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 thallium 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 thallium.

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

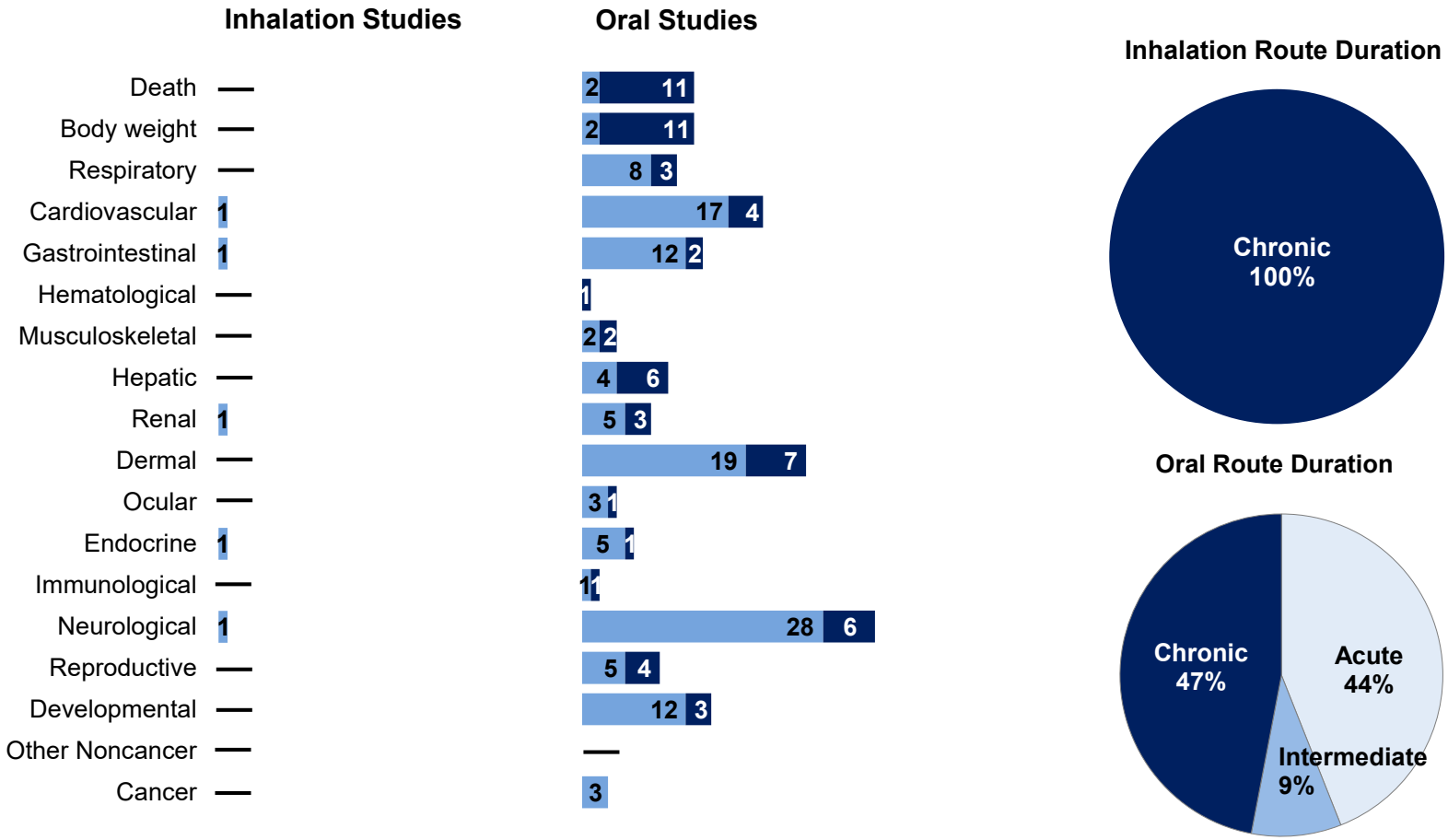
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to thallium that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of thallium. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies. Acute-duration oral studies in humans are limited to case studies and case series reports discussed in Chapter 2 (see Section 2.1 for additional information).

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 Thallium by Route and Endpoint*

Potential cardiovascular, dermal, and neurological effects were the most studied endpoints
The majority of the studies examined oral exposure in **humans** (versus **animals**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. No dermal studies in humans or animals were located. Many studies examined more than one endpoint.

