Toxicological Profile for Thallium

Draft for Public Comment

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U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute-, intermediate-, and chronic-duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA Section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health-related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under Section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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VERSION HISTORY

Date	Description
October 2024	Draft for public comment toxicological profile released
July 1992	Final toxicological profile released

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Thallium is a naturally occurring element in the earth's crust. In the environment, it combines with other elements (primarily oxygen, sulfur, and the halogens) to form inorganic compounds. Thallium is quite stable in the environment since it is neither transformed nor biodegraded.

Thallium compounds are generally soluble in water; thallium is primarily found as the monovalent ion (Tl^+). It tends to be sorbed to soils and sediments (Frantz and Carlson 1987; Karlsson 2006; Mathis and Kevern 1975; Wallwork-Barber et al. 1985; Wick et al. 2020) and to bioconcentrate in aquatic plants, invertebrates, and fish (Barrows et al. 1978; Lin et al. 2001; Zitko and Carson 1975). Terrestrial plants can also absorb thallium from soil (Ewers 1988; Rader et al. 2019; Sharma et al. 1986).

The primary sources of thallium releases to the environment are from processes such as coal-burning and smelting and the production of cement, in which thallium is a trace contaminant of the raw materials, rather than from facilities producing or using thallium compounds (Karbowska 2016). Humans may be exposed to thallium by ingestion, inhalation, or dermal absorption (EPA 1980, 1988; Ewers 1988). The general population is primarily exposed via ingestion of thallium-containing foods, particularly fruits and green vegetables. Inhalation exposure to thallium may also occur near emission sources or in the workplace.

1.2 SUMMARY OF HEALTH EFFECTS

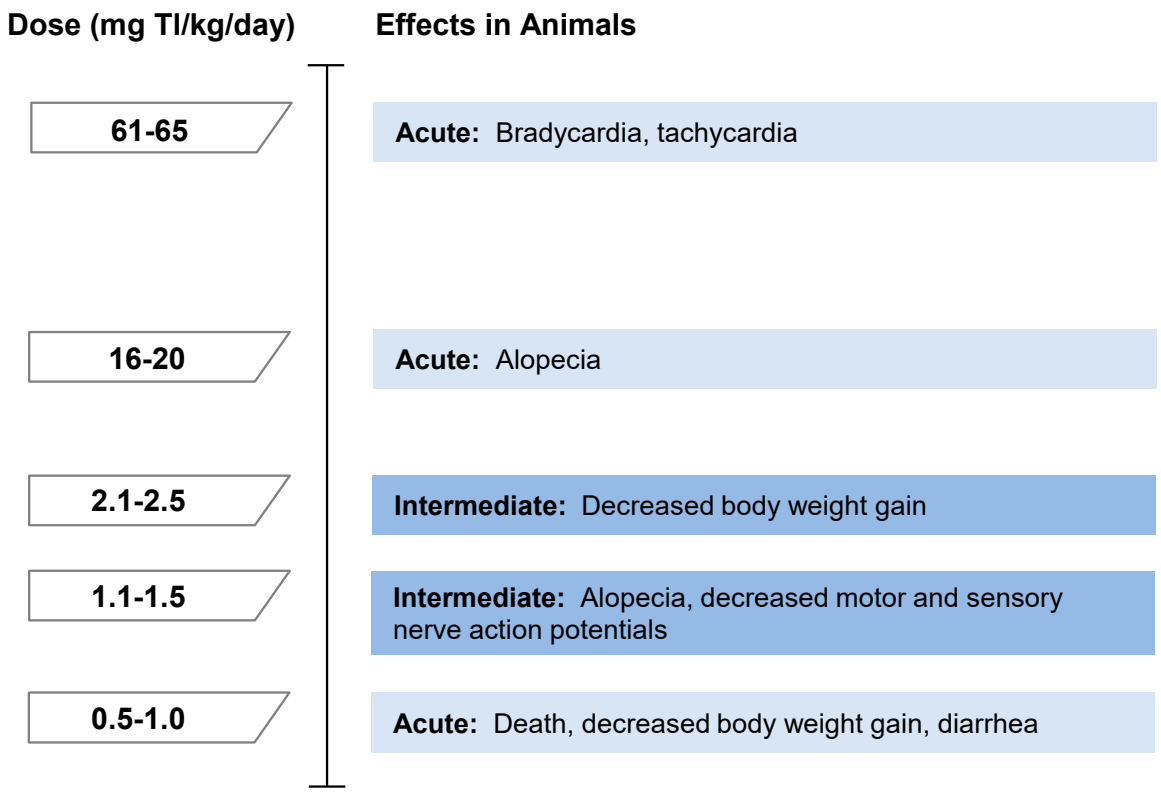
Information on the toxicity of thallium primarily comes from case studies and case series reports in humans orally exposed to thallium, epidemiological studies of the general population presumably orally exposed to thallium, and oral exposure studies in laboratory animals. Collectively, the epidemiological and toxicological studies have evaluated a wide range of potential endpoints following acute, intermediate, or chronic-duration exposure.

As illustrated in Figure 1-1, the most sensitive effects in animals appear to be alopecia, decreased body weight, decreased motor and sensory nerve action potentials, and diarrhea following oral exposure; Figure 1-1 only contains endpoints that have been corroborated in at least two animal studies or in human studies. Of these endpoints, only dermal effects (specifically alopecia) underwent a systematic review.

Systematic reviews of the other endpoints were not conducted because animal studies have not adequately evaluated the endpoint (e.g., only examined in one study or studies did not evaluate function). The systematic review of the alopecia endpoint resulted in the following hazard identification conclusion:

- Alopecia is a presumed health effect for humans.

Figure 1-1. Health Effects Found in Animals Following Oral Exposure to Thallium



There is also strong evidence that cardiovascular, gastrointestinal, and neurological systems are sensitive targets of thallium toxicity based on the consistency of these findings in individuals acutely poisoned with thallium, as reported in case studies and case-series reports.

Cardiovascular Effects. Tachycardia, hypertension, and alterations in electrocardiogram (EKG) have been reported in humans acutely exposed to oral thallium (Cavanagh et al. 1974; Davis et al. 1981; Meggs et al. 1994; Rayisyan et al. 2021; Riyaz et al. 2013; Roby et al. 1984; Sojáková et al. 2015; Tromme et al. 1998; Vrij et al. 1995; Zhao et al. 2008). In general, epidemiological studies either have not found associations or have found inverse associations between urinary thallium levels and cardiovascular disease (Fan et al. 2023; Guo et al. 2022; Li et al. 2023b; Nuvolone et al. 2021; Wang et al. 2022a). Bradycardia, tachycardia, and other EKG alterations were observed in rabbits administered a single lethal

dose of thallium (Grunfeld et al. 1963). Animal studies have not found histological alterations in the heart following intermediate-duration oral exposure (Downs et al. 1960; EPA 1986).

Gastrointestinal Effects. Gastrointestinal effects such as abdominal pain, nausea/vomiting, and/or diarrhea or constipation are often reported in individuals acutely exposed to oral thallium (Al Hammouri et al. 2011; Almassri and Sekkarie 2018; Cavanagh et al. 1974; Dai-xing and Ding-nan 1985; Davis et al. 1981; Meggs et al. 1994; Rayisyan et al. 2021; Wang et al. 2007, 2021; Zhang et al. 2014; Zhao et al. 2008). The effects often occur within the first 3 days of exposure. Diarrhea has also been reported in rats exposed to a high oral dose (Rusyniak et al. 2003).

Dermal Effects. Alopecia (hair loss) is a classic symptom of acute thallium poisoning (Al Hammouri et al. 2011; Almassri and Sekkarie 2018; Desenclos et al. 1992; Gastel 1978; Grunfeld and Hinostroza 1964; Lu et al. 2007; Meggs et al. 1994; Rayisyan et al. 2021; Sojáková et al. 2015; Sun et al. 2012; Villanueva et al. 1990; Wang et al. 2007, 2021; Zavaliy et al. 2021; Zhang et al. 2014; Zhao et al. 2008). It is typically observed several weeks after exposure, and in most cases, the hair loss is temporary. Alopecia is also frequently observed in animals following exposure to a high single dose of thallium (Rusyniak et al. 2003) or following intermediate-duration oral exposure to low thallium doses (Downs et al. 1960; EPA 1986; Gross et al. 1948; Manzo et al. 1983; Shipkowski et al. 2023). It has also been observed in the offspring of rats exposed to thallium during gestation and lactation (Shipkowski et al. 2023).

Neurological Effects. Peripheral nervous system effects are commonly reported after acute-duration oral exposure to high levels of thallium in humans. The observed effects include paresthesia (tingling and numbness) and hyperalgesia (abnormally increased sensitivity to pain) in the hands and feet (Al Hammouri et al. 2011; Almassri and Sekkarie 2018; Cavanagh et al. 1974; Davis et al. 181; Desenclos et al. 1992; Gastel 1978; Li et al. 2014; Meggs et al. 1994; Rayisyan et al. 2021; Roby et al. 1984; Sun et al. 2012; Wang et al. 2007, 2021; Zhao et al. 2008). The neurological effects are commonly reported within a week of exposure. Animal studies have not adequately evaluated the potential neurotoxicity of thallium. Some studies have reported overt signs of neurotoxicity such as convulsions (Grunfeld et al. 1963) and decreased spontaneous activity (Rusyniak et al. 2003). Decreases in the amplitude of motor and sensory action potentials were observed in rats (Manzo et al. 1983).

Cancer. There is limited information on the carcinogenicity of thallium. A study of workers did not find an increase in benign neoplasms, as compared to unexposed workers (Marcus 1985). Mixed results have been reported in epidemiological studies, with two studies finding inverse associations (Fan et al. 2023;

Nuvolone et al. 2021) and one study finding an association with prostate cancer (Cao et al. 2023). No animal studies have evaluated the carcinogenicity of thallium.

The U.S. Environmental Protection Agency (EPA) concluded that the database for thallium provides inadequate information to assess carcinogenic potential (IRIS 2009). The Department of Health and Human Services (HHS) and the International Agency for Research on Cancer (IARC) have not evaluated the carcinogenicity of thallium.

1.3 MINIMAL RISK LEVELS (MRLs)

MRLs for thallium have not been derived. No reliable inhalation studies were identified. Body weight decreases, dermal effects, nervous system effects, gastrointestinal effects, and death were the most sensitive targets following oral exposure to thallium; the lowest LOAELs for these endpoints are presented in Figure 1-2. The database for thallium was not considered adequate for derivation of inhalation or oral MRLs for thallium for any exposure duration (Table 1-1).

Figure 1-2. Summary of Sensitive Targets of Thallium – Oral

Available data indicate that body weight decreases, alopecia, nervous system effects, gastrointestinal effects, and death are the most sensitive targets of thallium oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

Table 1-1. Minimal Risk Levels (MRLs) for Thallium[a]

No MRLs were derived for any exposure route or duration for thallium.

[a]See Appendix A for additional information.

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of thallium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to thallium, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to thallium was also conducted; the results of this review are presented in Appendix C.

Summaries of the human observational studies are presented in Table 2-1. Animal oral studies are presented in Table 2-2 and Figure 2-2.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. Effects have been classified into “less serious LOAELs” or “serious LOAELs (SLOAELs).” “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause

significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

A User's Guide has been provided at the end of this profile (see Appendix D]). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

Information on the toxicity of thallium comes from a large number of case reports and case studies resulting from accidental and intentional ingestion and intentional poisoning. The thallium doses are not typically known in most cases; in some cases, urinary or blood thallium levels have been reported. Other types of studies evaluating thallium toxicity include occupational exposure studies, epidemiological studies of populations living near a point source, general population studies, and studies in laboratory animals. Most of the available studies involve oral exposure. Studies in laboratory animals have evaluated the toxicity of several monovalent thallium compounds including thallium I acetate, thallium I sulfate, thallium I oxide, thallium I nitrate, and thallium I oxalate. The toxicokinetic properties of these compounds, particularly absorption, would likely influence the toxicity of the compounds. Evaluation of the toxicity of trivalent thallium compounds in animals is limited to two studies testing thallium III nitrate or thallium III chloride. The limited available data are inadequate to assess whether there are differences in toxicity between monovalent and trivalent compounds. There is a small number of studies of workers exposed to airborne thallium and studies looking at health effects associated with the thallium content of particulate matter $\leq$2.5 μm ($PM_{2.5}$); no animal inhalation studies were identified. Additionally, no human or animal dermal exposure studies were identified. Although there are a large number of case reports of acute thallium poisonings, it is beyond the scope of this profile to discuss all of these reports; rather, ATSDR has relied on literature review publications and reports involving poisonings of multiple people.

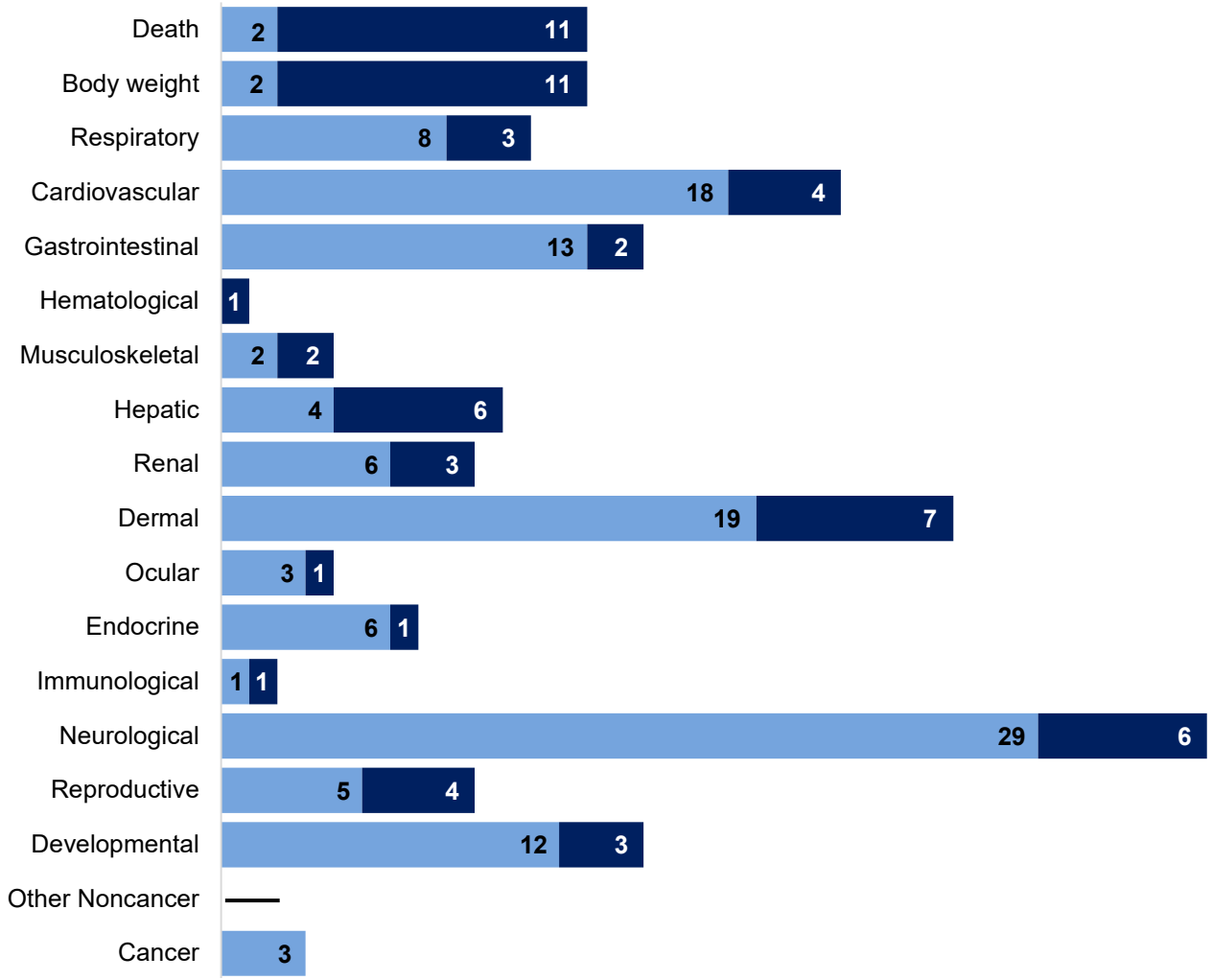
An overview of the types of studies and endpoints examined is presented in Figure 2-1. For this figure, case reports were treated as acute-duration oral exposure studies and most epidemiological studies were treated as chronic-duration oral studies, with the exception of occupational exposure studies and $PM_{2.5}$ exposure studies, which were categorized as chronic-duration inhalation studies. The most commonly examined endpoints are neurological, dermal, cardiovascular, and gastrointestinal in human studies and death, body weight, dermal, hepatic, and neurological in animal studies.

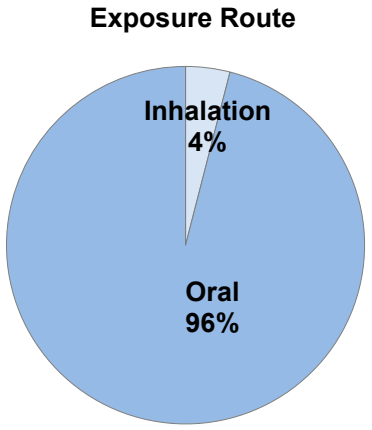
The human and animal studies suggest several sensitive targets of thallium toxicity: skin, gastrointestinal system, cardiovascular system, and neurological system. Of these endpoints, only dermal effects had sufficient data to undergo systemic review (see Appendix C for details).

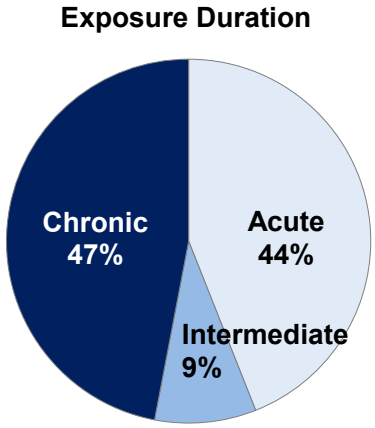
- **Dermal effects:** Alopecia is a presumed health effect in humans based on consistent evidence in humans acutely exposed to ingested thallium and a high level of evidence in animals orally exposed to thallium.
- **Gastrointestinal effects:** Symptoms of gastrointestinal effects including abdominal pain, nausea, diarrhea, and constipation have been reported in numerous case reports of thallium poisoning. Diarrhea has also been observed in rats exposed to high doses of thallium.
- **Cardiovascular effects:** Tachycardia and hypertension have been reported in individuals acutely exposed to thallium; tachycardia has also been observed in rabbits exposed to a lethal dose of thallium.
- **Neurological effects:** Neurological effects such as peripheral neuropathy, paresthesia, and hyperalgesia are commonly reported effects in individuals acutely ingesting thallium, communities chronically ingesting thallium, and workers chronically exposed to inhaled thallium. Damage to peripheral nerves and alterations in nerve conduction have been observed in rats orally exposed to thallium for an intermediate duration.

