarsals of the hindlimbs. Wolkowski-Tyl et al. (1983a, 1983a, 1981b, 1983b) also found increased incidences of heart malformations in the fetuses of mouse dams exposed to 500 ppm chloromethane during GDs 6–17. In a letter to an editor, John-Greene et al. (1985) summarized results of an experiment where heart malformations were not found in fetuses of mouse dams exposed to lower concentrations of chloromethane during GDs 11.5–12.5 (John-Greene et al. 1985). Theuns-van Vliet (2016) exposed rabbits to up to 1,000 ppm of chloromethane and did not observe heart malformations. The developmental toxicity of chloromethane is therefore not classifiable and may be only relevant in mice, with species differences in susceptibility. Further studies are needed to determine potential adverse effects on development from maternal and fetal exposure to chloromethane.

There is limited information on the movement of chloromethane or its metabolites across the placenta, into the developing young, or into breast milk. Information on potential transplacental transfer is limited to studies in animals. Wolkowski-Tyl et al. (1983a, 1983b) noted from unpublished observations that mouse dams exposed to 100, 500, or 1,500 ppm chloromethane for 6 hours on GD 17 had significant

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NPSH concentration reductions in both dams and fetuses, indicative of transplacental passage of chloromethane or its metabolites. Regarding nursing mothers, one study detected chloromethane in two of eight sample of human breast milk, but the potential source(s) of chloromethane exposure were not discussed (Pellizzari et al. 1982). Further studies are needed that examine the presence of chloromethane in breast milk samples that both quantify levels in breast milk as well as potential exposure sources and exposure levels. Since chloromethane is broken down and eliminated from the body very quickly in adults (Nolan et al. 1985) and animals (Landry et al. 1983a; von Oettingen et al. 1949), it is unlikely that chloromethane would be stored in maternal tissues and subsequently mobilized (i.e., released from stores) during pregnancy or lactation.

In adults, there appear to be two distinct populations with regard to metabolism and elimination of chloromethane. One population has higher amounts of the metabolizing enzyme, GST, and thus a higher rate of elimination of chloromethane from the body. The toxicity of chloromethane, however, is thought to result from toxic metabolites formed following the conjugation with GSH or from the depletion of GSH (Chellman et al. 1986b; Kornbrust and Bus 1983, 1984; Landry et al. 1985). It is anticipated that children would have a polymorphism similar to the adult population, although no specific data have been collected to test this hypothesis. If a polymorphism is present in children, then some children (i.e., those with higher levels of GST) would potentially be more susceptible to the toxic effects of chloromethane. Moreover, cytochrome P450 dependent metabolism of methanethiol may yield formaldehyde and formic acid whose carbon atoms can then enter the one-carbon pool for incorporation into macromolecules or formation of CO₂ (Heck et al. 1982; Kornbrust and Bus 1983). However, Jager et al. (1988) disputed this conclusion. Guengerich and Shimada (1991) suggested that the human cytochrome P450 enzyme 2E1 is a major catalyst in the oxidation of chloromethane. Formaldehyde may also be a direct product of chloromethane via oxidative dechlorination. Studies are therefore needed to evaluate the differences among and between children and adults for P450 and transferase levels and isoforms, and for differences in chloromethane metabolism.

There is only one PBPK model for chloromethane exposure based on data for GSTT1-deficient individuals. There are no reliable biomarkers of exposure for children (or adults), although clinical symptoms of drunkenness or food poisoning and a sweet odor of the breath may alert a physician to possible chloromethane exposure. Attempts to use urinary levels of S-methylcysteine as an indicator of chloromethane exposure have not been successful. Further studies are needed to evaluate the toxicokinetics of chloromethane and its metabolites in children and to develop reliable biomarkers of exposure and effects.

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Physical and Chemical Properties. Data regarding physical and chemical properties are essential for assessing the partitioning of a chemical and its fate in the environment. Experimental data on physical and chemical properties are available for chloromethane, and many of these have methodology descriptions accompanying them so that accuracy of the data can be evaluated. The data on known physical and chemical properties form the basis of many of the input requirements for environmental models that predict the behavior of a chemical under specific conditions including hazardous waste landfills. There are no data needs relating to the information of chloromethane's physical and chemical properties.

Production, Import/Export, Use, Release, and Disposal. Production methods for chloromethane are well-described in the literature (including the patent literature) and there does not appear to be a need for further information.

Uses of chloromethane have been documented, although a detailed description of all uses in industry may be difficult to obtain. This information is useful for estimating the potential for environmental releases from manufacturing and use industries as well as the potential environmental burden; however, it is difficult to obtain this information in the detail desired since generally, it is CBI for those industries that manufacture chloromethane.