Acute-Duration MRLs. No studies were found on the adverse effects of acute-duration inhalation exposure in humans or animals. Inhalation is not likely to lead to significant exposure of the general population near hazardous waste sites. Thallium and compounds are not volatile and are subject to precipitation washout. The available information on effects of acute-duration exposure to thallium and compounds in humans is limited to case reports that indicate neurological, gastrointestinal, cardiovascular, and dermal effects following oral exposure; most of studies did not report reliable exposure data. Human exposure data were not sufficient to derive an acute-duration oral MRL since reliable NOAEL and LOAEL values could not be determined. Acute-duration oral data in animals demonstrated lethal, body weight, gastrointestinal, neurological, and dermal effects of thallium, but data were not sufficient to derive an acute-duration oral MRL. Additional studies in animals would be useful to identify the most sensitive effect and establish dose response relationships following acute-duration oral exposure to thallium.

Intermediate-Duration MRLs. No studies are available on adverse health effects of intermediate-duration inhalation exposure in humans to thallium and compounds. Since thallium is not volatile, this route may not be a major concern to humans exposed near hazardous waste sites. No information is available on the effects of intermediate-duration inhalation exposure in animals. Oral studies in animals demonstrated dermal, neurological, reproductive, and developmental effects. Data from these studies were not sufficient to derive an intermediate-duration MRL. Many of the intermediate-duration studies employed one dose level, precluding dose-response evaluations. Additional oral studies evaluating a wide range of endpoints, particularly those observed in humans (e.g., dermal, neurological, cardiovascular) would be useful in identifying susceptible organs and establishing dose-response relationships.

Chronic-Duration MRLs. A few studies are available evaluating the effects on humans chronically exposed to thallium in workplace air; none were considered suitable for MRL derivation. No chronic-duration inhalation studies were identified in animals. Because thallium is not volatile and is subject to precipitation washout from the atmosphere, exposure by this route may not be a major concern at hazardous waste sites. A number of epidemiological studies evaluating the potential toxicity of thallium resulting from chronic-duration oral exposure to thallium have been identified. However, none of the studies measured intake and no pharmacokinetic models to convert urinary thallium levels to intakes have been identified. No studies are available on the effects of chronic-duration oral exposure in animals. Because long-term environmental exposure to thallium can occur in humans at hazardous waste sites, oral

chronic-duration animal studies at several dose levels would be useful in identifying susceptible target organs and defining chronic-duration thresholds.

Health Effects.

Cardiovascular. A number of case reports described cardiovascular effects following acute-duration oral exposure to thallium. However, only one study evaluated cardiac function in animals exposed to a lethal dose of thallium I sulfate (Grunfeld et al. 1963). Other animal studies have not found histological alterations in the heart. Additional animal studies evaluating cardiac function are needed at lower doses to evaluate whether the heart is a sensitive target of thallium toxicity.

Reproductive. Several epidemiological studies have been conducted in humans examining the possible associations between thallium and reproductive endpoints. Some associations have been found in women; however, additional studies are needed to confirm these findings. Reproductive function has not been adequately evaluated in animals. One study found decreases in sperm motility (Formigli et al. 1986), but this finding has not been confirmed in other studies. Additional studies are needed to evaluate potential male and female reproductive effects at various dose levels and identifying a threshold for these effects.

Developmental. A small number of studies have evaluated the potential developmental toxicity of thallium. The inconsistent results or lack of confirming studies preclude drawing conclusions from these studies. Developmental toxicity has not been adequately evaluated in animal studies. The three available studies have examined a limited number of potential endpoints and observed some effects such as decreased body weight, alopecia, and cardiovascular alterations. Additional studies examining a wider range of potential developmental effects, including neurodevelopmental, are needed in order to determine whether it is a sensitive target of thallium toxicity and establish dose-response relationships.

Immunotoxicity. There are limited data on the potential immunotoxicity of thallium in humans and animals. An epidemiological study and an acute-duration oral study in mice have examined immune endpoints. The animal study (Li et al. 2023a) did find some alterations but did not evaluate immune function. Additional studies are needed to assess whether the immune system is a target and to establish dose-response relationships.