Figure 2-1. Overview of the Number of Studies Examining Thallium Health Effects*

Most studies examined the potential cardiovascular, dermal, and neurological effects of thallium
Fewer studies evaluated health effects in **animals** than **humans** (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 78 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Summary of Epidemiological Studies of Thallium

Reference, study type, population	Biomarker	Outcome evaluated	Result
Death			
Fan et al. 2023 Prospective; 33,331 NHANES (1999–2014) participants (United States)	0.00146 10^{-1} ng/mL creatinine (median urinary thallium)	All-cause mortality	↓
Nuvolone et al. 2021 Prospective; 33,708 residents living in a municipality with thallium-contaminated water (n=6,854 living in contaminated area and 26,854 living in non-contaminated area) (Italy)	Not reported	All-cause mortality	↓
Body weight effects			
Padilla et al. 2010 Cross-sectional; 3,825 children and adult NHANES (1999–2002) participants (United States)	Urinary thallium levels not reported	BMI	↑
		Waist circumference	↑
Shan 2022 Cross-sectional; 27,946 NHANES (2001–2018) participants 6–19 years of age (United States)	0.12–0.19, 0.19–0.28, and >0.28 µg/L (urinary thallium levels for the 2nd, 3rd, and 4th quartiles, respectively)	Overweight	↔
		Obesity	↔
Respiratory effects			
Dai et al. 2019 Prospective; 1,243 workers at a coke oven plant evaluated in 2010 and 2014 (China)	0.41 µg/g creatinine (urinary thallium)	FVC	↔
		Decline in FVC	↔
		FEV_1	↔
		Decline in FEV_1	↑
Rahman et al. 2022a Cross-sectional; 2,885 adult NHANES (2013–2016) participants (United States)	Urinary thallium levels not reported	COPD	↔

Table 2-1. Summary of Epidemiological Studies of Thallium

Reference, study type, population	Biomarker	Outcome evaluated	Result
Rahman et al. 2022c Cross-sectional; 4,186 adult NHANES (2011–2016) participants (United States)	Urinary thallium levels not reported	Chronic bronchitis	↔
Rahman et al. 2022d Cross-sectional; 4,181 adult NHANES (2011–2016) participants (United States)	Urinary thallium levels not reported	Emphysema	↔
Nuvolone et al. 2021 Prospective; 33,708 residents living in a municipality with thallium-contaminated water (n=6,854 living in contaminated area and 26,854 living in non-contaminated area) (Italy)		Respiratory tract deaths	↔
		Chronic obstructive pulmonary disease deaths	↔
Cardiovascular effects			
Fan et al. 2023 Prospective; 33,331 NHANES (1999–2014) participants (United States)	0.00146 10^{-1} ng/mL creatinine (median urinary thallium)	Cardiovascular disease mortality	↔
Guo et al. 2022 Cross-sectional; 9,404 NHANES (2003–2016) participants (United States)	0.15 µg/g creatinine (median urinary thallium)	Cardiovascular disease risk	↓
Li et al. 2023b Cross-sectional; 42,749 NHANES (2003–2018) participants (United States)	0.14–0.16 ng/mL (mean urinary thallium)	Coronary heart disease risk	↑
Navas-Acien et al. 2005 Cross-sectional; 790 NHANES (1999–2000) participants ≥40 years of age (United States)	0.18 µg/L (median urinary thallium)	Peripheral arterial disease	↔

Table 2-1. Summary of Epidemiological Studies of Thallium

Reference, study type, population	Biomarker	Outcome evaluated	Result
Nuvolone et al. 2021 Prospective; 33,708 residents living in a municipality with thallium-contaminated water (n=6,854 living in contaminated area and 26,854 living in non-contaminated area) (Italy)		Circulatory system deaths	↔
		Ischemic heart disease deaths	↔
Rahman et al. 2022b Cross-sectional; 4,037 adult NHANES (2015–2016) participants (United States)	Urinary thallium levels not reported	High blood pressure (≥130 mm Hg systolic or ≥80 mm Hg diastolic)	↔
Wang et al. 2022a Cross-sectional; 6,867 adult NHANES (2011–2016) participants (United States)	0.152–0.218 and >0.218 ug/g creatinine (urinary thallium levels for 3rd and 4th quartiles)	Cardiovascular disease	↓, 3rd quartile
Gastrointestinal effects			
Nuvolone et al. 2021 Prospective; 33,708 residents living in a municipality with thallium-contaminated water (n=6,854 living in contaminated area and 26,854 living in non-contaminated area) (Italy)		Digestive system deaths	↓
Musculoskeletal effects			
Wu et al. 2022 Cross-sectional; 1,357 NHANES (2011–2014) participants aged 8–17 years (United States)	0.19 µg/g creatinine (median urinary thallium)	Handgrip strength	↓, 4th quartile
Hepatic effects			
Xie et al. 2023 Cross-sectional; 5,548 adult NHANES (2003–2018) participants (United States)	0.16 µg/L (median urinary thallium)	Metabolic-associated fatty liver disease	↑
		Non-alcoholic fatty liver disease	↑

Table 2-1. Summary of Epidemiological Studies of Thallium

Reference, study type, population	Biomarker	Outcome evaluated	Result
Yu et al. 2023 Cross-sectional; 2,363 adults (China)	0.48 µg/g creatinine (median urinary thallium)	Liver function abnormality[a]	↑, 4th quartile
Renal effects			
Peng et al. 2022 Longitudinal; 35 adults (China)	0.50 ng/m^3 (median thallium content of $PM_{2.5}$)	BUN	↑
		Serum creatinine	↔
		Urea acid	↔
		Estimated glomerular filtration rate	↔
		Endogenous creatinine clearance rate	↔
		Ratio of BUN to serum creatinine	↑
Weaver et al. 2014 Cross-sectional; 512 adolescents (Mexico)	0.27 µg/g creatinine (median urinary thallium)	Glomerular filtration rate	↑
Yu et al. 2023 Cross-sectional; 2,363 adults (China)	0.48 µg/g creatinine (median urinary thallium)	Kidney function abnormality[b]	↓, 4th quartile
Zhou et al. 2021b Cross-sectional; 592 adults ≥60 years of age with diabetes (China)	0.09 µg/L (median urinary thallium)	Chronic kidney disease[c]	↓
Dermal effects			
Brockhaus et al. 1981 Cross-sectional; residents living near a cement production facility (n=1,1191) (Germany)	2.6 µg/L (mean urinary thallium)	Alopecia	↔

Table 2-1. Summary of Epidemiological Studies of Thallium

Reference, study type, population	Biomarker	Outcome evaluated	Result
Endocrine effects			
Liu et al. 2021 Case-control; 197 subjects with thyroid tumor or goiter and 197 controls (China)	0.45 and 0.73 µg/L (median urinary thallium in cases and controls, respectively)	Thyroid tumor or goiter risk	↔
Nuvolone et al. 2021 Prospective; 33,708 residents living in a municipality with thallium-contaminated water (n=6,854 living in contaminated area and 26,854 living in non-contaminated area) (Italy)	Not reported	Diabetes deaths	↓
Qiu et al. 2022 Retrospective; 2,528 pregnant women (China)	10.69 ng/m^3 (median thallium in $PM_{2.5}$)	TSH	↔
		Free T4	↔
		Free T3	↓
		Ratio of free T4 to free T3	↑
Wang et al. 2020 Prospective; 1,237 women (United States)	0.15 and 0.15 µg/L (median urinary thallium in subjects with and without diabetes)	Diabetes	↔
Yorita Christensen 2013 Cross-sectional; 1,587 NHANES (2007–2008) adult participants (United States)	0.15 µg/L (median urinary thallium)	Total T3	↔
		Free T3	↔
		Total T4	↓
		Free T4	↓
		TSH	↔
Zhu et al. 2019 Prospective; 3,012 pregnant women (China)	0.062 µg/L (median serum thallium)	Gestational diabetes	↔
Immunological effects			
Ruan et al. 2022 Prospective; 628 mother-child (4 years of age) pairs	0.47 µg/g creatinine (median of 1st, 2nd, and 3rd trimester average maternal urinary thallium)	Allergic rhinitis	↔
		Wheeze	↔
		Eczema	↔

Table 2-1. Summary of Epidemiological Studies of Thallium

Reference, study type, population	Biomarker	Outcome evaluated	Result
Neurological effects			
Adams et al. 2013 Case-control; children aged 5–16 years with autism (n=55) and controls (n=44) (United States)	0.104 and 0.058 µg/g creatinine (mean urinary thallium in cases and controls, respectively)	Autism severity	↔
Adams et al. 2017 Case-control; children and adults with autism spectrum disorder (n=67) and neurotypical children and adults (n=50) (United States)	0.17 and 0.11 µg/g creatinine (mean urinary thallium in cases and controls, respectively)	Autism spectrum disorder	↑
Brockhaus et al. 1981 Cross-sectional; residents living near a cement production facility (n=1,1191) (Germany)	2.6 µg/L (mean urinary thallium)	Sleep disturbances	↑
		Paresthesia and muscle and joint pain	↑
Ludolph et al. 1986 Cross-sectional; workers (n=36) at a cement production facility with a mean employment duration of 22.9 years (Germany)	Not reported	Nerve conduction velocity	↔
		Somatosensory evoked potential	↓
		Visual evoked potential	↔
Sasaki and Carpenter 2022 Cross-sectional; 1,092 NHANES (2011–2014) participants ≥60 years of age (United States)	0.14 µg/L (median urinary thallium)	Cognitive function	↔
Wang et al. 2022b Cross-sectional; 840 NHANES (2011–2014) participants ≥60 years of age (United States)	0.1546 µg/g creatinine (median urinary thallium)	Performance on cognitive function tests	↔
Zou et al. 2022 Cross-sectional; 8,128 NHANES (2013–2018) participants (United States)	0.17 µg/L (urinary thallium)	Hearing loss (defined as being deaf or having serious difficulty hearing)	↔

Table 2-1. Summary of Epidemiological Studies of Thallium

Reference, study type, population	Biomarker	Outcome evaluated	Result
Reproductive effects			
Liang et al. 2022 Case-control; 74 women with early embryonic arrest and 157 controls (China)	41.12 and 31.07 ng/L (geometric mean blood thallium in cases and controls, respectively) 4th quartile blood thallium: >41.95 ng/L	Early embryonic arrest	↑, 4th quartile
Ma et al. 2022 Case-control; 169 women with premature ovarian insufficiency and 209 controls (China)	0.506 and 0.322 µg/g creatinine (mean urinary thallium in cases and controls, respectively)	Premature ovarian insufficiency	↑
		Follicle stimulating hormone	↑
		Luteinizing hormone	↑
		Estradiol	↔
		Anti-Mullerian hormone	↓
Tabassum et al. 2022 Case-control; 30 women with recurrent pregnancy loss and 30 controls (Saudia Arabia)	11.05 and 0.5 ppb (mean serum thallium in cases and controls)	Recurrent pregnancy loss	↑ (higher thallium levels in cases versus controls)
Wang et al. 2016 Cross-sectional; 1,052 male partners of couples attending an infertility clinic (China)	0.51 and 0.44 µg/L (median urinary thallium)	Estradiol	↔
		Follicle stimulating hormone	↔
		Luteinizing hormone	↔
		Sex hormone binding globulin	↔
		Total testosterone	↔
		Total testosterone: luteinizing hormone ratio	↔
Wang et al. 2023 Cross-sectional; 1,328 male NHANES (2001–2004) participants (United States)	0.19 µg/L (median urinary thallium)	Erectile dysfunction	↔

Table 2-1. Summary of Epidemiological Studies of Thallium

Reference, study type, population	Biomarker	Outcome evaluated	Result
Developmental effects			
Bloom et al. 2015 Prospective; 225 mothers/fathers-infant pairs (United States)	0.10 and 0.16 µg/L (median urinary thallium in mothers and fathers, respectively)	Gestational age	↔
		Birth weight	↔
Dou et al. 2022 Prospective; 1,275 mother-infant pairs (China)	0.20 µg/L (median maternal urinary thallium, adjusted for urine specific gravity)	Estimated fetal weight at mid and late pregnancy, 22–24, 30–32, and 34–36 weeks	↔, all time points
Nuvolone et al. 2021 Prospective; 33,708 residents living in a municipality with thallium-contaminated water (n=6,854 living in contaminated area and 26,854 living in non-contaminated area) (Italy)		Low birth weight	↔
		Preterm birth	↔
Qi et al. 2019 Prospective; 3,080 mother-infant pairs (China)	61.7, 60.1, and 38.4 ng/L (median serum thallium concentrations during 1st and 2nd second trimesters and in cord blood, respectively)	Weight for age	↔, 1st and 2nd trimesters ↓, cord blood, boys and girls and girls only
		Length for age	↔, 1st and 2nd trimesters ↓, cord blood, boys and girls and girls only
		Weight for length	↔, all blood collections
		BMI for age	↔, all blood collections
Tong et al. 2020 Prospective; 2,851 mother-child pairs (children evaluated at 3 years of age) (China)	61.99, 60.25,49.93, and 38.40 ng/L (median blood thallium levels in 1st, 2nd, and 3rd trimester samples and cord blood samples)	ADHD	↔, 1st and 3rd trimester and cord blood ↑, 2nd trimester boys only
Tong et al. 2022 Prospective; 2,164 mother-child pairs (children evaluated at 4.5 years of age) (China)	61.6, 59.8, 50.0, and 38.5 ng/L (median blood thallium levels in 1st, 2nd, and 3rd trimester samples and cord blood samples)	Visual spatial index	↓, 1st trimester boys, 3rd trimester girls ↔, 2nd trimester, cord blood boys and girls
		Full scale IQ	↔, 1st, 2nd trimester, cord blood ↓, 3rd trimester boys

Table 2-1. Summary of Epidemiological Studies of Thallium

Reference, study type, population	Biomarker	Outcome evaluated	Result
		Verbal comprehension index	↔, 1st, 2nd, 3rd trimester, cord blood
		Fluid reasoning index	↔, 1st, 2nd trimester, cord blood ↓, 3rd trimester boys
		Working memory index	↔, 1st, 2nd, 3rd trimester, cord blood
		Processing speed index	↔, 1st, 2nd, 3rd trimester, cord blood
Wu et al. 2023 Prospective; 2,394 mother-infant pairs (China)	0.36 and 0.37 µg/L (median urinary thallium for mothers and boys and girls, respectively)	Birth weight	↔, boys ↓, girls
Xia et al. 2016 Case-control; 204 cases of low birth weight and 612 controls (China)	≥0.78 µg/g creatinine (maternal urinary thallium, 3rd tertile)	Low birth weight	↑
Yao et al. 2022 Prospective; 358 mother-infant pairs (China)	0.40 and 0.56 µg/g creatinine (median urinary thallium, 1st and 3rd trimesters, respectively)	Growth between birth and 6 months of age (1st trimester thallium) Body weight Height Head circumference	 ↔, boys, girls ↔, boys, girls ↔, boys, girls
		Growth between birth and 6 months of age (3rd trimester thallium) Body weight Height Head circumference	 ↑, boys, ↔,girls ↔, boys, girls ↑, boys, ↔,girls
Zhou et al. 2021a Prospective; 2,748 mother-infant pairs (China)	0.38 and 0.25 µg/L (median urinary thallium in 1st and 3rd trimesters, respectively) 3rd tertile urinary thallium: ≥6.38 ng/g creatinine	Birth weight	↓, 1st and 3rd trimesters 3rd tertile thallium

Table 2-1. Summary of Epidemiological Studies of Thallium

Reference, study type, population	Biomarker	Outcome evaluated	Result
Other noncancer effects			
Wang et al. 2022c Prospective; 947 adult women (United States)	0.14 and 0.14 µg/L (median urinary thallium in subjects with and without metabolic syndrome)	Metabolic syndrome[d]	↔
Cancer effects			
Cao et al. 2023 Cross-sectional (NHANES 1999–2018); 94,337 adults (United States)	0.19603 ng/mL (mean urinary thallium)	Breast cancer	↔
		Ovarian cancer	↔
		Prostate cancer	↑
Fan et al. 2023 Prospective; 33,331 NHANES (1999–2014) participants (United States)	0.00146 10^{-1} ng/mL creatinine (median urinary thallium)	Cancer mortality	↓
Nuvolone et al. 2021 Prospective; 33,708 residents living in a municipality with thallium-contaminated water (n=6,854 living in contaminated area and 26,854 living in non-contaminated area) (Italy)		Cancer mortality	↓

[a]Liver function disorder defined as any abnormality in albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, or direct bilirubin levels.
[b]Kidney function disorder defined as altered creatinine estimated glomerular filtration rate.
[c]Chronic kidney disease defined as an estimated glomerular filtration rate of <60 mL/minute/1.73 m^2.
[d]Metabolic syndrome defined as having at least three of the five criteria: high blood pressure (≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure or current use of antihypertensive medication), fasting blood glucose ≥100 mg/dL or current use of antidiabetic medication; abdominal obesity (waist circumference ≥88 cm for White and Black women and ≥80 cm for Chinese and Japanese women), serum triglyceride ≥150 mg/dL; or HDL cholesterol of <50 mg/dL.

