

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 and 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 duration. The evidence on chloromethane's carcinogenicity is mixed in epidemiological studies (Barry et al. 2011; Dosemeci et al. 1999; Holmes et al. 1986; Jiao et al. 2012; 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 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).

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Jiao et al. (2012) found that the job matrix used in their study had insufficient statistical power to evaluate effects of chloromethane, so they combined all chlorinated solvents and found an association with NHL for women with two specific genotypes. 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.

There have been no studies to determine if children are more or less susceptible than adults to adverse health effects from a given amount or duration of exposure to chloromethane. In a study on experimental animals, Wolkowski-Tyl et al. (Wolkowski-Tyl et al. 1983b; Wolkowski-Tyl et al. 1983a) demonstrated there may be adverse impacts on the developing heart, though the technique used in the study to section the heart raises questions about the validity of the result. There is no direct information on the potential movement of chloromethane or its metabolites across the placenta in humans and into the developing young; information is limited on the potential transplacental transfer in animals. However, Wolkowski-Tyl et al. (Wolkowski-Tyl et al. 1983b; Wolkowski-Tyl et al. 1983a) noted from unpublished observations that mouse dams exposed to 100, 500, or 1,500 ppm chloromethane for 6 hours on gestation day 17 had significant NPSH concentration reductions in both dams and fetuses, indicative of transplacental passage of chloromethane or its metabolites. Chloromethane has been measured in 2 of 8 samples of human breast milk, however the source of the chloromethane is not known (Pellizzari et al. 1982). Additionally, it is not known whether chloromethane or its metabolites can migrate into breast milk.

A number of studies have evaluated the health effects of chloromethane exposure in animals for the inhalation route, although only a single comprehensive chronic study in rats and mice has been performed (CIIT 1981). Health effects of acute, intermediate, and chronic inhalation exposure 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