Neurotoxicity. Clinical neurological signs as well as histological lesions in cranial and peripheral nerves have been demonstrated in humans following inhalation and oral exposure to thallium. In most cases, limited information on exposure levels were provided. Structural and functional changes in peripheral nerves in animals following oral exposure (Manzo et al. 1983) confirm findings in humans. However, the potential neurotoxicity of thallium has not been adequately assessed in animal studies. Given the peripheral nervous system findings in humans resulting from acute-duration oral exposure to thallium and the results of the Manzo et al. (1983) animal study, additional studies are needed to establish dose-response relationships. These studies should also examine the central nervous system since parenteral studies in animals demonstrated biochemical changes in various parts of the brain (Brown et al. 1985; Hasan et al. 1977a, 1977b, 1978; Rios et al. 1989).

Carcinogenicity. There is limited information on the carcinogenicity of thallium. No chronic-duration animal inhalation, oral, or dermal exposure studies were identified and are needed to assess the carcinogenicity of thallium. The results of additional *in vitro* and *in vivo* genotoxicity studies might provide insight into the carcinogenic potential of thallium.

Epidemiology and Human Dosimetry Studies. A number of epidemiological studies evaluating the potential health effects of thallium have been identified. Most studies have evaluated exposure by measuring urinary thallium levels. However, a pharmacokinetic model to estimate thallium intake from urinary levels has not been identified. Some studies have found associations between urinary thallium levels and health outcomes, but findings have not been confirmed by other studies or conflicting results have been reported. Long-term epidemiological studies by the oral route evaluating low-dose exposure would be useful in characterizing the toxicity of thallium if appropriate cohorts can be identified.

Biomarkers of Exposure and Effect. The presence of thallium in urine is the most reliable biomarker of exposure. The metal can be detected in urine more than several days after exposure (Brockhaus et al. 1981; Schaller et al. 1980). Additional studies examining the relationship between urinary levels and oral intake would be useful. Until sensitive targets of thallium toxicity are identified, biomarkers of effect cannot be evaluated.

Absorption, Distribution, Metabolism, and Excretion. No quantitative information is available on absorption of thallium in humans or animals by inhalation or dermal exposure. However, animal studies following intratracheal administration suggested that uptake through respiratory epithelium was

rapid and complete (Lie et al. 1960). Data regarding absorption in humans are limited. Oral studies that provide data on rate and extent of absorption would be useful since this appears to be the primary exposure route. In one study in which rats were administered radiolabel thallium nitrate by oral or parenteral exposure, body burden of radioactivity was expressed as a percent of administered dose over time, suggesting virtually complete and rapid uptake by these routes of exposure (Lie et al. 1960).

No information was found on the distribution of thallium following inhalation or dermal exposure. There are a few studies by oral exposure, which indicate that thallium is found in many tissues of the body (Barclay et al. 1953). Data in humans reported tissue levels are highest in the scalp hair, kidney, heart, bone, and spleen. Lower levels were found in the brain (Barclay et al. 1953). Animal studies confirmed that thallium is widely distributed (Downs et al. 1960; Grunfeld et al. 1963; Lie et al. 1960). However, in animals, thallium is chiefly distributed to the kidneys and liver. Additional studies are needed as a basis for understanding species differences in distribution of thallium. Data exist suggesting that thallium can cross the placental barrier by parenteral administration (Olsen and Jonsen 1982; Rade et al. 1982). Additional animal studies by the oral route would be useful in confirming that thallium can locate in the fetus and providing a basis for assessing if there is potential human health risk. Thallium is not metabolized; however, studies evaluating whether it is transformed from one valence state to another would be useful.

No data are available on excretion of thallium in humans or animals by inhalation or dermal exposure. There are data on excretion in humans and animals by oral exposure. In one study in which a patient was administered radiolabel thallium nitrate, one half of the radioactivity was detected in the urine 21.7 days after exposure, suggesting that thallium is slowly excreted from the body (Barclay et al. 1953). In animals, excretion is more rapid (e.g., half in 3.3 days) and occurs primarily via feces (Lie et al. 1960; Pedro et al. 1985). Additional studies of other animal species by all routes of exposure would be useful in clarifying differences in excretion patterns.

Comparative Toxicokinetics. Since human and animal toxicokinetic data are limited, very little data exist on comparative kinetics across species. Human data are limited to one study (Barclay et al. 1953) and animal data are primarily in rats (Downs et al. 1960; Lie et al. 1960; Pedro et al. 1985). These data suggest some kinetics differences, particularly in distribution and excretion patterns. Additional studies using other animal species would be useful in clarifying species differences.