↑ = positive association; ↓ = inverse association; ↔ = no association; ADHD = attention deficit hyperactivity disorder; BMI = body mass index; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HDL = high-density lipoprotein; IQ = intelligence quotient; NHANES = National Health and Nutrition Examination Survey; PM2.5 = particulate matter ≤2.5 µm; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone

Table 2-2. Levels of Significant Exposure to Thallium – Oral (mg Tl/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Downs et al. 1960									**Thallium I acetate**
1	Rat (Wistar) 2–5 F	Once (G)	NR	LE	Death			32	LD_{50}
Downs et al. 1960									**Thallium I oxide**
2	Rat (Wistar) 2–5 F	Once (G)	NR	LE	Death			39	LD_{50}
Leloux et al. 1987									**Thallium I nitrate**
3	Rat (Wistar) 3 M, 3 F	Once (GO)	0, 15	LE	Death			15	100% mortality
Leloux et al. 1987									**Thallium I nitrate**
4	Rat (Wistar) 20 M, 20 F	4 days (GW)	0, 0.77	LE, CS	Death			0.77	Increased mortality (88–100%)
					Bd wt			0.77	Weight loss
					Gastro		0.77		Diarrhea
Mourelle et al. 1988									**Thallium I sulfate**
5	Rat (Wistar) 50 M	Once (GW)	0, 8	BC	Hepatic	8			
Rusyniak et al. 2003									**Thallium I sulfate**
6	Rat (Sprague-Dawley) 10 M	Once (GW)	0, 18.2, 29.9	LE, CS, BW, FI, WI	Death			29.9	70% mortality
					Bd wt	18.2		29.9	Body weight loss (22%)
					Gastro		18.2		Diarrhea
					Dermal		18.2		Hair loss
					Neuro		18.2		Decreased spontaneous activity
Li et al. 2022a									**Thallium I nitrate**
7	Mouse (C57BL/6J) 12 M	2 weeks (W)	0, 1.2	BW, FI, WI, OW, HP	Bd wt	1.2			
					Hepatic		1.2		Decreased relative liver weight, hepatic sinus congestion and necrosis (no incidence data reported)

Table 2-2. Levels of Significant Exposure to Thallium – Oral (mg Tl/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Li et al. 2022a									**Thallium III nitrate trihydrate**
8	Mouse (C57BL/6J) 12 M	2 weeks (W)	0, 0.7	BW, FI, WI, OW, HP	Bd wt	0.7			
					Hepatic		0.7		Decreased relative liver weight, hepatic sinus congestion and necrosis (no incidence data reported)
Li et al. 2022b									**Thallium I nitrate**
9	Mouse (C57BL/6J) 12 M	2 weeks (W)	0, 1.2	BW, FI, WI	Bd wt	1.2			
Li et al. 2023a									**Thallium I nitrate**
10	Mouse (C57BL/6J) 15 M	1 week (W)	0, 8	BW, FI, WI, OW, HP, IX	Bd wt			8	Decreased terminal body weight (21%)
					Musc/skel	8			
					Immuno		8		Decreased relative thymus weight, decreased B cell frequency in bone marrow, blood and spleen
Rao et al. 1993									**Thallium I oxalate**
11	Mouse (NS) 10 NS	Once (G)	2.5, 8.2, 25, 82, 250	LE	Death			2.5	40% mortality
Shipkowski et al. 2023									**Thallium I sulfate**
12	Mouse (B6C3F1) 5 M, 5 F	2 weeks (W)	M: 0, 0.4, 0.9, 1.9, 4.41; F: 0, 0.3, 0.7, 1.5, 2.5	CS, BW, WI, OW	Bd wt	0.7 F	1.5 F	2.5 F	LOAEL: Decreased terminal body weight (11%) SLOAEL: Decreased terminal body weight (24%)
						0.4 M	0.9 M	4.41 M	LOAEL: Decreased terminal body weight (16%) SLOAEL: Decreased terminal body weights (23%)

Table 2-2. Levels of Significant Exposure to Thallium – Oral (mg Tl/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Grunfeld et al. 1963									**Thallium I sulfate**
13	Rabbit (NS) 5–15 NR	Once (G)	0, 61	LE, CS, OF, HP	Death			61	100% mortality
					Cardio			61	Bradycardia, tachycardia, prolonged QT-interval
					Neuro			61	Convulsions
INTERMEDIATE EXPOSURE									
Downs et al. 1960									**Thallium I acetate**
14	Rat (Wistar) 5 M, 5 F	9–15 weeks (F)	M: 0, 0.4, 1.1, 2.1, 3.6 F: 0, 0.4, 1.2, 2.4, 4.0	LE, CS, BW, OW, HP	Death			2.4 F	60% mortality
								2.1 M	80% mortality
					Bd wt	2.4 F		4 F	Decreased terminal body weight (47%)
						1.1 M		2.2 M	Decreased terminal body weight (27%)
					Resp	1.2 F			
						1.1 M			
					Cardio	1.2 F			
						1.1 M			
					Hepatic	1.2 F			
						1.1 M			
					Renal	1.2 F			
						1.1 M			
					Dermal	0.4 F	1.2 F		Alopecia
						0.4 M	1.1 M		Alopecia
					Repro	1.1 M			

Table 2-2. Levels of Significant Exposure to Thallium – Oral (mg Tl/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Downs et al. 1960									**Thallium I oxide**
15	Rat (Wistar) 5 M, 5 F	15 weeks (F)	M: 0, 1.6, 2.9, 4.1, 8.2, 41 F: 0, 1.8, 3.2, 4.6, 9.2, 46	LE, CS, BW, OW, HP	Death			3.2 F	40% mortality
								2.9 M	80% mortality
					Bd wt	1.8 F		3.2 F	Decreased terminal body weight (26%)
							1.6 M	2.9 M	LOAEL: Decreased terminal body weight (17%) SLOAEL: Decreased terminal body weight (56%)
					Resp	1.8 F			
						1.6 M			
					Cardio	1.8 F			
						1.6 M			
					Hepatic	1.8 F			
						1.6 M			
					Renal	1.8 F			
						1.6 M			
					Dermal		1.8 F		Alopecia
							1.6 M		Alopecia
					Repro	1.6 M			
EPA 1986									**Thallium I sulfate**
16	Rat (Sprague-Dawley) 20 M, 20 F	90 days (G)	0, 0.008, 0.04, 0.20	CS, BW, HE, BC, OW, HP, NX	Bd wt	0.2			
					Resp	0.2			
					Cardio	0.2			
					Gastro	0.2			
					Hemato	0.2			
					Musc/skel	0.2			
					Hepatic	0.2			
					Renal	0.2			
					Dermal	0.04 F	0.2 F		Alopecia

Table 2-2. Levels of Significant Exposure to Thallium – Oral (mg Tl/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Ocular	0.2			
					Endocr	0.2			
					Neuro	0.2			
					Repro	0.2			
Formigli et al. 1986									**Thallium I sulfate**
17	Rat (Wistar) 10 M	60 days (W)	0, 1.3	OW, HP, RX	Bd wt	1.3			
					Repro		1.3		Decreased sperm motility
Gregotti et al. 1985									**Thallium I sulfate**
18	Rat (Wistar) 10 M	30 or 60 days (W)	0, 1.2	CS, BW, FI, WI, BC, OW	Bd wt	1.2			
					Neuro		1.2		Irritability on handling
					Repro	1.2			
Gross et al. 1948									**Thallium I acetate**
19	Rat (Long-Evans) 8–16 M, F	6 days/week, 21 weeks (G)	1.3, 1.6, 2.0	LE, CS, BW, FI	Death			2	Death of 6/8 rats
					Dermal		2		Alopecia
Manzo et al. 1983									**Thallium I sulfate**
20	Rat (Sprague-Dawley) 80 F	36 weeks (W)	0, 1.5	CS, HP, NX	Death			1.5	Increased mortality (21%)
					Dermal		1.5		Hair loss
					Neuro		1.5		Decreased motor and sensory action potentials and increased motor action potential latency
Rossi et al. 1988									**Thallium I sulfate**
21	Rat (NOS albino) 30 F	GD 0–LD 22 (W)	0, 1	BW, DX	Develop	1			
Salehi et al. 2017									**Thallium III chloride tetrahydrate**
22	Rat (Wistar) 5 M	60 days (G)	0, 20, 40	BW, HE	Bd wt		20	40	LOAEL: Decreased body weight (10%) SLOAEL: Decreased body weight (20.5%)

Table 2-2. Levels of Significant Exposure to Thallium – Oral (mg Tl/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Shipkowski et al. 2023									**Thallium I sulfate**
23	Rat (Sprague-Dawley) 12–20 F	GD 6–PND 28 (W)	0,0.53, 1.0, 2.2, 2.6	CS, BW, WI, DX	Death			2.6	Deaths in 8/17 dams
					Bd wt	2.2	2.6		Decreased body weight gain during gestation (13%)
					Dermal	1	2.2		Alopecia in dams and pups
					Develop	1	2.2		Decreased pup body weight gain (9.8%)

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

BC = serum (blood) chemistry; Bd wt or BW = body weight; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; (G) = gavage; Gastro = gastrointestinal; GD = gestation day; (GO) = gavage in oil; (GW) = gavage in water; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immune function; LD = lactation day; LD_{50} = median lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NR = not reported; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; PND = postnatal day; Repro = reproduction; Resp = respiratory; RX = reproductive toxicity; SLOAEL = serious lowest-observed-adverse-effect level; (W) = water; WI = water intake

Figure 2-2. Levels of Significant Exposure to Thallium – Oral
Acute (≤14 days)

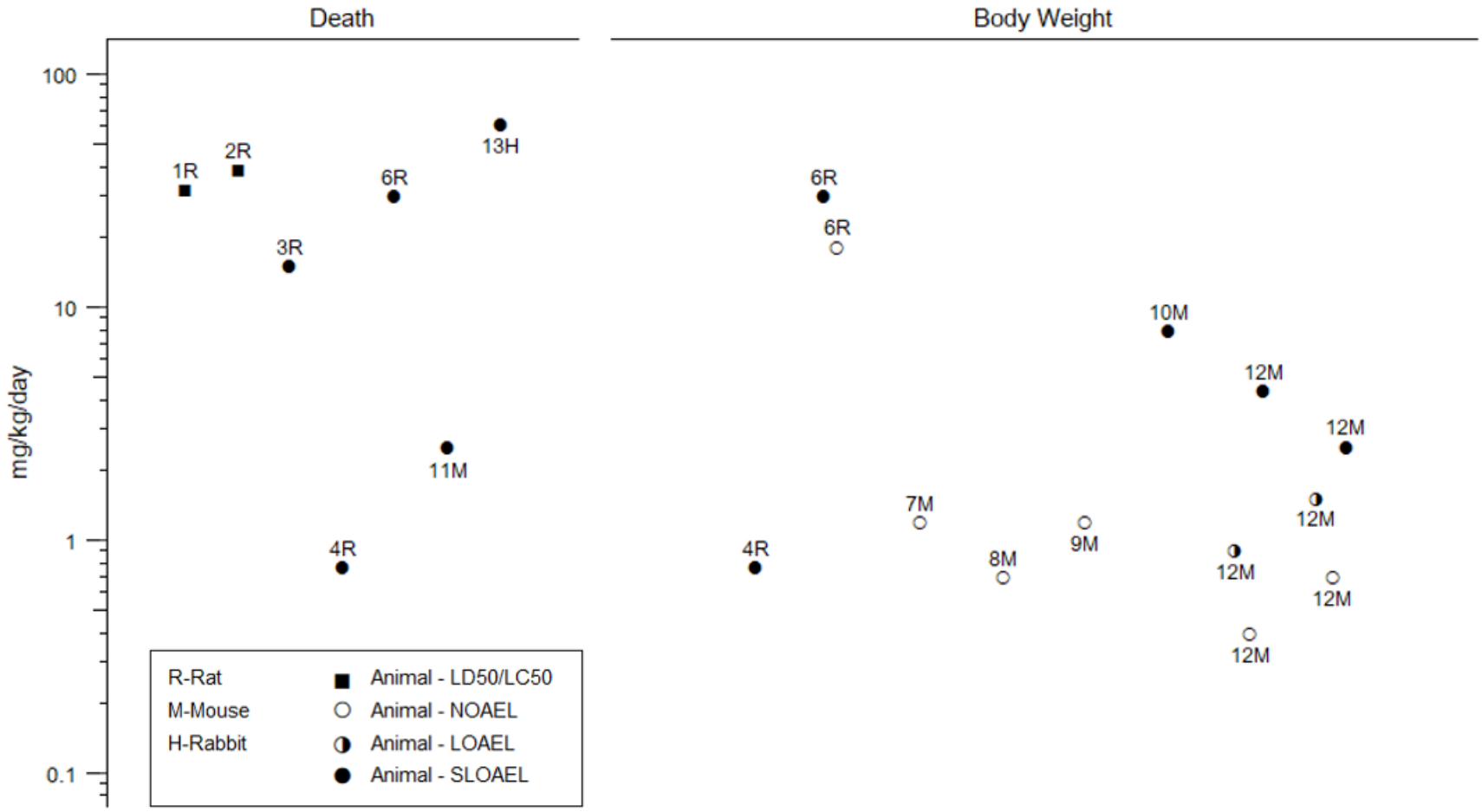


Figure 2-2. Levels of Significant Exposure to Thallium – Oral
Acute (≤14 days)

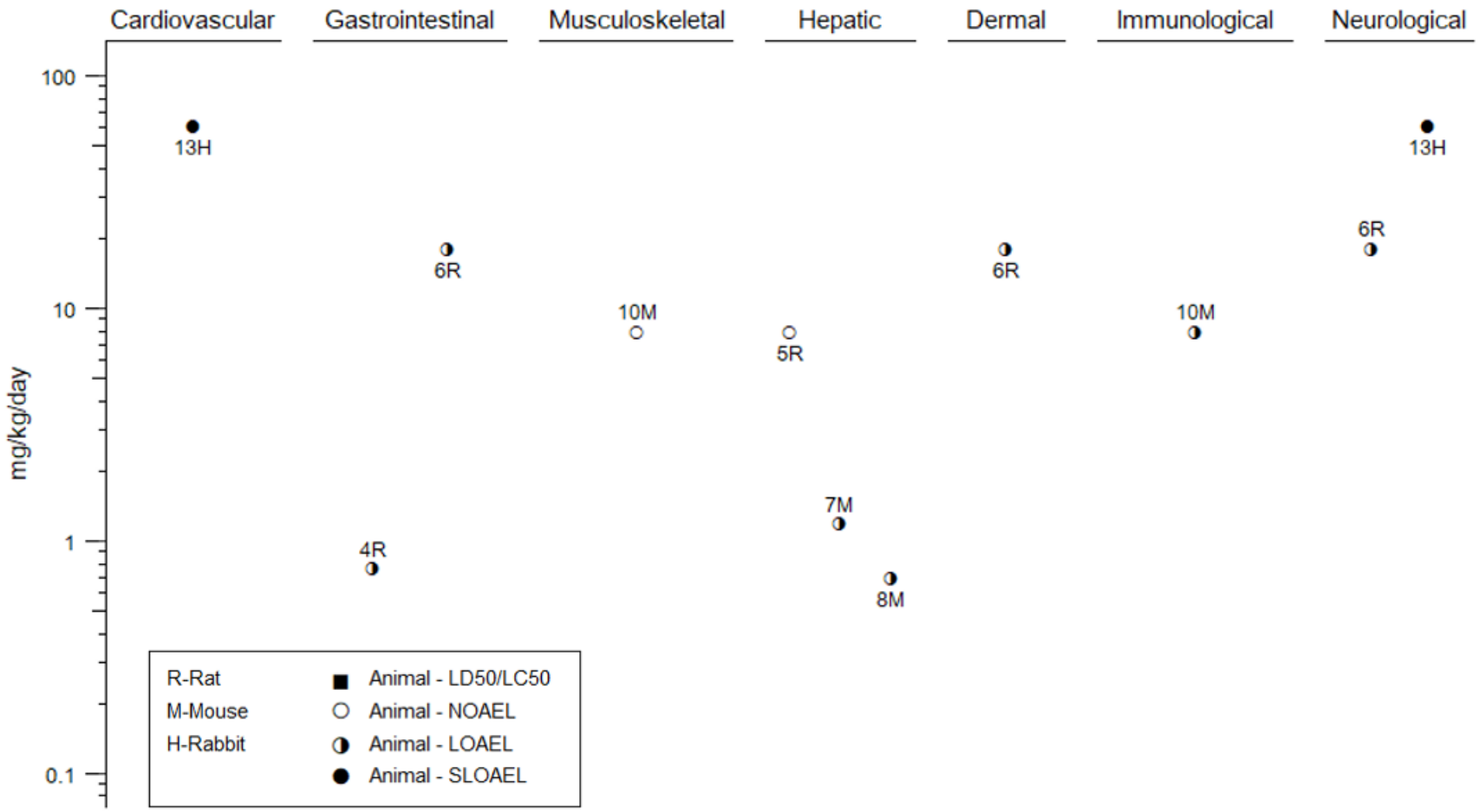


Figure 2-2. Levels of Significant Exposure to Thallium – Oral
Intermediate (15–364 days)

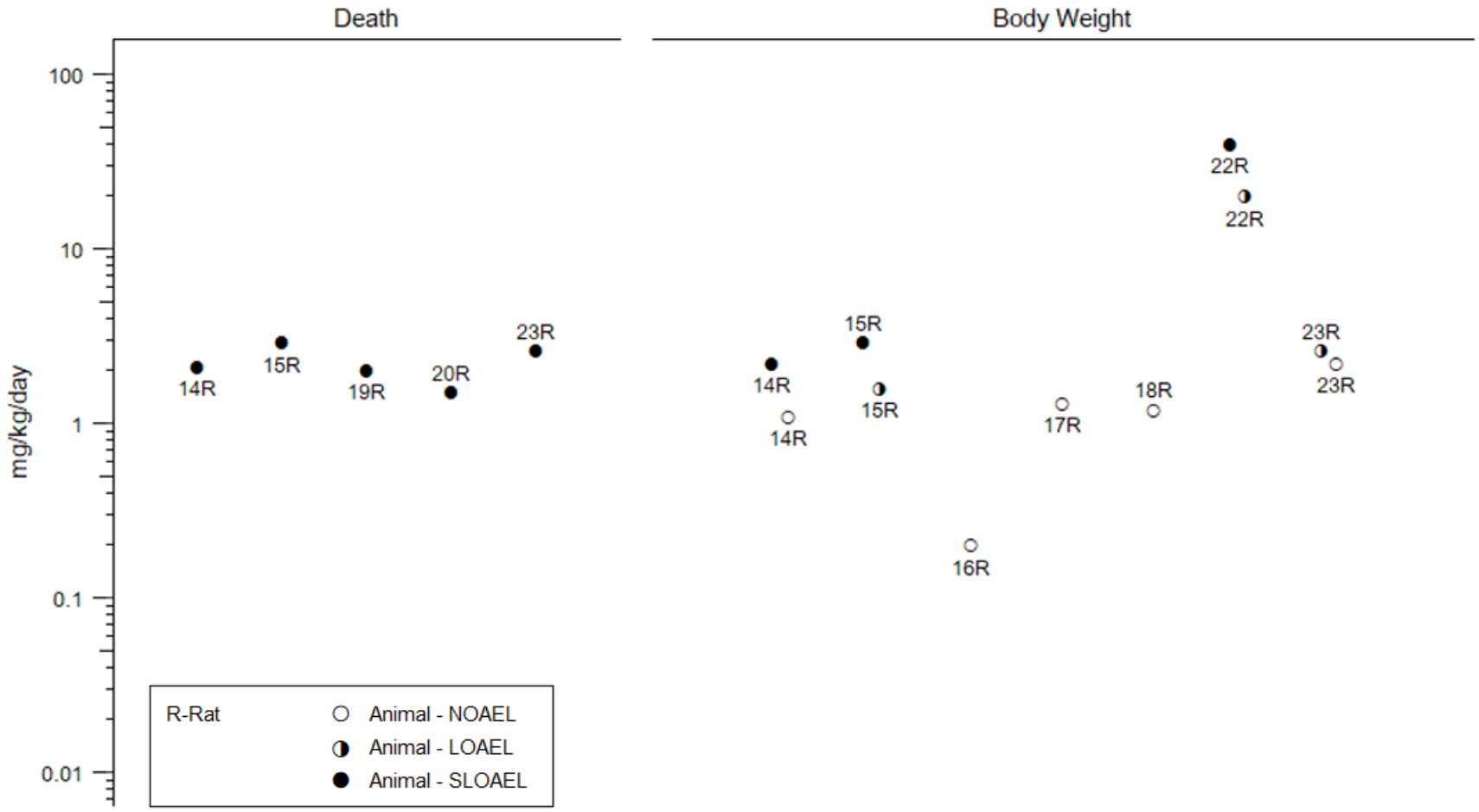


Figure 2-2. Levels of Significant Exposure to Thallium – Oral
Intermediate (15–364 days)