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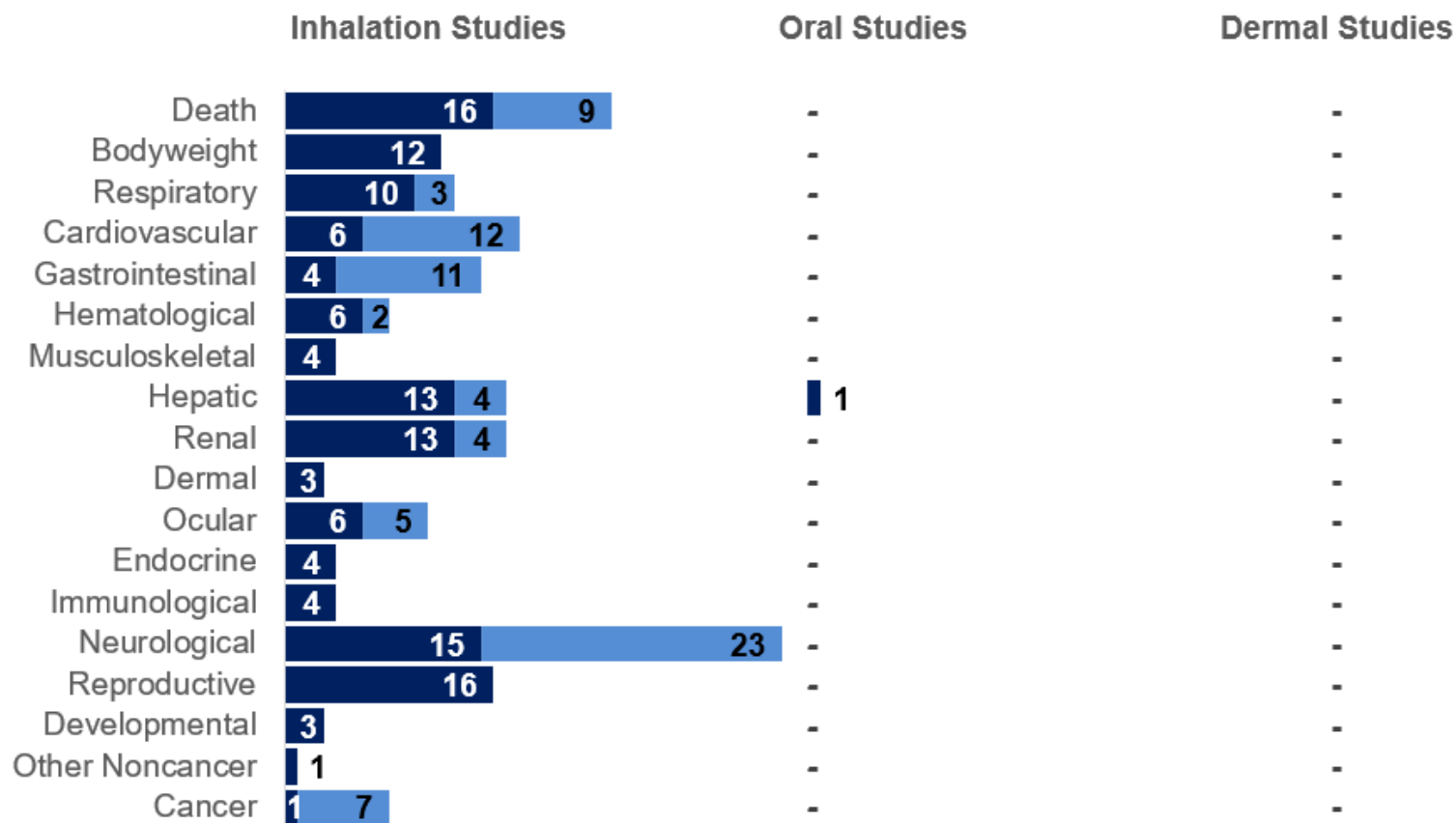
health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Chloromethane is highly volatile, and chloromethane in surface water or soil will likely evaporate to the air (CHAPTER 5.). Given the volatility of chloromethane, inhalation exposures and toxicity are of primary concern and have been the most studied. The oral and dermal routes of exposure are less of a potential exposure concern given that chloromethane is a gas at normal temperature and pressure, making inhalation the main route of exposure. Other than the Reynolds and Yee (1967) study, no information was located regarding the health effects of chloromethane in humans or animals after oral or dermal exposure. It is not possible to predict whether effects following oral or dermal exposure to chloromethane would be similar to those following inhalation exposure, partially because the pharmacokinetic disposition of chloromethane has not been compared for the three routes of exposure. Differences in absorption, distribution, and metabolic pathways could lead to differences in toxic response and different target organs following the three routes of exposure. Since the most likely route of exposure is inhalation, these studies would be the most relevant, and oral and dermal exposure to a lesser extent.

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Figure 6-1. Summary of Existing Health Effect 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. Some studies may have looked at more than endpoint.

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Acute-Duration MRLs. The data for acute effects in animals were sufficient to derive an acute inhalation provisional MRL for chloromethane based on a NOAEL for neurological effects in mice. Some information on the mechanism of hepatic, renal, neurological, and reproductive effects in mice is available, but more is needed. Only one acute oral study was reported, and this was not sufficient to derive a provisional MRL. In this study, rats were dosed orally with chloromethane, livers were examined for pathology, and measures of potential to induce liver toxicity were assessed. The administered dose did not cause hepatic effects, and higher doses were neither administered nor warranted because they traumatized the animals and produced deep anesthesia and death within minutes. Orally administered chloromethane did not suppress glucose 6-phosphatase activity, it did not increase cell sap RNA, and little of the radioactive ^{14}C from labeled chloromethane was incorporated into the lipid constituents of microsomes (Reynolds and Yee 1967). Several case studies and environmental epidemiologic studies support the association between chloromethane exposure and adverse neurologic outcomes. No studies were located regarding effects in animals after dermal exposure to chloromethane. Pharmacokinetic data are insufficient to identify whether target organs of chloromethane are the same for inhalation, oral, and dermal exposure and more studies are needed. As discussed above, the potential for humans to be exposed to chloromethane is likely greater through the inhalation route than for the oral and dermal routes therefore inhalation studies would be the most relevant to ongoing exposure scenarios in humans.