Children's Susceptibility. There are limited data on whether children are unusually susceptible to the toxicity of thallium. Case reports that included children suggest similar toxic effects as adults; however, these reports do not include reliable intake data, which would be useful for evaluating potency. Animal studies of young animals would be useful for evaluating children's susceptibility.

Physical and Chemical Properties. Additional measurements of the aqueous solubility of environmentally relevant thallium compounds would provide a more accurate basis for applying mineral equilibria to predict the fate of thallium in water (EPA 1988).

Production, Import/Export, Use, Release, and Disposal. Data on production, use, and disposal (U.S. Bureau of Mines 1988; USGS 2023) are adequate. Additional information is unlikely to significantly affect estimates of human exposure.

Environmental Fate. Little information is available on partitioning of thallium in the atmosphere (EPA 1988). This lack of data is not important since thallium is nonvolatile. The reaction mechanisms controlling the fate of thallium in water are not well known. Adsorption-desorption reactions with soils and sediments (Frantz and Carlson 1987; Magorian et al. 1974; Mathis and Kevern 1975) suggest that movement of thallium can be reduced. Additional research would provide a more accurate basis for predicting the fate of thallium in water. Very little is known about potential transformation mechanisms for thallium in air, water, or soil (EPA 1979, 1988), but this lack of detailed data may not be a major limitation because many transition metals are not susceptible to transformation or degradation-type processes.

Bioavailability from Environmental Media. Thallium can be absorbed following inhalation of contaminated workplace air, ingestion of contaminated food, or dermal contact (Dai-xing and Ding-nan 1985; Dolgner et al. 1983; Marcus 1985). The most significant routes of exposure near hazardous waste sites are likely to be through drinking thallium-contaminated water and skin contact with or ingestion of thallium that is attached to soil particles. Information on the percent of thallium taken into the body from environmental media that is actually absorbed or bioavailable would be useful in clarifying the toxic potential of thallium in humans. The relative absorption of different species/forms of thallium from inorganic and biological matrices would also be useful.

Food Chain Bioaccumulation. There are no specific data on the bioaccumulation of thallium or its potential to be transferred from lower trophic levels to higher organisms. Because thallium can be

bioconcentrated, it may be that it can also be accumulated in living tissues. Thallium may be bioconcentrated by aquatic plants, invertebrates, and fish (Barrows et al. 1978; Zitko and Carson 1975; Zitko et al. 1975). Information on biotransformation in aquatic biota would provide further insight into the extent of chemical speciation and forms of thallium to which humans could be exposed near hazardous waste sites. Terrestrial plants absorb thallium from soil (Cataldo and Wildung 1983). Additional measurements of the bioconcentration of thallium by plants and animals and information on soil types and conditions that enhance thallium uptake by plants would be helpful to better define the tendency of thallium to partition to living tissues. Detectable levels of thallium have been found in many foods (Ewers 1988; Sharma et al. 1986; Sherlock and Smart 1986). Data suggests that thallium can accumulate in living organisms, with BCFs in fish in Lake Michigan as high as 10,000 (Lin et al. 2001). Additional information on food chain bioaccumulation would be useful in assessing the potential for human exposure to thallium from food.

Exposure Levels in Environmental Media. Data on thallium levels in all environmental media are abundant (Belzile and Chen 2017; Karbowska 2016). More research using sensitive analytical methods for all media, especially in the vicinity of potential thallium pollution sources and waste sites, and specific data on the thallium content of the American diet would increase the accuracy of human exposure estimates.

Exposure Levels in Humans. Thallium has been detected in human urine and urinary thallium excretion is used as a measure of thallium absorption (CDC 2023; Dai-xing and Ding-nan 1985; Dolgner et al. 1983; Marcus 1985). Reliable data on urinary thallium in unexposed individuals and correlating urinary thallium levels with environmental exposures at hazardous waste sites would help to identify populations at risk in the vicinity of these sites from thallium exposure.

Exposures of Children. There are no comprehensive data on thallium content of total diet samples in the United States, so it is not possible to estimate the average daily intake from foods. This is a data need for both children and adult exposures.

Data on exposures of children to thallium in the vicinity of hazardous waste sites would be useful to clearly establish whether thallium poses acute or chronic exposure hazards to children living near these sites. This information should include data on background concentrations in all media.

6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2024) database.