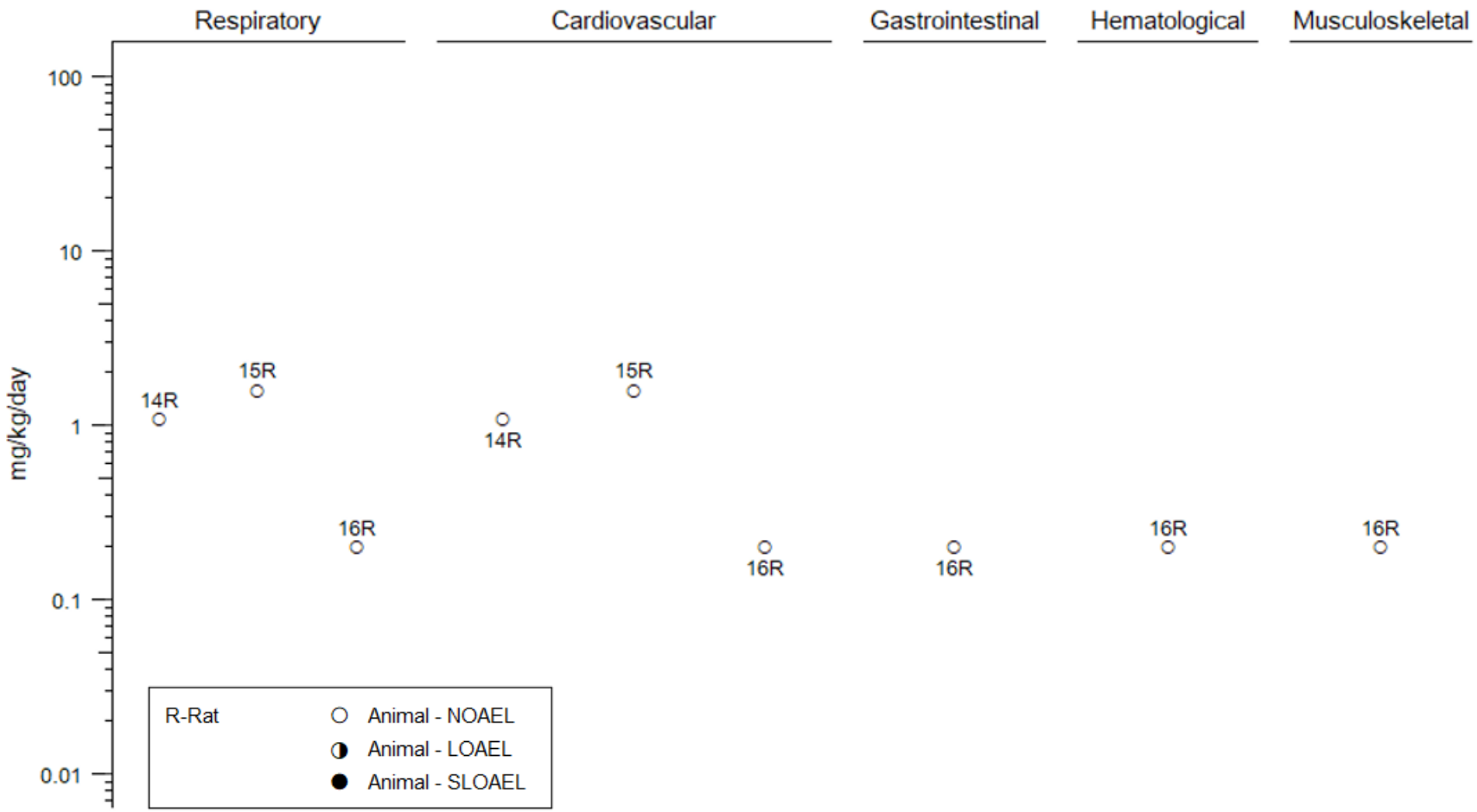


Figure 2-2. Levels of Significant Exposure to Thallium – Oral
Intermediate (15–364 days)

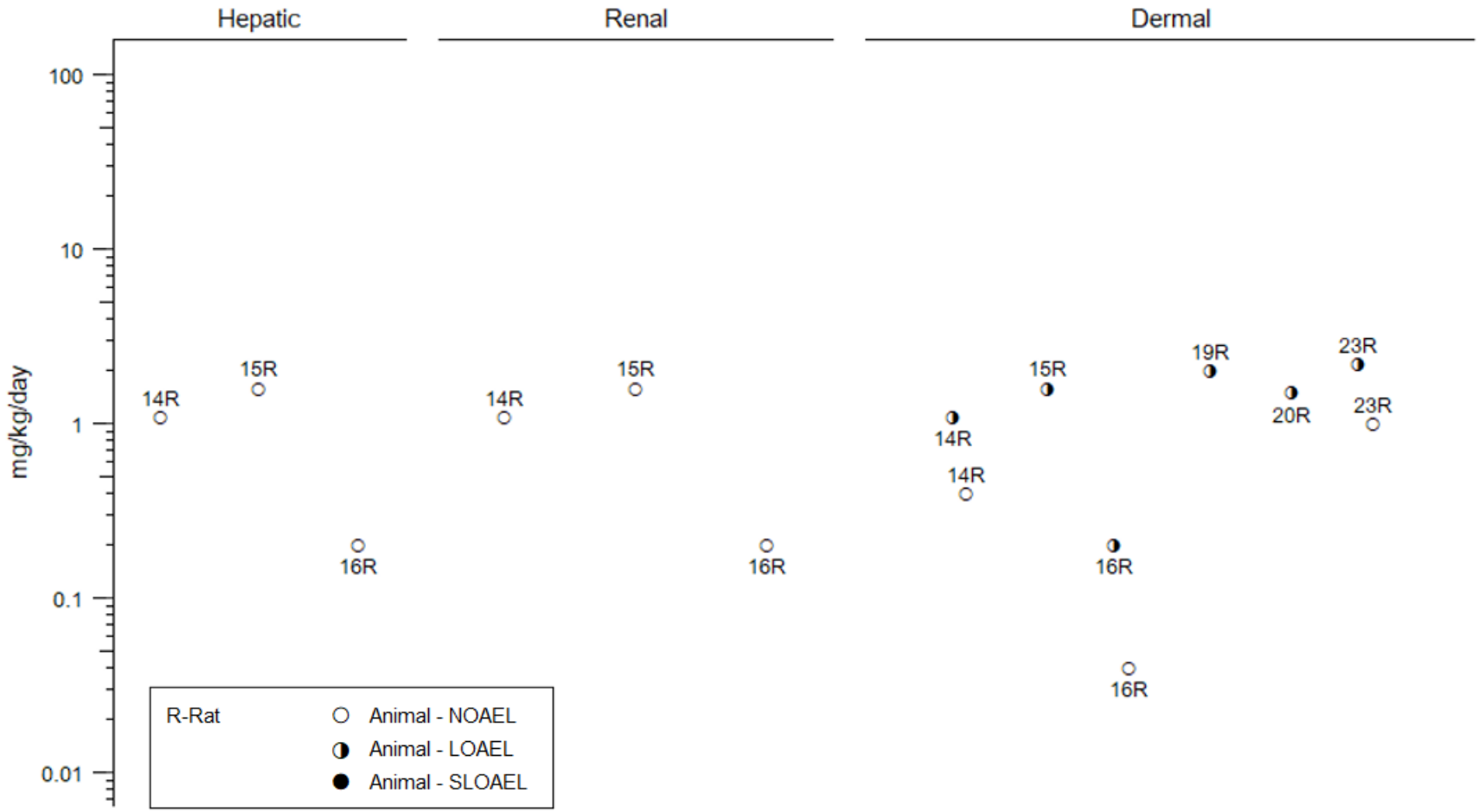
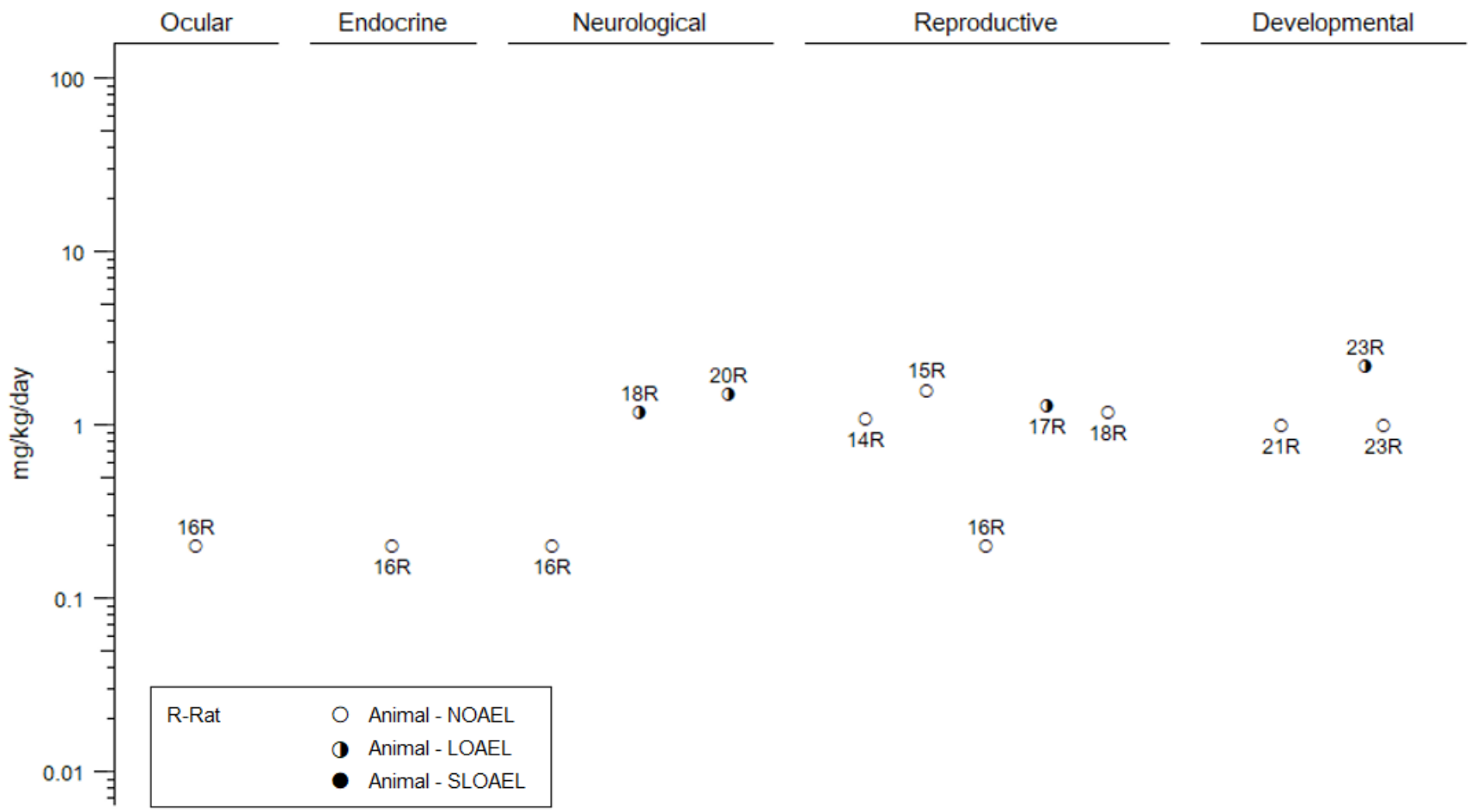


Figure 2-2. Levels of Significant Exposure to Thallium – Oral
Intermediate (15–364 days)



2.2 DEATH

No studies were located in humans or animals regarding death after inhalation or dermal exposure to thallium.

There are numerous case reports of human lethality following acute-duration oral exposure to thallium; in most cases, the doses were not reported. As summarized by WHO (1996), lethality has been observed at doses of 10–15 mg/kg in adults.

An epidemiological study by Fan et al. (2023) found an inverse association between urinary thallium levels and all-cause mortality. Similarly, decreases in all-cause mortality were found in a community with thallium-contaminated drinking water (Nuvolone et al. 2021).

In rats, estimates of the median lethal doses (LD_{50}) for thallium compounds were 32 and 39 mg thallium/kg (as thallium I acetate and thallium I oxide, respectively) (Downs et al. 1960). Increased mortality has also been observed in rats following single doses of 15 mg thallium/kg as thallium I nitrate (Leloux et al. 1987) or 29.9 mg thallium/kg/day as thallium I sulfate (Rusyniak et al. 2003), in mice exposed to 2.5 mg thallium/kg as thallium I oxide (Rao et al. 1993), and in rabbits exposed to 61 mg thallium/kg/day as thallium I sulfate (Grunfeld et al. 1963). In a repeated-exposure study, increased mortality was observed in rats administered 0.77 mg thallium/kg/day as thallium I nitrate for 4 days (Leloux et al. 1987); the first deaths occurred after the fourth dose. The data are inadequate to evaluate potential differences between thallium compounds or animal species.

Rats exposed for 15 weeks to diets containing thallium showed increased mortality at doses of 2.1 mg thallium/kg/day as thallium I acetate and 2.9 mg thallium/kg/day as thallium I oxide (Downs et al. 1960). Exposure to 1.5 mg thallium/kg/day as thallium I sulfate in drinking water resulted in 15 and 21% mortality in rats after 40 and 240 days of treatment, respectively (Manzo et al. 1983). Increases in mortality were observed in rat dams exposed to ≥2.6 mg thallium/kg/day as thallium I sulfate during gestation and lactation (Shipkowski et al. 2023). When rats were administered up to 0.20 mg thallium/kg/day as thallium sulfate by gavage for 90 days, no deaths were reported (EPA 1986).

2.3 BODY WEIGHT

There are limited epidemiological data on the associations between thallium exposure and body weight effects. In an evaluation of National Health and Nutrition Examination Survey (NHANES) participants, no association between urinary thallium levels and the risk of obesity or overweight was observed (Shan 2022). Another study of NHANES participants found associations between urinary thallium levels and body mass index (BMI) and waist circumference in children and adults (Padilla et al. 2010).

Decreases in body weight gain and/or weight loss have been observed in animals following acute- or intermediate-duration oral exposure to thallium compounds. Leloux et al. (1987) reported weight loss in rats following a 4-day exposure to 0.77 mg thallium/kg/day as thallium I nitrate; this dose was also associated with increased mortality. In contrast, a 2-week drinking water study in mice did not find alterations in body weight gain resulting from exposure to 1.2 or 0.7 mg thallium/kg/day as thallium I nitrate or thallium III nitrate, respectively (Li et al. 2022a, 2022b). The investigators did find a 21% decrease in terminal body weights in mice exposed via drinking water to 8 mg thallium/kg/day as thallium I nitrate for 1 week (Li et al. 2023a). Studies with thallium I sulfate reported a >20% decrease in terminal body weight in rats exposed to a single lethal dose of 29.9 mg thallium/kg (Rusyniak et al. 2003) and in mice exposed to ≥2.5 mg thallium/kg/day for 2 weeks (Shipkowski et al. 2023); a 16% decrease in body weight was observed at 0.9 mg thallium/kg/day (Shipkowski et al. 2023).

As with acute-duration studies, intermediate-duration oral exposure to lethal doses resulted in >20% decreases in terminal body weight in rats exposed to 1.6–4 mg thallium/kg/day as thallium I acetate or thallium I oxide (Downs et al. 1960). Exposure to thallium I sulfate at doses of 1.2 or 1.3 mg thallium/kg/day did not result in alterations in body weight gain in rats (Formigli et al. 1986; Gregotti et al. 1985), whereas, 2.6 mg thallium/kg/day as thallium I sulfate resulted in a 13% decrease in maternal body weight gain in rats (Shipkowski et al. 2023).

2.4 RESPIRATORY

Limited data in humans show that thallium can cause respiratory damage following acute-duration oral exposure. Lungs showed diffuse alveolar damage with hyaline membrane and focal organization in one case following acute ingestion of an estimated 54–110 mg thallium/kg (as thallium nitrate). Bronchopneumonia was also reported in this study (Davis et al. 1981). Similar findings were reported after ingestion of thallium acetate; however, the doses that produced these effects were not clearly defined

(Cavanagh et al. 1974; de Groot et al. 1985; Roby et al. 1984). A large study on residents in Northern Italy with thallium-contaminated drinking water did not find alterations in respiratory tract or chronic obstructive pulmonary disease deaths (Nuvolone et al. 2021).

A series of studies of NHANES participants examined the possible associations between urinary thallium levels and respiratory disease and found no associations with chronic obstructive pulmonary disease (Rahman et al. 2022a), chronic bronchitis (Rahman et al. 2022c), or emphysema (Rahman et al. 2022d). A longitudinal study of workers at a coke oven facility did not find associations between urinary thallium levels and forced vital capacity (FVC) or forced expiratory volume in 1 second (FEV_1) (Dai et al. 2019). However, there was an association between urinary thallium levels and a decline in FEV_1 (measured over a 4-year period); when the subjects were segregated based on smoking habits, the association was found in smokers but not in nonsmokers. No association between the decline in FVC and urinary thallium levels were found among all subjects, an association was found among heavy smokers.