Intermediate-Duration MRLs. Information regarding effects in humans after intermediate-duration exposure to chloromethane is limited to findings of neurological symptoms in humans occupationally exposed. Inhalation studies conducted in rats, mice, and dogs have identified the liver as a target organ in rats and mice (CIIT 1981; Mitchell et al. 1979; Smith and Von Oettingen 1947a); the testes as a target organ in rats (CIIT 1981; Hamm et al. 1985); and the kidney and spleen as targets in mice (CIIT 1981). The data were insufficient to derive an intermediate-duration inhalation provisional MRL. Although CIIT (1981) evaluated neurological effects in their chronic duration study these effects were not assessed in their 6-month study. No studies were located regarding effects in humans or animals after intermediate-duration oral or dermal exposure, and pharmacokinetic data are insufficient to identify or predict target organs of chloromethane for these routes of exposure. As discussed above, the potential for humans to be exposed to chloromethane is likely greater through the inhalation route than for the oral and dermal routes therefore inhalation studies would be the most relevant to ongoing exposure scenarios in humans.

Chronic-Duration MRLs. Only one study was located regarding effects of chloromethane in humans after chronic inhalation exposure. No chronic-duration studies were located for other routes. A 2-year inhalation study in animals has been conducted in which both sexes of rats and mice were exposed to several concentrations of chloromethane (CIIT 1981). The liver, kidneys, spleen, and brain were

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identified as target organs in mice, and the testes were identified as target organs in rats and mice. Data were sufficient to derive a chronic inhalation provisional MRL. No studies were located regarding effects in animals after chronic oral or dermal exposure to chloromethane, subsequently no provisional MRLs were developed for these exposure routes. Pharmacokinetic data are insufficient to identify or predict target organs of chloromethane for these routes of exposure. As discussed above, the potential for humans to be exposed to chloromethane is likely greater through the inhalation route than for the oral and dermal routes therefore inhalation studies would be the most 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.

Cardiovascular. Case reports and epidemiological studies have indicated a potential for chloromethane to result in adverse cardiovascular outcomes (Hansen et al. 1953; Kegel et al. 1929; McNally 1946; Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014; Scharnweber et al. 1974; Spevak et al. 1976; Stewart et al. 1980; Verriere and Vachez 1949). However, these studies are lacking quantitative exposure level information, and the epidemiological studies are lacking data on key confounders such as smoking, alcohol consumption, and lifestyle factors. Additionally, Holmes et al. (1986) found no apparent cardiovascular outcomes. Most animal studies evaluating cardiovascular effects due to chloromethane exposure did not find an association. When cardiovascular effects were found they included increased relative heart weight (not accompanied by lesions) (CIIT 1981), increased pulse, and decreased blood pressure (Kegel et al. 1929), likely related to effects of a metabolite since some effects were delayed to times when blood levels were low (von Oettingen et al. 1949, 1950). Additional data elucidating whether cardiovascular impacts are associated with chloromethane exposure are needed.

Dermal. No studies evaluated the effects of dermal exposure to chloromethane on humans. Only one study examined dermal effects in animals following acute inhalation exposure to chloromethane. However, the authors questioned if the effects observed were secondary to fighting with cage mates (McKenna et al. 1981b). Intermediate exposures ranging from 400 ppm to 1,500 ppm did not produce similar dermal effects; however, chloromethane was reported to penetrate human skin in vitro (Gaskin et al. 2018). Therefore, additional data is needed to understand if the alopecia noted in the acute exposure study was a result of chloromethane exposure or another cause (i.e., fighting).

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Ocular. The relationship between chloromethane exposure and ocular effects is not clear as some short-term studies noted mucopurulent conjunctivitis with total destruction of the eye; however, other longer-term studies did not find the same impact. Additionally, in CIIT (1981) ocular impacts were seen at various time points for different species or sexes, but there was no consistency in the results (e.g., experimental animals exposed for 24 months did not show any ocular effects, whereas some animals with shorter term exposure did). A case report identified blindness in a woman who had been cleaning a toilet with a mixture that resulted in exposure to a chlorine gas; however, this was suspected to be due to a neurological effect rather than an ocular effect (Wilken et al. 2017). Therefore, additional data are needed to understand if chloromethane is associated with ocular effects.