Data on chloromethane releases to air, water, and landfills, which can be used to estimate environmental burdens and potentially exposed populations, are obtained from EPA's TRI. Data from industries that are not required to report to the TRI are difficult to obtain and is a data need.

Limited data are available in the literature on disposal of chloromethane. Data on the disposal of chloromethane would be valuable in determining whether industrial activities pose an important source of human exposure to chloromethane.

As a hazardous air pollutant (HAP), chloromethane is regulated by the Clean Air Act (CAA). Chloromethane is also regulated under RCRA, CERCLA, and by OSHA.

Environmental Fate. The fate of chloromethane in air is well-described because extensive air photolysis and photo-oxidation studies are available that characterize these processes. Biodegradation studies in surface water and groundwater are not as complete. These kinds of studies are important

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because they would provide information about fundamental removal mechanisms for chloromethane in the environment and might aid in understanding the behavior of chloromethane at hazardous waste sites or municipal landfills. The vapor pressure of chloromethane and its presence in groundwater suggest that these processes are important, particularly at hazardous waste sites, and may account for some of the losses of chloromethane from the site. Limited research suggests that common soil fungi may be able to generate chloromethane as well as to dehalogenate it, and thus degrade it. Since these wood rot fungi can also break down other halogenated aliphatic compounds, there is the possibility that some of the chloromethane found at waste sites could have been produced through the action of such fungi on other waste compounds. More research is needed to document the importance of these biodegradation mechanisms, and to determine whether the net effects tend toward a progressive reduction in the levels of chloromethane found in contaminated soils and sediments at waste sites.

Inferences based on modeling indicate that chloromethane is not expected to accumulate in sediment or biota. Measured values are needed to confirm (or refute) these predictions.

Bioavailability from Environmental Media. Experimental inhalation studies in animals and humans indicate that chloromethane is bioavailable from the atmosphere. Studies examining inhalation pathways and the bioavailability of chloromethane from water, soil, and other environmental media would be useful.

Food Chain Bioaccumulation. The log K_{ow} for chloromethane is in the range of 0.91–1.086 (see Table 4-2). Such low values generally mean that the BCF will be low, suggesting that chloromethane will not tend to concentrate in aquatic organisms. However, no information was identified on experimental determinations of BCF levels for chloromethane. Determinations of BCF values for organisms at various trophic levels are needed to estimate human dietary intake of chloromethane.

Exposure Levels in Environmental Media. Extensive environmental monitoring data are available for chloromethane in air, while the available data are very limited for drinking water, surface water, and groundwater. The air monitoring data describe the concentrations that populations are exposed to through inhalation of ambient air. The data for water are not sufficient to accurately characterize the concentrations of chloromethane present in drinking water, surface water, or groundwater. Almost no data are available for soils. These data are needed to determine the ambient concentrations of chloromethane so that exposure of the general population as well as of terrestrial and aquatic organisms can be estimated.

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Reliable monitoring data for the levels of chloromethane in contaminated media at hazardous waste sites are needed to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. No recent exposure level data are available for the general population. A complete database is needed to determine the current exposure levels and to estimate the average daily dose associated with various scenarios (e.g., living near a hazardous waste site). The available NOES database of potential occupational exposures was assembled in the late 1980s and is outdated. Updated information in the format of this statistically-based database of potential occupational exposures would be helpful. An environmental media monitoring program may provide the necessary information for estimating environmental exposures, while workplace monitoring at use sites, using personal dosimeters and remote sensing devices, would probably provide useful workplace exposure information.

Exposures of Children. Chloromethane was detected in two of eight samples of mothers' milk from Bayonne and Jersey City, New Jersey; Bridgeville, Pennsylvania; and Baton Rouge, Louisiana (Pellizzari et al. 1982). No concentrations were reported, and no information was given concerning the potential source(s) of the chloromethane in the breast milk. Studies to determine current chloromethane residues and sources in breast milk of women in the general population and in the workforce are needed. Drinking water sources should be surveyed in areas near landfills where chloromethane has been detected at significant levels in recent years. Ingestion of chloromethane contaminated drinking water could be an important route of exposure in children since it may be used to prepare baby formula or baby food.

Current information on whether children are different in their weight-adjusted intake of chloromethane via oral and dermal exposures was not available. A study to determine this information is needed. Additionally, it is not known if children's exposure is impacted by pica behavior. Genetic polymorphisms have been seen in adults that affect chloromethane metabolism in adults. A study to examine the effect of this polymorphism in children would be useful.

6.3 ONGOING STUDIES

No ongoing studies were found that address the health effects of chloromethane (RePORTER 2022).