There is limited information on the potential respiratory toxicity of thallium following oral exposure. No adverse effects were observed on the respiratory system of rats administered 0.20 mg thallium/kg/day as thallium I sulfate by gavage for 90 days (EPA 1986), in rats exposed 1.1 mg thallium/kg/day as thallium I acetate in the diet for 15 weeks (Downs et al. 1960), or in rats exposed to 1.6 mg thallium/kg/day as thallium I oxide in the diet for 15 weeks (Downs et al. 1960).

2.5 CARDIOVASCULAR

A number of case reports describe cardiovascular effects such as tachycardia, hypertension, and EKG alterations following acute thallium poisoning (for example, Cavanagh et al. 1974; Davis et al. 1981; Meggs et al. 1994; Rayisyan et al. 2021; Riyaz et al. 2013; Roby et al. 1984; Sojáková et al. 2015; Sun et al. 2012; Tromme et al. 1998; Vrij et al. 1995; Zhao et al. 2008). Davis et al. (1981) described extensive damage of the myocardium with myofiber thinning, accumulation of lipid droplets, myocardial necrosis, and inflammatory reaction in a man ingesting a single estimated lethal dose of 54–110 mg thallium/kg as thallium nitrate. In another case report, a lethal dose of 0.93 g thallium as thallium acetate administered in three divided doses (approximately 13 mg/kg assuming a 70-kg body weight) resulted in sinus tachycardia (Cavanagh et al. 1974).

A study of magnesium seawater battery plant workers did not find an increase in cardiovascular effects as compared to non-exposed workers (Marcus 1985); however, the study authors did not clearly define the

cardiovascular parameters measured. Workplace air levels of thallium were 0.014 and 0.022 mg/m^3 in the machining and alloying operation areas, respectively.

Several epidemiological studies have examined possible associations between thallium and cardiovascular disease. Fan et al. (2023) found no association between urinary thallium levels and deaths from cardiovascular disease, and Nuvolone et al. (2021) did not find alterations in circulatory system deaths or ischemic heart disease deaths in a community with thallium-contaminated drinking water. Two studies of NHANES participants found inverse associations between urinary thallium levels and cardiovascular disease risk (Guo et al. 2022; Wang et al. 2022a); a third study found an association (Li et al. 2023b). Studies of NHANES participants did not find associations between urinary thallium levels and the risk of high blood pressure (Rahman et al. 2022b) or peripheral arterial disease (Navas-Acien et al. 2005).

Limited studies were located regarding cardiovascular effects in animals after oral exposure to thallium. Electrocardiographic changes were observed in rabbits administered a lethal dose of 61 mg thallium/kg/day as thallium I sulfate (Grunfeld et al. 1963). Abnormalities reported included T-wave fluttering, prolonged Q-T intervals, bradycardia, and tachycardia (Grunfeld et al. 1963). However, there were no histological alterations to the myocardium. Intermediate-duration studies also did not find histological alterations in rats administered up to 0.20 mg thallium/kg/day as thallium I sulfate by gavage for 90 days (EPA 1986) or exposed to 1.1 mg thallium/kg/day as thallium I acetate or 1.6 mg thallium/kg/day as thallium I oxide in the diet for 15 weeks (Downs et al. 1960).

2.6 GASTROINTESTINAL

Gastrointestinal effects are commonly reported in humans after acute ingestion of thallium. Symptoms include abdominal pain, nausea/vomiting, and/or diarrhea or constipation (for example, Al Hammouri et al. 2011; Almassri and Sekkarie 2018; Cavanagh et al. 1974; Dai-xing and Ding-nan 1985; Davis et al. 1981; Meggs et al. 1994; Rayisyan et al. 2021; Sun et al. 2012; Wang et al. 2007, 2021; Zhang et al. 2014; Zhao et al. 2008). Although the gastrointestinal symptoms can occur shortly after ingestion (Lu et al. 2007), in many cases, symptoms occurred 12–72 hours after ingestion (Al Hammouri et al. 2011; Meggs et al. 1994).

Based on available medical records, there was a lower incidence of gastrointestinal effects in a cohort of 86 workers exposed to thallium in a magnesium seawater battery plant in England, compared with 79 unexposed controls (Marcus 1985). Maximum thallium levels in workplace air were 0.014 and

0.022 mg/m^3 during machining and alloying operations, respectively. In a study of a community exposed to thallium-contaminated drinking water, an inverse association between thallium exposure and deaths from digestive system effects were observed (Nuvolone et al. 2021).

Gavage administration of a single dose of 18.2 mg thallium/kg as thallium I sulfate resulted in diarrhea in rats (Rusyniak et al. 2003). When rats were administered up to 0.20 mg thallium/kg/day as thallium I sulfate by gavage for 90 days, no adverse effects were observed on the gastrointestinal system (EPA 1986).

2.7 HEMATOLOGICAL

Information on the potential toxicity of thallium to the hematological system is limited to an intermediate-duration oral study that found alterations in hematological parameters in rats exposed to 0.20 mg thallium/kg/day as thallium I sulfate for 90 days (EPA 1986). No other studies were located in humans or animals regarding hematological effects after inhalation, oral, or dermal exposure to thallium.

2.8 MUSCULOSKELETAL

There are limited data regarding the muscular/skeletal effects in humans. Histopathological examination of muscle biopsies from two cases revealed myopathic changes associated with thallium poisoning (Limos et al. 1982). Fiber necrosis, central nucleation, and fiber splitting were reported. No data were provided on exposure levels. One epidemiological study found an inverse association between handgrip strength and urinary levels in NHANES participants (Wu et al. 2022).

There are limited data on musculoskeletal effects in laboratory animals. No histological alterations in muscle or bone were observed in mice exposed to 8 mg thallium/kg/day as thallium I nitrate for 1 week (Li et al. 2023a) or in rats exposed to 0.20 mg thallium/kg/day as thallium I sulfate for 90 days (EPA 1986).

2.9 HEPATIC

Case reports in humans have reported liver effects following acute-duration oral exposure. Centrilobular necrosis with fatty changes has been reported (Cavanagh et al. 1974; Davis et al. 1981). It was not clear whether the effects observed were a result of a direct effect on the liver or secondary to other effects.

Serum aspartate aminotransferase, serum alanine aminotransferase, and alkaline phosphatase levels were elevated; the biological relevance of these alterations is unclear.

Epidemiological studies found an association between urinary thallium levels and the risks of metabolic-associated fatty liver disease and nonalcoholic fatty liver disease (Xie et al. 2023) and liver function abnormality (Yu et al. 2023).

No biologically relevant alterations in serum γ-glutamyl transpeptidase or alanine aminotransferase levels were observed in rats administered a single dose of 8 mg thallium/kg as thallium I sulfate (Mourelle et al. 1988). An increase in hepatic triglycerides (130%) and decreased glycogen levels (38%) were also observed; the biological relevance of these alterations in the absence of a histopathological examination is not known. Li et al. (2022a, 2022b) reported decreased relative liver weight and hepatic sinus congestion and necrosis in mice exposed to 0.7 or 1.2 mg thallium/kg/day as thallium III nitrate or thallium I nitrate, respectively, in drinking water for 2 weeks; however, interpretation of these results is limited by the lack of incidence data. No histological alterations were reported in the livers of rats administered 0.20 mg thallium/kg/day as thallium I sulfate by gavage for 90 days (EPA 1986) and in rats exposed to 1.1 mg thallium/kg/day as thallium I acetate or 1.6 mg thallium/kg/day as thallium I oxide administered in drinking water for 15 weeks (Downs et al. 1960).

2.10 RENAL

Human case studies report that thallium can affect the kidneys (Cavanagh et al. 1974; Gastel 1978). Histological examination of the kidneys in one case revealed extensive recent necrosis of the cortex (Cavanagh et al. 1974). The study authors reported that the effects were probably the result of infarction. Renal function is also impaired following thallium exposure. Diminished creatinine clearance, a raised blood urea, and proteinuria are common (Cavanagh et al. 1974).

In a small longitudinal study of adults, the levels of thallium in $PM_{2.5}$ were associated with blood urea nitrogen (BUN) levels and the ratio of BUN to serum creatinine; however, there were no associations with serum creatinine, urea acid, estimated glomerular filtration rate, or endogenous creatinine clearance rate (Peng et al. 2022). Inverse associations between urinary thallium levels and kidney function abnormalities (Yu et al. 2023) and chronic kidney disease (Zhou et al. 2021b) have been reported in general population epidemiological studies. A study of adolescents found an association between urinary thallium (adjusted for creatinine) and estimated glomerular filtration rate (Weaver et al. 2014); however,

no associations were found when unadjusted urinary thallium levels or urine osmolarity-adjusted urinary thallium levels were used as the biomarker of exposure.

Information on the potential renal toxicity of thallium in laboratory animals is limited to three intermediate-duration oral studies in rats. No histological alterations were observed following 90-day gavage administration of 0.20 mg thallium/kg/day as thallium I sulfate (EPA 1986) or 15-week drinking water exposures to 1.1 mg thallium/kg/day as thallium I acetate or 1.6 mg thallium/kg/day as thallium I oxide (Downs et al. 1960).

2.11 DERMAL

Alopecia is one of the classical signs of thallium poisoning in humans and has been reported in numerous case reports (for example, Al Hammouri et al. 2011; Almassri and Sekkarie 2018; Desenclos et al. 1992; Gastel 1978; Grunfeld and Hinostroza 1964; Lu et al. 2007; Meggs et al. 1994; Rayisyan et al. 2021; Sojáková et al. 2015; Sun et al. 2012; Villanueva et al. 1990; Wang et al. 2007, 2021; Zavaliy et al. 2021; Zhang et al. 2014; Zhao et al. 2008). Hair loss can occur as early as 8 days after exposure (Grunfeld and Hinostroza 1964) but is typically seen after 2–3 weeks (Liu and Liao 2021; Lu et al. 2007; Sojáková et al. 2015; Zhao et al. 2008). In most cases, the hair loss is temporary. Alopecia has also been observed in approximately 10% of residents living in a community near a cement factory that were likely exposed to thallium in home-grown vegetables and fruit contaminated with thallium dust (Brockhaus et al. 1981); the incidence of alopecia was not related to urinary thallium levels.

Other dermal effects include acneiform lesions, lip edema, hyperkeratotic lesions on soles and palms (Misra et al. 2003); seborrheic dermatitis of the face (Sojáková et al. 2015); dry and cracked skin on lips, back of fingers and toes (Wang et al. 2021); nail changes (Mees lines) (Almassri and Sekkarie 2018; Zhao et al. 2008); and erosion of fingernails from the proximal end (Saha et al. 2004).

Alopecia has been reported in laboratory animals following acute and intermediate oral exposure. It was noted in rats following a single gavage administration of 18.2 mg thallium/kg as thallium I sulfate (Rusyniak et al. 2003). In intermediate studies, it has been reported at doses of ≥1.1 mg thallium/kg/day as thallium I acetate (Downs et al. 1960; Gross et al. 1948), ≥1.6 mg thallium/kg/day as thallium I oxide (Downs et al. 1960), and ≥0.20 mg thallium/kg/day as thallium I sulfate (EPA 1986; Manzo et al. 1983; Shipkowski et al. 2023). Alopecia was also noted in the pups of rats exposed to 2.2 mg thallium/kg/day as thallium I sulfate (Shipkowski et al. 2023). There is some uncertainty in identifying a LOAEL for

alopecia in the EPA (1986) study. The study reported dose-related increases in alopecia in female rats; the reported incidences were 4/20, 1/20, 4/20, 9/20, and 12/20 female rats in the untreated control, vehicle control, and 0.008, 0.04, and 0.20 mg thallium/kg/day groups, respectively (as presented in EPA 2009a). However, the investigators attributed some of the alopecia to barbering behavior (defined as abnormal whisker or fur plucking behavior). In the 0.20 mg thallium/kg/day group, five incidences of alopecia were not attributed to barbering; this incidence was significantly higher than controls (p=0.02, Fisher Exact test conducted by ATSDR). The incidence of alopecia in the male rats was 2/20, 1/20, 4/20, 9/20, and 4/20 in the untreated control, vehicle control, and 0.008, 0.04, and 0.20 mg thallium/kg/day groups (as presented in EPA 2009a). EPA (1986) attributed the non-barbering alopecia to the cyclic pattern of hair growth in rats and did not consider it to be toxicologically relevant. Given the consistency of the alopecia in case reports of thallium poisonings in humans and across intermediate-duration animal studies, ATSDR considers the alopecia to be exposure related but acknowledges the uncertainty of categorizing the 0.20 mg thallium/kg/day as a LOAEL and did not include it in the LSE table and figure. Histological alterations have been observed in examinations of skin samples. In the EPA (1986) study, atrophy of the hair follicles was observed in two of the female rats with alopecia in the 0.20 mg/kg/day group. A marked decrease in the number of hair follicles and hair shafts and atrophy of the remaining hair follicles were observed in rats exposed to 1.6/1.8 mg thallium/kg/day as thallium I oxide (Downs et al. 1960); the study also found a decrease in the size of sebaceous glands.

2.12 OCULAR

No studies were located regarding the direct effects of thallium on the eyes of humans. However, thallium can cause damage to certain cranial nerves, which can lead to eye disturbances. Decreased visual acuity due to bilateral central scotomas and progressive optic atrophy have been associated with optic nerve damage (Moeschlin 1980). Exposure can lead to degenerative changes in cranial nerves, which innervate the extraocular muscles. External ophthalmoparesis (weakness of extraocular muscles) is a common manifestation of eye disturbance (Cavanagh et al. 1974; Davis et al. 1981). In a 90-day study in rats, gavage administration of 0.20 mg thallium/kg/day did not result in ophthalmological alterations (EPA 1986).

2.13 ENDOCRINE

Epidemiological studies have evaluated possible associations between thallium and thyroid effects and diabetes. A case control study found no associations between urinary thallium levels and the risk of

thyroid tumor or goiter (Liu et al. 2021). A study of pregnant women examined potential associations between thallium levels in $PM_{2.5}$ and thyroid hormones and found no associations with thyroid stimulating hormone or free thyroxine (T4) levels but found an inverse association with free triiodothyronine (T3) levels and an association with the ratio of free T4 to free T3 levels (Qiu et al. 2022). A study of NHANES participants found inverse associations between urinary thallium levels and total T4 and free T4 levels (Yorita Christensen 2013). However, when adjusted for exposure to other metals, there was no association with free T4 levels and an inverse association with total T4 levels. The study did not find associations between urinary thallium and total or free T3 levels or with thyroid stimulating hormone levels.

Mixed results were found for associations with diabetes. A decrease in diabetes deaths was found in a community with contaminated drinking water (Nuvolone et al. 2021). No associations were found between with urinary thallium and diabetes in women (Wang et al. 2020) or serum thallium and gestational diabetes (Zhu et al. 2019).

A study in rats did not find histological alterations in the thyroid/parathyroid, adrenals, or pancreas following a 90-day exposure to 0.20 mg thallium/kg/day (EPA 1986).

2.14 IMMUNOLOGICAL

In a study of allergic diseases in 4-year-old children, no associations between maternal urinary thallium levels and odds of allergic rhinitis, wheeze, or eczema were found when the models were adjusted for other metals (vanadium, nickel, chromium, arsenic, cadmium, and lead) (Ruan et al. 2022).

Information on the potential immunotoxicity of thallium is limited to a study that reported decreased thymus weight and decreased B cell frequency in bone marrow, blood, and spleen in mice exposed to 8 mg thallium/kg/day as thallium I nitrate in drinking water for 1 week (Li et al. 2023a); the study did not evaluate immune function.

2.15 NEUROLOGICAL

Human case studies revealed that the nervous system is susceptible to thallium toxicity after acute-duration oral exposure. Progressive peripheral neuropathy developing into paresthesia and hyperalgesia of the hands and feet are commonly reported within a week following acute-duration oral exposure to

presumably high doses of thallium (Al Hammouri et al. 2011; Almassri and Sekkarie 2018; Cavanagh et al. 1974; Davis et al. 1981; Desenclos et al. 1992; Gastel 1978; Li et al. 2014; Meggs et al. 1994; Rayisyan et al. 2021; Roby et al. 1984; Sun et al. 2012; Wang et al. 2007, 2021; Zhao et al. 2008). Severe cranial and peripheral neuropathy were reported following ingestion of a single estimated lethal dose of 54–110 mg thallium/kg as thallium nitrate (estimated using a reference body weight of 70 kg) (Davis et al. 1981). Examination of nerves obtained on days 7 and 9 demonstrated axonal degeneration with secondary myelin loss. Axons were swollen and contained distended mitochondria and vacuoles (Davis et al. 1981). Distal peripheral axonal degeneration with preserved proximal fibers was observed in another case in which death occurred; however, reliable exposure data (dose and duration) were not reported (Cavanagh et al. 1974; Roby et al. 1984). In another case report, sural nerve biopsy revealed loss of axons and active axonal degradation (Misra et al. 2003).

Other neurological effects observed in acute-duration oral exposure poisoning included loss of consciousness, seizures, and insomnia (Al Hammouri et al. 2011); weakness in the lower extremities (Almassri and Sekkarie 2018; Desenclos et al. 1992; Tromme et al. 1998; Villanueva et al. 1990; Vrij et al. 1995; Zavaliy et al. 2021); impaired walking (Zavaliy et al. 2021); and vision alterations (Jha et al. 2006). Nerve conduction velocity was measured in some case reports. Decreases in sensory and motor nerve amplitude of response (Kuo et al. 2005; Li et al. 2014; Zhao et al. 2008), with no alteration in motor nerve conduction velocity, have been observed (Zhao et al. 2008). A case report of two subjects found altered performance on neurobehavioral tests of memory which slowly improved over time (Tsai et al. 2006).

Neurological effects have also been reported following chronic-duration inhalation and oral exposure. A study of cement plant workers reported paresthesia, numbness of toes and fingers, the "burning feet" phenomenon, and muscle cramps (Ludolph et al. 1986). A decrease in somatosensory evoked potential was observed with no alterations in nerve conduction velocity or visual evoked potential. It is noted that the study did not evaluate unexposed workers and approximately half of the workers had concurrent disease including diabetes, obesity, malabsorption syndrome, (alcoholic) liver disease, disorders of joints and connective tissues, and hypertensive vascular disease. These may have contributed to the neurological effects observed. An increase in sleep disturbances and signs of polyneuropathy and psychasthenia (e.g., weakness, nervousness, headache, and other psychic alterations) were observed in residents living near a cement production facility (Brockhaus et al. 1981); both categories of effects were correlated with urinary thallium levels. The likely source of exposure was thallium contaminated home-grown fruits and vegetables. In another study of a community consuming thallium-contaminated

vegetables, peripheral neuropathy was reported in residents (Dai-xing and Ding-nan 1985); the mean urinary thallium level in affected residents was 1.52 mg/L compared to 0.24 mg/L in unaffected residents.