Immunological. No information was located regarding immunotoxic effects in humans after exposure to chloromethane by any route. The immunotoxic effects reported in the literature in animals from exposure to chloromethane were lymphoid depletion of the spleen and splenic atrophy observed in mice exposed by inhalation to 1,000 ppm chloromethane for 2 years (CIIT 1981). Cats exposed continuously to chloromethane for 3 days had higher incidences of brain lesions than controls (McKenna et al. 1981a), but the lesions were consistent with infection or post-vaccinal reaction (the cats were vaccinated for panleukopenia by the supplier). Exacerbation of viral-induced central nervous system disease could not be ruled out. Additional studies are needed to further evaluate the potential immunotoxicity of chloromethane to humans.

Neurological. The neurotoxic effects in humans from inhalation exposure to chloromethane are described in numerous case studies (Baird 1954; Battigelli and Perini 1955; Gudmundsson 1977; Hansen et al. 1953; Hartman et al. 1955; Jones 1942; Kegel et al. 1929; Lanham 1982; Macdonald 1964; McNally 1946; Raalte and van Velzen 1945; Spevak et al. 1976; Wood 1951), but the mechanism is unclear. S-methylcysteine appears to be a metabolite in humans (Kornbrust and Bus 1983), and mechanisms involving conjugation with glutathione are likely to be relevant to human toxicity. Methanethiol produces similar central nervous system effects as seen in humans and animals exposed to chloromethane (Jager et al. 1988; Kornbrust and Bus 1983). The neurotoxic effects of inhalation exposure to chloromethane are also well defined in animals (Burek et al. 1981; Chellman et al. 1986a, Chellman et al. 1986b; CIIT 1981; Landry et al. 1985; McKenna et al. 1981a; Morgan KT et al. 1982; Smith and Van Oettingen 1947b). The mechanism for the induction of cerebellar lesions in mice exposed by inhalation may involve conjugation of chloromethane with glutathione, with further metabolism leading to production of methanethiol (Chellman et al. 1986b). The relative importance of conjugation with glutathione in other species has not been determined. More studies in animals are needed to understand the mechanisms of neurotoxicity from inhalation exposure to chloromethane.

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Reproductive. One case study described potential reproductive effects (i.e., impotence) in an occupationally exposed individual. No data on exposure levels were provided in this study (Mackie 1961). Several inhalation studies, however, have demonstrated that chloromethane is a reproductive toxicant in male rats (Burek et al. 1981; Chapin et al. 1984; Chellman et al. 1986a, Chellman et al. 1986b, Chellman et al. 1987; CIIT 1981; Hamm et al. 1985; Morgan KT et al. 1982; Working and Bus 1986; Working et al. 1985a, Working et al. 1985b). The mechanism of this reproductive toxicity has been studied extensively only in rats because testicular lesions in mice occurred at lower incidences and later time periods than in rats in the 2-year inhalation study by CIIT (1981). Testicular effects were not observed in male dogs and cats exposed to chloromethane by inhalation (McKenna et al. 1981a), but the exposure concentrations may not have been high enough. Species differences in sensitivity exist for other end points as well. No studies were located regarding the reproductive effects of chloromethane in animals after oral or dermal exposure, and pharmacokinetic data are insufficient to support the potential for reproductive effects across routes of exposure. Therefore, additional studies for reproductive effects in other species at higher exposure levels are needed to further evaluate the potential adverse reproductive effects in humans from exposure to chloromethane.

Developmental. No information was located regarding developmental effects in humans after exposure to chloromethane by any route.

The teratogenicity of inhalation exposure to chloromethane has been studied in rats, mice, and rabbits (Wolkowski-Tyl et al. 1983a, Wolkowski-Tyl et al. 1983ab, Theuns-van Vliet 2016). In rats, delayed fetal development was found at a concentration that also resulted in maternal toxicity. The same was not seen in mice (Wolkowski-Tyl et al. 1981a, 1983a). Mice demonstrated cardiac heart malformations after gestational exposure to chloromethane (Wolkowski-Tyl et al. 1983a, Wolkowski-Tyl et al. 1983ab). However, neither rats nor rabbits have experienced these effects after chloromethane exposure (Wolkowski-Tyl et al. 1981a, 1983a, Theuns-van Vliet 2016). Therefore, additional studies are needed to further evaluate the relevance of the delayed fetal development and cardiac effects seen in rats and mice, respectively, to humans given no other species has demonstrated the same effects.