Two epidemiological studies examined the possible association between urinary thallium levels and cognitive function in NHANES participants who were ≥60 years of age; neither study found associations (Sasaki and Carpenter 2022; Wang et al. 2022b). Another study of NHANES participants did not find an association between urinary thallium levels and hearing loss (Zou et al. 2022); hearing loss was defined as the participant reporting being deaf or having serious difficulty hearing. Two case-control studies evaluated possible associations between thallium and autism. Adams et al. (2017) found an association between autism spectrum disorder and urinary thallium in a study of children and adults. Adams et al. (2013) examined autism severity and did not find an association with urinary thallium in children.

Animal studies have reported overt signs of neurotoxicity and impaired performance on neurobehavioral tests. Convulsions were observed in rabbits following administration of a lethal dose of 61 mg thallium/kg/day as thallium I sulfate (Grunfeld et al. 1963) and decreased spontaneous activity was observed in rats following administration of a single gavage dose of 18.2 mg thallium/kg/day as thallium I sulfate (Rusyniak et al. 2003). Irritability was also reported in rats exposed to 1.2 mg thallium/kg/day as thallium I sulfate in drinking water for up to 60 days (Gregotti et al. 1985).

Structural and functional changes were observed in peripheral nerves of rats exposed to 1.5 mg thallium/kg/day as thallium I sulfate for 240 days, but effects were not found at 40 days (Manzo et al. 1983). There was a 44% decrease in the amplitude of motor action potential (MAP), a 30% decrease in the amplitude of the sensory action potential, and a 25% increase in MAP latency. Wallerian degeneration of scattered fibers and vacuolization and delamination of the myelin sheath of 10% of the fibers were reported in 50% of the test animals (Manzo et al. 1983). Ultrastructural examination of fibers with Wallerian degeneration showed complete destruction of the axon, with mitochondrial degeneration, neurofilamentous clustering, and evidence of extensive lysosomal activity (Manzo et al. 1983). No neurological effects were observed in a light microscopic examination of the brains of rats administered up to 0.20 mg thallium/kg as thallium sulfate by gavage for 90 days (EPA 1986). No electron microscopic evaluations were performed in this study.

2.16 REPRODUCTIVE

No studies were located in humans or animals regarding reproductive effects after inhalation or dermal exposure to thallium.

Several epidemiological studies have evaluated possible associations between thallium and reproductive effects in males and females. In males, no associations between urinary thallium levels and reproductive hormone levels (testosterone, estradiol, follicle stimulating hormone, luteinizing hormone, sex hormone binding globulin) (Wang et al. 2016) or erectile dysfunction (Wang et al. 2023) were found. Case-control studies of women found associations between blood thallium levels and early embryonic arrest (Liang et al. 2022) and recurrent pregnancy loss (Tabassum et al. 2022). Associations between urinary thallium levels and premature ovarian insufficiency, follicle stimulating hormone, and luteinizing hormone levels, and an inverse association with anti-Mullerian hormone levels were reported in another case-control study (Ma et al. 2022).

A small number of studies have evaluated the potential reproductive toxicity of thallium in animals. A decrease in sperm motility was observed in rats exposed to 1.3 mg thallium/kg/day as thallium I sulfate in drinking water for 60 days (Formigli et al. 1986). There were no alterations in relative testes weight or seminiferous tubule diameter. The investigators noted seminiferous epithelial changes consisting of increased release of later spermatids into the tubular epithelium with numerous vacuole-like spaces between germ cells; however, no incidence data were provided. Electron microscopic findings consisting of diffuse cytoplasmic vacuolization and distension of the smooth endoplasmic reticulum were also reported. Testicular β-glucuronidase activity was reduced significantly in the thallium-treated males, but plasma testosterone levels were unaffected. Abnormalities in testicular morphology, function, or biochemistry were not observed in rats exposed for 30 days (Formigli et al. 1986). No histological alterations were observed in the testes of rats following 15-week dietary exposure to 1.1 mg thallium/kg/day as thallium I acetate or 1.6 mg thallium/kg/day as thallium I oxide (Downs et al. 1960) or in the testes, epididymis, prostate, ovaries, or uterus of rats administered 0.20 mg thallium/kg/day as thallium I sulfate for 90 days (EPA 1986).

2.17 DEVELOPMENTAL

A literature review of 18 cases on thallium poisoning in pregnant woman reported alopecia in five of the infants; no other overt developmental effects were consistently reported (Hoffman and Hoffman 2000).

An evaluation of the possible relationship between thallium exposure and congenital malformations was conducted in a community near a cement production facility (Dolgner et al. 1983); maternal exposure was suspected but thallium levels were not evaluated. The rate of congenital malformations in this community were compared to the rate for the region. Although the rate in the community (5/297) was higher than the expected rate of 0.8/297, the investigators noted that congenital malformations in the reference population may have been under reported and concluded that there was no increase in the occurrence of congenital malformations in the study population.

Epidemiological studies have examined the possible association between thallium and developmental outcomes. No alterations in the risk of preterm birth were observed in residents of a community with thallium contaminated drinking water (Nuvolone et al. 2021). Studies evaluating associations between maternal thallium levels and birth weight found mixed results. Zhou et al. (2021a) found an inverse association, Wu et al. (2023) found an inverse association in female infants but no association in male infants, and Bloom et al. (2015) found no association. Estimated fetal weights measured at several time points during the third trimester were not associated with maternal urinary thallium (Dou et al. 2022). Nuvolone et al. (2021) did not find an increased risk of low-birth-weight infants in residents with contaminated drinking water, whereas Xia et al. (2016) found an association between maternal urinary thallium and the risk of low birth-weight infants. Early childhood growth (0–2 years of age) was not associated with maternal first or second trimester serum thallium levels, but weight for age and length for age were inversely associated with cord blood thallium levels for boys and girls combined and for girls only (Qi et al. 2019). When first trimester maternal urinary levels were used as a biomarker, no associations with growth between birth and 6 months of age were found (Yao et al. 2022). Associations with body weight in boys and head circumference in boys were found when third trimester maternal urinary thallium levels were used as the biomarker of exposure (Yao et al. 2022). Two studies conducted by Tong et al. (2020, 2022) evaluated potential neurodevelopmental toxicity of thallium in a cohort of children evaluated at 3 and 4.5 years of age. No associations between maternal blood thallium levels and attention deficit/hyperactivity disorder (ADHD) in 3-year-olds were observed when first and third trimester blood thallium levels were used as a biomarker; however, an association was found when second trimester fourth quartile blood thallium levels were used (Tong et al. 2020). When the results were analyzed by sex, the association was only found in boys in the fourth quartile. Mixed results were found in other cognitive tests depending on the exposure biomarker (Tong et al. 2022), with inverse associations between third-tertile maternal blood thallium levels and visual spatial index (first trimester in

boys and third trimester in girls), full scale intelligence quotient (third trimester in boys), and fluid reasoning index (third trimester in boys).

Three studies have evaluated the developmental toxicity of thallium in animals. In a brief communication, Bornhausen and Hagen (1984) reported impaired performance on operant behavior test in the rat pups of dams exposed to thallium I sulfate on gestation days (GDs) 6–8; however, the limited reporting of the results does not support identifying a LOAEL for the study. The study did not evaluate any other potential developmental endpoints. Shipkowski et al. (2023) reported decreased rat pup body weight gain at ≥2.2 mg thallium/kg/day as thallium I sulfate. No alterations in the number of live pups per litter or pup sex ratio were observed. Uneven hair growth on postnatal days (PNDs) 11–24, which progressed to alopecia on PNDs 18–28, were also observed in the pups at ≥ 2.2 mg thallium/kg/day. Another developmental toxicity study did not find alterations in pup body weight in the offspring of rats exposed to 1 mg thallium/kg/day as thallium I sulfate on GD 0 to lactation day (LD) 22 (Rossi et al. 1988). Impaired development of the pilus apparatus was observed in pups exposed during gestation and lactation and post-weaning (PNDs 22–60); no effect on systolic blood pressure on PND 30 or 60 was observed (Rossi et al. 1988). A decreased hypertensive response to 1-noradrenaline was observed. Doses for the cardiovascular effects in pups exposed pre- and postnatally could not be determined because water intake was not reported for the pups.

Cultured rat embryos exposed to thallium at concentrations of 10, 30, or 100 µg/mL showed dose-related growth retardation at all levels, suggesting embryotoxic effects (Anschutz et al. 1981). Complete growth inhibition was reported at 100 µg/mL. At 3 µg/mL (lowest dose tested), the treated and control embryos did not differ significantly. Administration by intraperitoneal injection to pregnant rats at a dose of 2.0 mg thallium/kg/day as thallium sulfate during GDs 8–10 resulted in reduced fetal body weights, hydronephrosis, and the absence of vertebral bodies (Gibson and Becker 1970). The significance of these types of exposure studies is not understood and does not allow a conclusive decision about the human health implications.

2.18 OTHER NONCANCER

Information on other noncancer effects is limited to one epidemiological study. Wang et al. (2022c) did not find an association between urinary thallium and metabolic syndrome in women.

2.19 CANCER

A study of workers at a magnesium sea water battery production facility did not find differences in the incidence of benign neoplasms between thallium exposed workers and nonexposed controls (Marcus 1985). Three epidemiological studies evaluated the possible association between thallium and carcinogenicity. An inverse association between urinary thallium and cancer mortality was observed in NHANES participants (Fan et al. 2023) and in residents exposed to thallium in drinking water (Nuvolone et al. 2021). Another study of NHANES participants found an association between urinary thallium levels and prostate cancer but no associations with breast cancer or ovarian cancer (Cao et al. 2023).

No inhalation, oral, or dermal animal studies examining cancer endpoints were identified.

EPA concluded that the database for thallium provides inadequate information to assess carcinogenic potential (IRIS 2009). HHS and IARC have not evaluated the carcinogenicity of thallium.

2.20 GENOTOXICITY

Mixed results have been reported in *in vitro* bacterial and mammalian cell assays (Table 2-3). Thallium I nitrate induced DNA damage in *Bacillus subtillis* but did not induce reverse mutations in *Salmonella typhimurium* or *Escherichia coli* (Kanematsu et al. 1980). In mammalian cells, thallium compounds increased the incidence of chromosomal aberrations (Rodríguez-Mercado et al. 2015, 2017) but did not increase sister chromatid exchanges or micronuclei formation (Migliore et al. 1999; Rodríguez-Mercado et al. 2015). Thallium I carbonate induced single-strand DNA breaks in rat fibroblasts and in only one strain of mouse embryo fibroblast cells (Zasukhina et al. 1983). There are limited data on the genotoxicity of thallium from *in vivo* assays (Table 2-4). In a case report, Hantson et al. (1997) reported no increases in chromosomal aberrations or sister chromatid exchanges in a patient ingesting 200 mg thallium sulfate, as compared to laboratory historical control levels. An increase in binucleated cells with micronuclei was observed (10% compared to 3.5% in historical controls). Thallium induced dominant lethal mutations in male rats (Zasukhina et al. 1983). Increases in somatic mutations and recombinations were observed in *Drosophila* exposed to high concentrations of thallium I sulfate but were not found following thallium I acetate exposure (Reyes-Rodríguez et al. 2021).

Table 2-3. Genotoxicity of Thallium *In Vitro*

Species (test system)	Compound	endpoint	Results[a]	Reference
Prokaryotic organisms				
Bacillus subtillis	$TlNO_3$	DNA damage/repair	+	Kanematsu et al. 1980
Salmonella typhimurium TA1535, TA100, TA98, TA1537, TA1538	$TlNO_3$	Reverse mutations	–	Kanematsu et al. 1980
Escherichia coli B/r WP2, WP2			–	
Mammalian cells				
Human peripheral blood cells	$TlC_2H_3O_2$	Sister chromatid exchanges	–	Rodríguez-Mercado et al. 2015
		Chromosomal aberrations	+	
		DNA damage	+	
Human peripheral blood cells	Tl_2SO_4	Chromosomal aberrations	+	Rodríguez-Mercado et al. 2017
	$TlCl_3$		+	
Human lymphocytes	Tl_2SO_4	Micronuclei formation	–	Migliore et al. 1999
C57BL/6 mouse embryo fibroblast cells	Tl_2CO_3	Single-strand DNA breaks	+	Zasukhina et al. 1983
CBA mouse embryo fibroblast	Tl_2CO_3	Single-strand DNA breaks	–	Zasukhina et al. 1983
Rat embryo fibroblast cells	Tl_2CO_3	Single-strand DNA breaks	+	Zasukhina et al. 1983
Syrian hamster embryo cells/SA7	$TlC_2H_3O_2$	Enhancement of viral transformation	+	Casto et al. 1979

[a]All studies evaluated genotoxicity without metabolic activation.

– = negative result; + = positive result; DNA = deoxyribonucleic acid; $TlC_2H_3O_2$ = thallium I acetate; Tl_2CO_3 = thallium I carbonate; $TlCl_3$ = thallium III chloride; $TlNO_3$ = thallium I nitrate; Tl_2SO_4 = thallium I sulfate

Table 2-4. Genotoxicity of Thallium *In Vivo*

Species (exposure route)	Compound	Endpoint	Results	Reference
Drosophila melanogaster (oral)	$TlC_2H_3O_2$	Somatic mutation and recombination	–	Reyes-Rodríguez et al. 2021
D. melanogaster (oral)	Tl_2SO_4	Somatic mutation and recombination	+	Reyes-Rodríguez et al. 2021
Rats (oral)	Tl_2CO_3	Dominant lethality	+	Zasukhina et al. 1983

– = negative result; + = positive result; TlC_2H3O_2 = thallium I acetate; Tl_2CO_3 = thallium I carbonate; Tl_2SO_4 = thallium I sulfate

2.21 MECHANISMS OF ACTION

The exact mechanism of thallium toxicity is not known; however, several possible mechanisms have been proposed: interference with potassium transport, reaction with thiol groups, disturbances in mitochondrial function, and induction of oxidative stress. The discussion of the thallium mechanisms of action was taken from several reviews (Cvjetko et al. 2010; EPA 2009a; Peter and Virarghayan 2005; WHO 1996).

Interference with Potassium Transport. Because monovalent thallium and potassium have similar ionic radii and electrical charge, thallium can mimic potassium in most biological processes. Monovalent thallium has a 10-fold higher affinity for sodium/potassium ATPase than the potassium ion and the permeability of thallium across cell membranes is 10–100 times greater than potassium. Thus, thallium can accumulate within the cell at the expense of potassium. Thallium does not appear to affect the transport of sodium across membranes. A study in *Daphnia magna* provides support for the interference with potassium transport as being a mechanism of action demonstrating a reduction of thallium toxicity when water levels of potassium were increased (Nagel et al. 2023).

Reactions with Thiol Groups. Thallium has a high affinity for sulfhydryl groups and thiol groups, enabling it to interfere with a variety of processes. However, thallium does not appear to interfere with the metabolism of sulfur-containing amino acids. It has been suggested that binding of thallium to cysteine sulfhydryl groups in hair follicles may lead to the hair loss associated with thallium poisoning.

Disturbances in Mitochondrial Function. Thallium has been shown to disturb mitochondrial function. Thallium I acetate has been shown to uncouple oxidative phosphorylation and result in swelling of isolated mitochondria. Thallium-induced reductions in available energy has been postulated as a mechanism of peripheral nerve damage. Thallium may also disturb flavoprotein-dependent reactions by decreasing available levels of riboflavin in tissues. This suggestion is supported by the similarities of the effects associated with thallium toxicity and those resulting in riboflavin deficiency such as peripheral neuropathy and hair loss.

Induction of Oxidative Stress. There is evidence suggesting that thallium induces oxidative stress. Thallium appears to affect the metabolism of glutathione, which could result in the accumulation of oxidant species. Thallium III hydroxide has been shown to decrease levels of glutathione and inhibit glutathione peroxidase and glutathione reductase activity. Investigators have suggested that the thallium-

enhanced production of reactive oxygen species (ROS) and decreased mitochondrial functionality could promote apoptosis. Monovalent thallium could promote mitochondrial depolarization, with a subsequent production of hydrogen peroxide and triggering of the intrinsic pathway of apoptosis, whereas trivalent thallium increases Fas content and activates caspase 8 and the extrinsic apoptosis pathway (Pino et al. 2017).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Thallium is well absorbed following oral exposure; one study suggested 100% absorption.
- Thallium is rapidly distributed throughout the body following oral exposure, with the highest concentrations found in the kidneys.
- Thallium is not metabolized.
- Thallium is primarily excreted in the urine; some is also excreted in feces. A half-life of 21.7 days has been estimated in humans.

3.1.1 Absorption

No quantitative studies were located regarding absorption in humans or animals after inhalation exposure to thallium.

Limited data were located regarding absorption in humans after oral exposure to thallium. Following oral administration of a single tracer dose of 500 microcuries (μCi) of thallium-204 (^{204}Tl) as thallium nitrate and 45 mg daily for 5 days of thallium sulfate in a patient with terminal osteogenic sarcoma, 0.4% of the administered radioactivity was recovered in feces and 11% was recovered in urine during a 72-hour collection period. In 5.5 days, the patient had excreted 15.3% of the administered dose in the urine. These data suggest that most of the thallium was absorbed (Barclay et al. 1953).

Animal studies suggest that thallium is completely absorbed when ingested. Lie et al. (1960) administered a single trace dose of ^{204}Tl as thallium nitrate orally to rats at a dose of 0.767 mg thallium/kg. The body burden of ^{204}Tl, as percent dose, decreased with a single exponential function, which extrapolated to 100% at zero time. The study authors therefore concluded that thallium was completely absorbed from the gastrointestinal tract.

No reliable quantitative studies were located regarding absorption in humans or animals after dermal exposure to thallium.

3.1.2 Distribution

No studies were located regarding distribution in humans or animals after inhalation exposure to thallium.

There is little information on distribution of thallium in humans. Analyses of human tissues indicate that thallium is distributed throughout the body. A female cancer patient was administered a tracer dose of 1.8 mg ^{204}Tl as thallium nitrate orally and thereafter an oral doses of 36 mg thallium as thallium sulfate every 3 days for a total of five doses (Barclay et al. 1953). The thallium tissue levels, reported as percent of average body distribution per gram, were highest in scalp hair (420%), renal papilla (354%), renal cortex (268%), heart (236%), bone tumor (233%), and spleen (200%). Lower levels were found in the brain (39–70%).