Cancer. Epidemiological studies have evaluated the relationship between occupational exposures to chloromethane and subsequent cancer outcomes. In the cohort of Icelandic fisherman there was an increased risk of death from renal cancer in the exposed cohort compared to unexposed fisherman (Rafnsson and Kristbjornsdottir 2014). However, as previously noted, there are limitations with these studies which limit their generalizability. An association between occupational exposure to chloromethane and non-Hodgkin's lymphoma has been observed in a small number of individuals with the TT genotype of the genetic phenotype CYP2E1 rs2070673 for which the functional significance is

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unclear (Barry et al. 2011). Additional research is needed to validate whether chloromethane exposure is associated with non-Hodgkin's lymphoma.

In animal studies, carcinogenic effects of chloromethane were observed in male, but not female mice, nor in rats of either sex (CIIT 1981). Male mice had increased incidences of kidney tumors at the highest exposure level. The rats and mice were exposed to the same concentrations, but differences in ventilation rate, the ability to conjugate chloromethane with glutathione, the further metabolism of the glutathione conjugate, and body weight effects make it probable that mice received a higher internal dose than rats. It is possible, therefore, that the exposure concentration was not sufficient in rats to produce detectable increases in kidney tumors. Additional chronic inhalation studies are needed to provide more information on differences in species susceptibility and to further evaluate the potential for and the mechanisms of chronic and carcinogenic effects of chloromethane exposure in humans.

Genotoxicity. Chloromethane has been shown to be genotoxic (Chellman et al. 1986c; Ristau et al. 1990; Rushbrook 1984; Working et al. 1985a). DNA strand breaks have been evaluated in human lymphoblasts (Fostel et al. 1985). Genotoxic effects have also been evaluated for mutations in *S. typhimurium* (Andrews et al. 1976; DuPont 1977; Simmon et al. 1977), sister-chromatid exchange (Fostel et al. 1985) unscheduled DNA synthesis in rat hepatocytes (Working et al. 1986), effects on spermatocytes and tracheal epithelial cells (Working et al. 1986), and DNA viral transformation in primary hamster embryo cells (Hatch et al. 1982; Hatch et al. 1983). According to the study authors, dominant lethal mutations in rat sperm resulting from inhalation exposure of male rats to chloromethane suggest that the dominant lethal effects may be secondary to inflammation of the epididymides (Chellman et al. 1986c). However, this is not definitively known and dominant lethal effects are still a concern. Research has explored why male mice were susceptible to renal tumors, whereas animals of different sex and species were not. Genotoxicity a result of the metabolites of chloromethane were explored as a potential mechanism given there may be sex and species differences in metabolizing enzymes. However, it is unclear if this is the reason for the difference. Therefore, additional data is needed to elucidate if the renal cancers seen in CIIT (1981) were due to genotoxicity.

Mechanisms of Action. Additional studies are needed to further define the mechanism of chloromethane's toxicity. Especially important are studies to determine whether depletion or protection of glutathione pools is needed to protect against toxicity for any given exposure route or target organ. The mechanisms and the beneficial or detrimental contribution of glutathione may be different for different species or genders.

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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 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; Jiao et al. 2012; 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. No biomarker that can be associated quantitatively with exposure to chloromethane has been identified (see Section 3.3.1). Methods are available for the analysis of chloromethane in blood, expired air, and breast milk. In addition, a method exists for the analysis of 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. 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. Thus, methods for biomarkers of exposure and effect are needed.

Exposure. A number of 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). The blood and alveolar air levels of chloromethane and the urinary levels of S-methylcysteine are highly variable. Symptoms resembling drunkenness and food poisoning, along with a sweet odor on the breath, may alert a physician that a

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person has been exposed to chloromethane, but such symptoms could easily be mistaken for the conditions they resemble.

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 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. Attempts to correlate blood levels and expired air concentrations of chloromethane with health effects of occupational and experimental inhalation exposures of humans were successful on a group average basis (Putz-Anderson et al. 1981a; Repko et al. 1976). Since blood and alveolar levels show individual variability they may be of limited use as indicators of neurological function or behavior. Further studies are needed to identify a metabolite or biomarker that can be correlated with the known toxic end point and that would lead to early detection and potential treatment.