In animals, distribution of thallium from the blood stream is rapid and widespread. One study found thallium to accumulate in the kidney (17 µg/g) followed by the heart (7 µg/g), brain (6 µg/g), bone (8 µg/g), skin (3 µg/g), and blood (0.67 µg/g) in rats administered approximately 1.4 mg thallium/kg as thallium sulfate in drinking water (Manzo et al. 1983). In male rats administered 740 µg thallium/kg as thallium sulfate in drinking water, 6.3 µg thallium/g tissue was found in the testes compared to <0.08 µg thallium/g tissue in untreated controls (Formigli et al. 1986). In rats fed 2.3–3.0 mg thallium/kg as thallium I acetate or thallium I oxide, the largest amount of thallium was detected in the kidney (24–31 µg/g wet tissue) with lower levels in the liver (13–16 µg thallium/g) and bone (19 µg thallium/g). Smaller amounts (5–9 µg/g) were found in the brain, lung, and spleen (Downs et al. 1960).

Lie et al. (1960) studied the tissue distribution of thallium in rats administered a single tracer dose of ^{204}Tl as thallium nitrate orally at a dose of 0.76 mg thallium/kg. No day-to-day variation in relative organ content was found with the exception of hair levels, which increased over time; hair thallium levels contained 1.56% of the body burden 7 days post-exposure and 60% of the body burden 21 days post-exposure. Approximately 7 days post treatment, the highest percentage body burden (per gram of tissue) was detected in kidneys (4.7% of the body burden per gram of tissue). Smaller percentages of body burden were detected in salivary glands (1.08%), testes (0.88%), muscle (0.79%), bone (0.74%), gastrointestinal tract (0.62%), spleen (0.56%), heart (0.54%), liver (0.52%), respiratory system (0.47%), hair (0.37%), skin (0.37%), and brain (0.27%). The biological half-life for thallium was 3.3 days.

No studies were located regarding distribution in humans or animals after dermal exposure to thallium.

Parenteral studies also indicate extensive tissue distribution of thallium. Adult white mice dosed intraperitoneally with ^{204}Tl at a dose of 4 mg thallium/kg as thallous sulfate showed high thallium concentrations in bone tissue, kidney (particularly in the medulla), pancreas, and large intestine approximately 1 hour after dosing (Andre et al. 1960). Thallium levels in bone decreased after ≥10 days, but thallium was still detectable 28 days post treatment. Intraperitoneal administration of ^{204}Tl mixed with thallium nitrate resulted in peak concentrations in the brain, spinal cord, spleen, liver, and kidney (Ducket et al. 1983). Some apparent differences in the time to peak concentrations were observed between adult rats (33 days of age) and young rats (17 days of age), with peak levels in nervous system tissues (brain, spinal cord and sciatic nerve) occurring 24 hours post-exposure in the adults and 48 hours post-exposure in the young rats. The respective biological half-times in the brain, spinal cord, and sciatic nerve were 1.4, 2.5, and 1.2 days in young rats and 2.7, 4.0, and 3.0 days in adult rats.

^{204}Tl as thallous sulfate has been shown to cross the placenta and locate in the fetus within 15 minutes following intraperitoneal injection (50 μCi, specific activity not stated) (Olsen and Jonsen 1982) and 32 minutes after intravenous administration (0.16–5.2 mg thallium/min/kg) (Rade et al. 1982). The concentration of thallium in the fetus was substantially lower than that in maternal tissues by both routes of administration.

3.1.3 Metabolism

Thallium is not metabolized because it is an element. No human or animal studies were located to assess whether it is transformed from one valence state to another valence state.

3.1.4 Excretion

There are limited data on the excretion of thallium in humans. Elevated urinary thallium levels have been observed in workers in a magnesium seawater battery plant (Marcus 1985) or a cement factory (Schaller et al. 1980). Elevated thallium levels have also been observed in residents living near a cement plant emitting thallium containing dust (Dolgner et al. 1983); consumption of contaminated home-grown vegetables and fruit was considered to be the main source of exposure. The urinary thallium levels decreased after the subjects were advised to decrease consumption of home-grown produce. In a study of a terminally ill cancer patient, 15.3% of the orally administered radiolabelled thallium nitrate was detected in urine 5.5 days postdosing and 0.4% in feces in 3 days (Barclay et al. 1953). A total of 45% of

the radioactivity remained in the body at the time of her death 24 days post-exposure to the isotope. Using the data from Barclay et al. (1953), EPA (1980) estimated an excretion half-life of 21.7 days.

No studies regarding excretion in animals after inhalation or dermal exposure were located. In rats administered 10 mg thallium/kg as thallium sulfate by gavage, 32% of the administered dose was eliminated in feces and 21% was eliminated in urine (Pedro et al. 1985) by 8 days postdosing. Lie et al. (1960) administered a single tracer dose of ^{204}Tl as thallium nitrate via six exposure routes (oral, intramuscular, intraperitoneal, intratracheal, intravenous, and subcutaneous) to rats at a dose of 767 µg thallium/kg. The ratio of fecal to urinary excretion of thallium increased from about 2 to 5 between days 2 and 16. The biological half-life was 3.3 days regardless of the exposure routes.

In rats injected intraperitoneally with ^{204}Tl mixed with thallium nitrate, the biological half-times were 2.6 and 3.8 days, respectively, for young and adult rats. Thallium concentrated in the cerebral cortex, neurons of the caudate nucleus and putamen, and renal proximal tubules and periglomerular spaces. The 95% elimination times for organs in adult rats were fastest for the nervous system, kidney, and liver (range 11.6–17.4 days) and slowest for the spleen (25.8 days), while in young rats, they were fastest for the nervous system, spleen, and kidney (range 6.1–13.6 days) and slowest for the liver (22.0 days) Ducket et al. (1983).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to extrapolate from animal more accurately to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical

descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

The ICRP developed two thallium models: a Human Respiratory Tract Model (HRTM) (Bailey et al. 2007; ICRP 1994, 1995), and a systemic model (ICRP 2022). The HRTM simulates the deposition, clearance, and absorption of inhaled particulates and has absorption parameter values for thallium. The systemic model simulates the distribution and excretion of thallium absorbed from the respiratory or gastrointestinal tract.

The ICRP (2022) has published HRTM parameter values for absorption of thallium compounds (Table 3-1). The HRTM assumes that absorption into blood occurs at equivalent rates in all parts of the respiratory tract, except in the anterior nasal passages, where no absorption occurs. Absorption is simulated as a two-stage process that begins with particle dissolution, followed by transfer of dissolved material into blood. Dissolution is simulated as a biphasic process, with a rapid phase and a slow phase. Dissolution parameters include fraction f_{rapid} dissolving at rate k_{rapid} (day^{-1}) and fraction, f_{slow} ($1-f_{rapid}$) dissolving at rate k_{slow} (day^{-1}). A fraction of the dissolved material can be bound (f_{bound}) transferred to blood at rate (k_{bound}). The unbound fraction, $1-f_{bound}$, is transferred instantaneously to blood. In the absence of specific estimates for absorption kinetics, compounds are classified into absorption types F (fast), M (medium), and S (slow).

Table 3-1. ICRP (2022) Absorption Parameters for the Human Respiratory Tract and Systemic Models

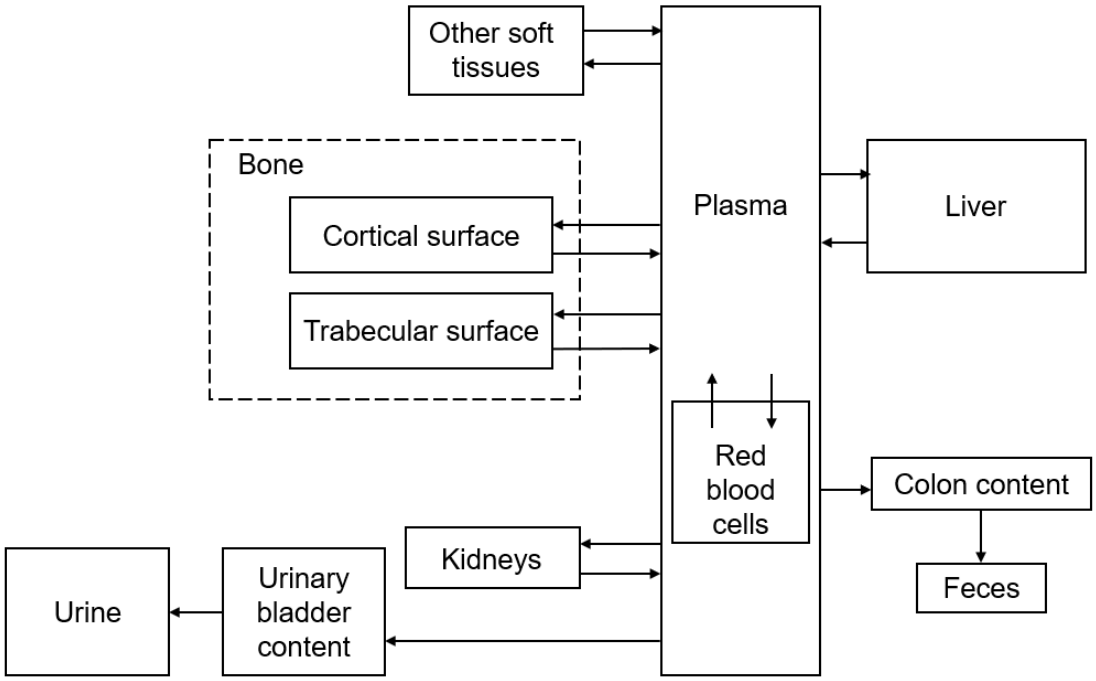
Inhaled thallium							
Type	Rapid fraction	Slow fraction	Rapid Rate (day^{-1})	Slow rate (day^{-1})	Bound fraction	Bound rate (day^{-1})	GI tract absorption fraction[a]
Fast (F)	1.0	0	30	NA	0	NA	1
Medium (M)[b]	0.2	0.8	3	0.005	0	NA	0.2
Slow (S)	0.01	0.99	3	$1X10^{-4}$	0	NA	0.01
Ingested thallium							
All compounds							1

[a]Thallium cleared from the respiratory tract to the gastrointestinal tract.
[b]Type M: default for all thallium compounds in the absence of specific estimates for absorption kinetics.

GI = gastrointestinal; HRTM = Human Respiratory Tract Model; ICRP = International Commission for Radiological Protection; NA = not applicable

The ICRP (2022) systemic model includes compartments representing plasma (central distributing compartment), red blood cells, bladder, bone, colon, kidney, liver, other soft tissues (Figure 3-1). The bone compartment includes sub-compartments representing cortical and trabecular bone surfaces. Transfers of thallium between blood and tissues occurs to and from the plasma compartment. Transfers between compartments are governed by first-order rate coefficients (day^{-1}). Transfer coefficients are presented in Table 3-2. Absorption from the gastrointestinal tract into the plasma is simulated with an absorption fraction. ICRP (2022) assigned an absorption fraction of 1 (100%) for all thallium compounds.

Figure 3-1. Structure of ICRP (2022) Thallium Systemic Model



Source: ICRP 2022, with permission from the International Commission on Radiological Protection

Table 3-2. ICRP Transfer Coefficients for the Human Systemic Model

From	To	Transfer coefficient (day^{-1})
Plasma	Liver	10
Plasma	Kidneys	10
Plasma	RBCs	5
Plasma	Trabecular bone surface	15
Plasma	Cortical bone surface	15
Plasma	Other soft tissues	140

Table 3-2. ICRP Transfer Coefficients for the Human Systemic Model

From	To	Transfer coefficient (day^{-1})
Plasma	Urinary bladder	1.5
Plasma	Colon	3.5
RBCs	Plasma	3.7
Liver	Plasma	2.5
Kidneys	Plasma	2.5
Trabecular bone surface	Plasma	2.5
Cortical bone surface	Plasma	2.5
Other soft tissues	Plasma	2.5

ICRP = International Commission for Radiological Protection; RBC = red blood cell

Source: ICRP 2022, with permission from the International Commission on Radiological Protection

3.1.6 Animal-to-Human Extrapolations

Based on limited available data, the toxicity and toxicokinetic properties of thallium appear to be similar between humans and animals and support extrapolations from animals to humans.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to thallium are discussed in Section 5.7, Populations with Potentially High Exposures.

There are limited data available to identify whether children or other populations are unusually susceptible to the toxicity of thallium. Case series reports of thallium poisoning do not identify differences between adults and children (for example, Sun et al. 2012). A toxicokinetic study in rats administered thallium nitrate suggests some differences in the half-lives of tissue thallium between adult and young rats (Ducket et al. 1983), with longer half-lives in nervous system tissue of the adults. In the liver, a longer half-time was observed in the young rats, as compared to the adult rats.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 2006).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for thallium from this report are discussed in Section 5.6, General Population Exposure.

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 2006). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to thallium are discussed in Section 3.3.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 2006). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by thallium are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Thallium levels in urine, blood, and hair have been used as indications of exposure to thallium. The determination of thallium in urine has been the most widely used of biological indicators of thallium exposure, often expressed in terms of urinary creatinine levels. Higher values have been detected in areas where thallium is used or emitted.

While thallium can be detected in blood, it is cleared from the blood very rapidly. In one case in which a patient with osteogenic sarcoma was administered oral doses of 1.8 mg ^{204}Tl as thallium nitrate (approximately 4 ng thallium/kg), 3% of the administered dose was detected in blood within 2 hours post treatment while 1.6% was detected within 24 hours (Barclay et al. 1953). Since measurements of blood thallium reflect only recent exposures, it is not generally considered to be a reliable means of monitoring human populations for exposure to thallium.

Thallium is excreted in hair and measurement of hair levels may be an indicator of thallium exposure. The normal concentration range of thallium in human hair is approximately 5–10 ng/g. Seven percent of the administered radioactivity was detected in scalp hair of a cancer patient who had been administered 1.8 mg ^{204}Tl as thallium nitrate (Barclay et al. 1953). It should be noted that thallium may adsorb to hair and become incorporated into the hair matrix, making it difficult to distinguish between thallium incorporated into the hair from the body burden and external deposition of thallium.

3.3.2 Biomarkers of Effect

Neurological damage is the primary toxic effect associated with exposure to thallium. Various effects on the nervous system of people exposed to thallium can be detected by monitoring the incidence of signs and symptoms such as ataxia, lethargy, painful extremities, and numbness of toes and fingers. Electromyographic measurements of nerve conduction velocity and amplitude can be monitored to detect early signs of neurotoxicity. However, since neurological damage occurs with other compounds, these

tests are not specific for thallium exposure. Thallium also accumulates in hair. Dark pigmentation of the hair roots and hair loss are common diagnostic features (Gastel 1978). Depletion and inhibition of several enzymes in the brain have been associated with thallium exposure. Hasan et al. (1977a, 1977b) reported depletion of succinic dehydrogenase and guanine deaminase in the rat cerebrum after parenteral administration of 5 mg thallium/kg (as thallium acetate) as well as depletion of monoamine oxidase, acid phosphatase, and cathepsin activity (Hasan et al. 1977b). The significance of this finding as a biomarker of effect is not known.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Studies have shown that trace metals can influence the toxicity of thallium. Potassium has been shown to increase renal excretion of thallium (Gehring and Hammond 1967; Lund 1956a), decrease the degenerative effects of thallium on epiphysial cartilage in mouse limb bud cultures, decrease placental transport of thallium (Sabbioni et al. 1980), and increase the lethality of thallium in animals (Gehring and Hammond 1967). Other interactions can influence thallium toxicity through accelerated elimination. Potent diuretics such as furosemide enhanced the urinary excretion of thallium in rats (Lameijer and van Zwieten 1977, 1978; Pedro et al. 1985). Oral administration of activated charcoal and Prussian blue accelerated the elimination of orally administered thallium in rats (Lund 1956b; Pedro et al. 1985). These agents adsorb thallium in the gastrointestinal tract, and are themselves unabsorbed, thus reducing gastrointestinal absorption of thallium.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of thallium and thallium compounds is presented in Table 4-1.

Table 4-1. Chemical Identity of Thallium and Compounds[a]

Characteristic	Thallium	Thallium I acetate	Thallium III chloride	Thallium I nitrate
Synonym(s) and registered trade name(s)	Ramor[b]	Thallous acetate; thallium (1+) salt	Thallic chloride	Thallous nitrate; nitric acid, thallium (1+) salt
Chemical formula	Tl	$TlC_2H_3O_2$	$TlCl_3$	$TlNO_3$
SMILES	[Tl]	CC(=O)[O-].[Tl+]	[Tl](Cl)(Cl)Cl	[Tl+].[O-][N+](=O)[O-]
Chemical structure	Not applicable	Not applicable	Not applicable	Not applicable
CAS Registry Number	7440-28-0	563-68-8	13453-32-2	10102-45-1

Characteristic	Thallium III oxide	Thallium I sulfate	Thallium I carbonate
Synonym(s) and registered trade name(s)	Thallic oxide	Thallous sulfate	Thallous carbonate; carbonic acid; dithallium carbonate
Chemical formula	Tl_2O_3	Tl_2SO_4	Tl_2CO_3
SMILES	O=[Tl]O[Tl]=O	[Tl+].[Tl+].[O-]S([O-])(=O)=O	[Tl+].[Tl+].[O-]C([O-])=O
Chemical structure	Not applicable	Not applicable	Not applicable
CAS Registry Number	1314-32-5	7416-18-6	6533-73-9

Characteristic	Thallium I bromide	Thallium I iodide	Thallium I fluoride
Synonym(s) and registered trade name(s)	Thallium monobromide; thallous bromide	Thallous iodide	Thallium monofluoroide; thallous fluoride
Chemical formula	TlBr	TlI	TlF
SMILES	Br[Tl]	I[Tl]	F[Tl]
Chemical structure	Not applicable	Not applicable	Not applicable
CAS Registry Number	7789-40-0	7790-30-9	7789-27-7

[a]All information obtained from EPA (1998a), except where noted.
[b]NLM 2024

CAS = Chemical Abstracts Service; SMILES = simplified molecular-input line-entry system

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of thallium and thallium compounds is presented in Table 4-2. Thallium only possesses two stable isotopes: ^{203}Tl and Tl^{205} with natural abundances of 29.54 and 70.48%, respectively (Migaszewski and Gałuszka 2021). Thirty-five short-lived thallium radionuclides have been generated, including ^{204}Tl (half-life of 3.78 years), ^{202}Tl (half-life of 12.2 days), and ^{201}Tl (half-life of 73 hours) (Belzile and Chen 2017). Thallium occurs in two oxidation states: as the monovalent form (thallous, Tl^{+}) such as Tl_2O, Tl_2SO_4, or Tl_2S in strongly reducing conditions and as the trivalent form under oxidizing and alkaline conditions (thallic, Tl_3^{3+}) such as Tl_2O_3, $Tl(OH)_3$ and $TlCl_3$ (Migaszewski and Gałuszka 2021). The monovalent form is more stable and is the predominant chemical species in the environment. Pure thallium is scarce in nature because the surface of metallic thallium is readily oxidized.