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; Landry et al. 1983b; Putz-Anderson et al. 1981b; Putz-Anderson et al. 1981a; 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 is 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; Kornbrust and Bus 1984; Kornbrust et al. 1982; Landry et al. 1983a; Landry et al. 1983b; Putz-Anderson et al. 1981b; Putz-Anderson et al. 1981a; Redford-Ellis and Gowenlock 1971a; Redford-Ellis and Gowenlock 1971b; Repko et al. 1976; van Doorn et al. 1980; von Oettingen et al. 1949, 1950). The kinetics of chloromethane in humans were

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similar to those in rats and dogs, with data for each species consistent with a 2-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 differences in potential toxic metabolites. Additional studies are especially needed to resolve the relative importance of glutathione conjugation and P-450 oxidation to the toxicity of chloromethane. These studies should be performed in different tissues, species, and sexes to resolve potential differences. Additional studies are needed to evaluate the importance of varying levels of human endogenous erythrocyte glutathione transferase (as has been recently shown to exist) to the toxicity of chloromethane, 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 more or less 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 hind limbs. 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 gestation day 6-17. In a letter to an editor, John-Green 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 gestation day 11.5-12.5 (John-Greene et al. 1985). Theunsvan Vliet exposed rabbits to up to 1000 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 no information on the movement of chloromethane or its metabolites across the placenta or into the developing young nor information on the movement of chloromethane or its metabolites into a

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nursing women's milk. Information is limited on the potential transplacental transfer in animals. Wolkowski-Tyl et al. (Wolkowski-Tyl et al. 1983b; Wolkowski-Tyl et al. 1983a) noted from unpublished observations that mouse dams exposed to 100, 500, or 1,500 ppm chloromethane for 6 hours on gestation day 17 had significant NPSH concentration reductions in both dams and fetuses, indicative of transplacental passage of chloromethane or its metabolites. 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). Thus, it is unlikely that chloromethane would be stored in maternal tissues or be mobilized (i.e., released from stores) during pregnancy or lactation. However, one study measured chloromethane in 2 of 8 sample of human breast milk but the source of the substance is not known (Pellizzari et al. 1982). Further studies are needed that examine the presence of chloromethane in breastmilk sample of exposed populations.

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, glutathione-S-transferase (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 glutathione or from the depletion of glutathione (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 glutathione-S-transferase) would potentially be more susceptible to the toxic effects of chloromethane. Moreover, cytochrome P-450 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) disputes this conclusion. Guengerich and Shimada (1991) suggest that the human cytochrome P-450 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 P-450 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

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toxicokinetics of chloromethane and its metabolites in children and to develop reliable biomarkers of exposure and effects.

Physical and Chemical Properties. Data regarding physical and chemical properties are essential for estimating the partitioning of a chemical in the environment. Most of the necessary data on physical and chemical properties are available for chloromethane, and many of these have experimental descriptions accompanying them so that accuracy 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. 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.

Use. 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 considered to be confidential business information (CBI) for those industries that manufacture chloromethane.

Release. Release information, which can be used to estimate environmental burdens and potentially exposed populations, is obtained from the Toxic Release Inventory. Data from industries that are not required to report to the TRI is difficult to obtain and is a data need.

Disposal. Limited data is 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.

Regulatory Information. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 2017, became available in October of 2018. This database is updated yearly and should provide a list of industrial production facilities and emissions required to report to TRI.

6. ADEQUACY OF THE DATABASE

As a HAP, chloromethane is regulated by the Clean Air Act. 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 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, 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 are made regarding chloromethane's tendency to accumulate in sediment or biota. Measured values are needed to better understand chloromethane's tendency to bioaccumulate.

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 to 1.086 (see CHAPTER 4. , 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

6. ADEQUACY OF THE DATABASE

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.

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. The database for chloromethane exposure levels in humans is limited to determinations of chloromethane in breast milk. A more 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). 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 information. The available NOES database of potential occupational exposures was assembled in the late 1980s and is outdated. An update to this statistically based database of potential occupational exposures is needed. Additionally, information on background levels in the general population would be useful.

Exposures of Children. Chloromethane was present in 2 of 8 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 source of the chloromethane in the milk. Studies to determine current chloromethane residues and sources in breast milk of women in the general population and in the workforce are needed. Well water surveys should be conducted 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.

APPENDIX F

exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.