Table 4-2. Physical and Chemical Properties of Thallium and Compounds[a]

Property	Thallium	Thallium I acetate	Thallium III chloride	Thallium I nitrate
Molecular weight	204.38	263.43	310.74	266.39
Color	Blush-white	White	White	White
Physical state	Metal	Solid	Solid	Solid
Melting point	303.5°C	131°C	25°C	205°C[b]
Boiling point	1,457±10°C	No data	Decomposes	430°C[b]
Density at 20°C	11.85	3.76 at 137°C	No data	5.5
Odor	Odorless[c]	Odorless[c]	No data	Odorless[c]
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Taste threshold	No data	No data	No data	No data
Solubility:				
Water	Insoluble	Very soluble	Very soluble	95.5 g/L
Organic solvent(s)	Soluble in nitric or sulfuric acid	Very soluble in alcohol; insoluble in acetone	Soluble in alcohol and ether	Insoluble in alcohol; soluble in acetone
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure at 1,000°C	10 mmHg[b]	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Thallium and Compounds[a]

Property	Thallium III oxide	Thallium I sulfate	Thallium I carbonate
Molecular weight	456.76	504.82	468.78
Color	Colorless	Colorless	Colorless
Physical state	Solid	Solid	Solid
Melting point	717±5°C	632°C	273°C
Boiling point	-20 at 875°C	Decomposes[b]	No data
Density	9.65–10.19 at 21°C	6.77	7.11
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Taste threshold	No data	No data	No data
Solubility:			
Water	Insoluble	48.7 g/L	40.3 g/L at 15.5°C
Organic solvent(s)	Soluble in acids; insoluble in alkalis	No data	Insoluble in alcohol, ether, and acetone
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure at 1,000°C	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Thallium and Compounds[a]

Property	Thallium I bromide	Thallium I iodide	Thallium I fluoride
Molecular weight	284.29	331.29	223.38
Color	Yellowish-white	Yellow red (at 170°C)	Colorless
Physical state	Solid	Solid	Solid
Melting point	480°C	440°C[c]	327°C
Boiling point	815°C	824°C[c]	655°C
Density	7.56 at 17.3°C	7.29	8.23 at 4°C
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Taste threshold	No data	No data	No data
Solubility:			
Water	0.5 g/L at 25°C	0.006 g/L	786 g/L at 15°C
Organic solvent(s)	Soluble in alcohol, insoluble in acetone	Insoluble in alcohol, slightly soluble in nitric acid	Slightly soluble in alcohol
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure at 1,000°C	10 mm Hg at 517°C[b]	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data

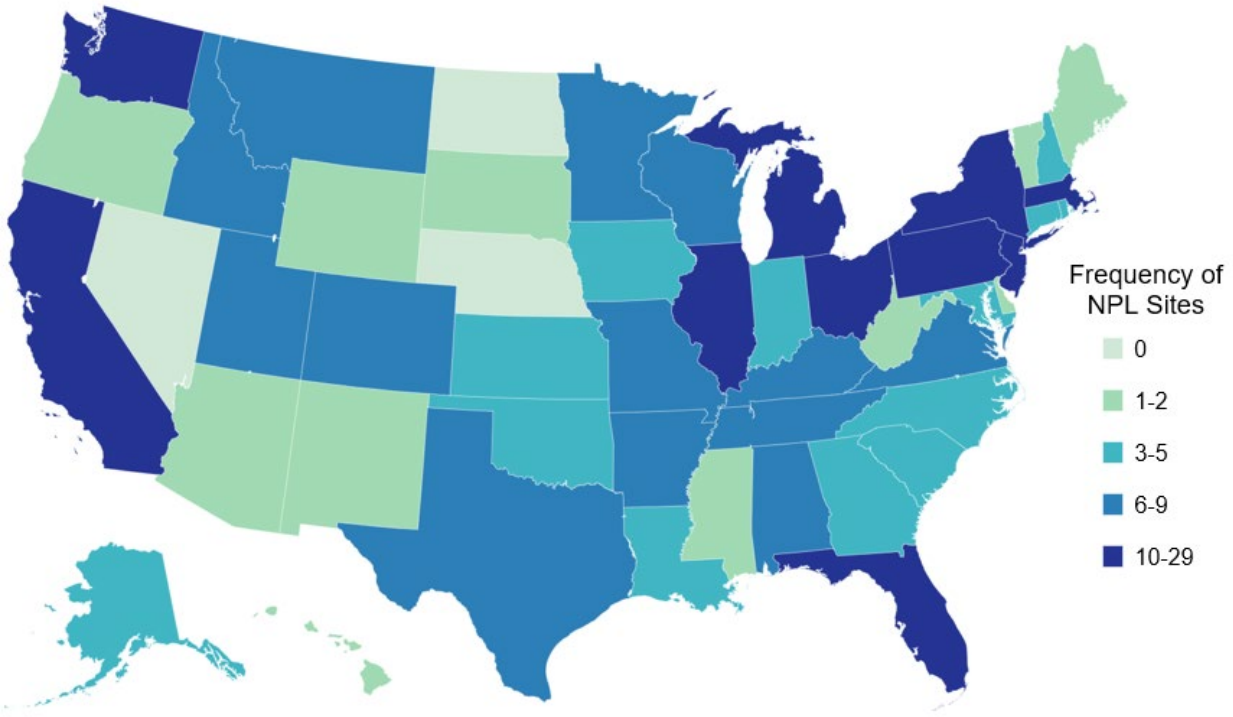
[a]All information obtained from Lide (2005), except where noted.
[b]EPA 1988.
[c]NLM 2024.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Thallium has been identified in at least 346 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022). However, the number of sites in which thallium has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 343 are located within the United States and 3 are located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with Thallium Contamination



Source: ATSDR 2022

- Thallium is released into the environment from both natural and anthropogenic sources. Atmospheric emission and deposition are primarily from mineral smelters and coal-burning facilities.
- Thallium naturally occurs in the Earth's crust, with an estimated concentration of 0.7 ppm.
- Exposure to thallium occurs primarily via consumption of vegetables and fruit.

- Thallium compounds are mobile in soil, tend to have high water solubility, and may bioaccumulate in living organisms.

Thallium is a trace metal that exists naturally in the environment mainly combined with other elements (primarily oxygen, sulfur, and the halogens) in inorganic compounds. Thallium is quite stable in the environment since it is neither transformed nor biodegraded.

Compounds of thallium are generally soluble in water and the element is found primarily as the monovalent ion (Tl+). Thallium tends to be sorbed to soils and sediments (Frantz and Carlson 1987; Mathis and Kevern 1975; Wallwork-Barber et al. 1985) and to bioconcentrate in aquatic plants, invertebrates, and fish (Barrows et al. 1978; Lin et al. 2001; Zitko and Carson 1975). Terrestrial plants can also absorb thallium from soil (Ewers 1988; Sharma et al. 1986).

Major releases of thallium to the environment are from processes such as coal-burning and smelting and cement production, in which thallium is a trace contaminant of the raw materials, rather than from facilities producing or using thallium compounds (Karbowska 2016). Humans may be exposed to thallium by ingestion, inhalation, or dermal absorption (EPA 1980, 1988; Ewers 1988). However, the general population is exposed most frequently by ingestion of thallium-containing foods, especially fruits and green vegetables home-grown in thallium-contaminated soil. Inhalation of contaminated air near emission sources or in the workplace may also contribute to thallium exposure of some individuals.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

The domestic production of thallium ceased in 1981 (USGS 2023). Prior to this, thallium had been recovered as a byproduct from the flue dust and residuals that resulted from the smelting of zinc, copper, and lead ores through treatment by electrolysis, precipitation, or reduction (Sax and Lewis 1987; U.S. Bureau of Mines 1983, 1988). Based upon the estimated thallium content of zinc ores, U.S. mine production of thallium was 0.45 metric tons in 1986 and 1987 and 14.06 metric tons in the rest of the world (U.S. Bureau of Mines 1983, 1988). No data were located regarding the production of thallium acetate, thallium nitrate, thallium chloride, thallium sulfate, or thallium oxide.

Tables 5-1 and 5-2 summarize information on companies that reported the production, import, or use of thallium and thallium compounds, respectively, for the Toxics Release Inventory (TRI) in 2022 (TRI22 2024). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Thallium

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
CA	1	1,000	9,999	12
ID	1	10,000	99,999	12
TX	1	1,000	9,999	1, 4

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI22 2024 (Data are from 2022)

Table 5-2. Facilities that Produce, Process, or Use Thallium Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	2	0	99,999	1, 3, 4, 5, 12, 13, 14
AR	1	1,000	9,999	12
CO	1	10,000	99,999	1, 13
GA	1	1,000	9,999	1, 3, 4, 5, 13, 14
IN	4	1,000	99,999	1, 5, 8, 12, 14
KY	4	10,000	99,999	1, 5, 10, 12, 13
MT	1	10,000	99,999	1, 5, 12, 14
NV	4	1,000	999,999	1, 12, 13, 14
OH	1	100	999	12
PA	1	100	999	1, 5, 12
SC	2	10,000	999,999	1, 5, 12, 13, 14
TN	1	10,000	99,999	1, 5
TX	4	1,000	99,999	1, 2, 3, 4, 5, 9, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Thallium Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
UT	3	1,000	99,999	1, 3, 5, 9, 12, 13

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/uses:
1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI22 2024 (Data are from 2022)

Thallium is produced commercially in only a few nations as a byproduct recovered from flue dust in the roasting of copper, lead, and zinc ores. Since most producers withhold thallium production data, global production data are limited. In 2022, the U.S. Geological Survey (USGS) estimated that global production of thallium was approximately 10,000 kg (USGS 2023).

5.2.2 Import/Export

All thallium used in the United States is obtained from thallium reserves or is imported. In a USGS commodity summary from 2022, it was reported that since August of 2021, there were no imports of unwrought thallium metal and powder or thallium waste and scrap (USGS 2023). According to the same survey, no exports of thallium waste and scrap were reported through August 2021, but 359 kg were estimated for the year based on data from the prior year (USGS 2023).

5.2.3 Use

Thallium compounds have a variety of uses. The leading global uses for thallium are gamma radiation detection equipment, high-temperature superconductors, infrared optical materials, low-melting glasses, photoelectric cells, and radioisotopes (USGS 2024). Other thallium uses include as a catalyst in organic compound synthesis, in the manufacture of highly refractive glass, and as a component in high-density liquids for gravity separation of minerals (USGS 2023). Radioactive thallium^{201} is used in the diagnosis of coronary artery disease (Strauss et al. 2008). Intravenously administered radioactive thallium is used to measure blood flow through the heart during exercise and at rest. Thallium and compounds were once

used as a pesticide for control of rodents and insects, but the use of thallium as a pesticide was banned in 1972 (EPA 1985).

5.2.4 Disposal

Thallium is listed as a hazardous substance; therefore, disposal of waste thallium is controlled by a number of federal regulations, including land disposal restrictions (see Chapter 7). Land disposal restrictions were implemented by EPA in 1987. Prior to this time, disposal of pesticides had been to municipal and industrial landfills. Since thallium is relatively stable in the environment, it is possible that landfills, as well as other Superfund sites, contain thallium or thallium-containing products.

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2022). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022).

Thallium is released to environmental media from natural and anthropogenic sources. Natural geologic emissions include thallium-bearing, near-surface metal ore deposits or shallow subsurface mineralized rock formations. Anthropogenic sources include atmospheric emissions, solid wastes, and wastewaters derived mostly from sulfide ore and coal mining and processing (sometimes classified as geoanthropogenic sources), metal sulfide ore smelting, industrial and domestic bituminous (hard) coal and lignite combustion, waste incineration, petroleum refining, and cement manufacturing (Migaszewski and Gałuszka 2021).

5.3.1 Air

Estimated releases of 3 pounds (~0.001 metric tons) of thallium to the atmosphere from three domestic manufacturing and processing facilities in 2022, accounted for about 0.01% of the estimated total

environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-3.

Estimated releases of 3,226 pounds (~1.46 metric tons) of thallium compounds to the atmosphere from 29 domestic manufacturing and processing facilities in 2022, accounted for about 0.24% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-4.

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Thallium[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
CA	1	1	0	0	27,221	0	27,222	0	27,222
ID	1	1	0	0	11,661	0	11,662	0	11,662
TX	1	2	1	0	0	0	3	0	3
Total	3	3	1	0	38,883	0	38,887	0	38,887

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI22 2024 (Data are from 2022)

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Thallium Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	2	57	0	0	46,600	2,300	31,657	17,300	48,957
AR	1	0	0	0	9,205	0	9,205	0	9,205
CO	1	6	0	0	975	0	980	0	980
GA	1	20	0	0	9,200	0	9,220	0	9,220
IN	4	1,175	15	0	85,703	285	86,894	285	87,179
KY	4	85	7	0	86,502	0	86,594	0	86,594
MT	1	911	0	0	14,800	0	15,711	0	15,711
NV	3	8	0	26	794,017	0	794,051	0	794,051
OH	1	0	0	19,132	38	0	19,132	38	19,170
PA	1	8	0	0	0	0	8	0	8
SC	2	283	0	0	1,600	0	1,884	0	1,884
TN	1	21	0	0	12,000	0	12,021	0	12,021
TX	4	621	1	0	147,650	0	148,270	2	148,272
UT	3	31	500	0	91,011	220	86,599	5,163	91,762
Total	29	3,226	523	19,158	1,299,301	2,805	1,302,225	22,789	1,325,014

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI22 2024 (Data are from 2022)

Thallium is a highly volatile element at high temperatures and is released into the atmosphere in the form of fly ash, vapors, and liquids during cement manufacturing, metal sulfide ore smelting, or industrial and domestic coal combustion when facilities lack emission control devices (Migaszewski and Gałuszka 2021). Thallium emissions in the United States were estimated at 140 tons/year each from coal-burning power plants and from iron and steel production (Ewers 1988; Schoer 1984). The global annual release of

thallium from different pollution sources into the environment is estimated as 2,000–5,000 metric tons (Migaszewski and Gałuszka 2021). Karbowska (2016) also reported annual anthropogenic releases of thallium as 5,000 metric tons.

5.3.2 Water

Estimated releases of 1 pound (~0.0005 metric tons) of thallium to surface water from three domestic manufacturing and processing facilities in 2022, accounted for about 0.003% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI22 2024). These releases are summarized in Table 5-3.

Estimated releases of 523 pounds (~0.24 metric tons) of thallium compounds to surface water from 29 domestic manufacturing and processing facilities in 2022, accounted for about 0.04% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI22 2024). These releases are summarized in Table 5-4.

The major sources of thallium release to water are from the industrial combustion of coal and the cement and mining industries. Past concentrations of thallium in waste waters from these industries contained up to 2,400 µg/L (WHO 1996). In 2014, concentrations of thallium above the recommended reference value were measured in some parts of the drinking water distribution system in Tuscany, Italy, with values as high as 79.5 µg/L. The source of the contamination was a spring adjacent to an abandoned mining site (Nuvolone et al. 2021).

5.3.3 Soil

Estimated releases of 38,883 pounds (~17.64 metric tons) of thallium to soil from three domestic manufacturing and processing facilities in 2022, accounted for about 99% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). No thallium was released via underground injection (TRI22 2024). These releases are summarized in Table 5-3.

Estimated releases of 1,299,301 pounds (~589.35 metric tons) of thallium compounds to soil from 29 domestic manufacturing and processing facilities in 2022, accounted for about 98% of the estimated

total environmental releases from facilities required to report to the TRI (TRI22 2024). An additional 19,158 pounds (~8.69 metric tons), constituting about 1.4% of the total environmental emissions, were released via underground injection (TRI22 2024). These releases are summarized in Table 5-4.

Thallium releases to soil are mainly solid wastes from coal combustion and smelting operations (Ewers 1988). Although direct soil releases are likely to be small, since thallium-containing wastes are subject to EPA land disposal restrictions, atmospheric thallium pollution may contribute to soil contamination in the vicinity of thallium emission sources (Brockhaus et al. 1981). It should be noted that land disposal restrictions were implemented by EPA in 1987. Prior to this time, disposal of pesticides had been to municipal and industrial landfills. Since thallium is relatively stable in the environment, it is possible that landfills, as well other Superfund sites, contain thallium or thallium-containing products.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. Thallium is a nonvolatile heavy metal, and if released to the atmosphere by anthropogenic sources, may exist as an oxide (thallium oxide), hydroxide (TlOH), sulfate (thallium sulfate), or as the sulfide Tl_2S (EPA 1988). These thallium compounds are not volatile (EPA 1983; Lide 2005). It has been speculated that thallium sulfate and TlOH will partition into water vapor (such as clouds and raindrops) because they are soluble in water; thus, precipitation may remove these forms of thallium from the atmosphere (EPA 1988). Thallium oxides are less soluble in water and may be subject to only atmospheric dispersion and gravitational settling; no corroborative information was located. The atmospheric half-life of suspended thallium particles is unknown.

Water. Thallium will predominantly exist in water as a monovalent ion (thallium+); thallium may be trivalent ($T1^{3+}$) in very oxidizing water (EPA 1979; Lin and Nriagu 1998). Tl^+ forms complexes in solution with halogens, oxygen, and sulfur (Lin and Nriagu 1998). Thallium may precipitate from water as solid mineral phases. However, thallium chloride, sulfate, carbonate, bromide, and hydroxide are very soluble in water (Lin and Nriagu 1998). For example, the solubility of thallium sulfate at 20°C is 46 g/L (Lin and Nriagu 1998). In extremely reducing water, thallium may precipitate as a sulfide (Tl_2S), and in oxidizing water, $T1^{3+}$ may be removed from solution by the formation of $Tl(OH)_3$ (Lin and Nriagu 1998). Stephenson and Lester (1987a, 1987b) postulated that the partial removal of thallium from water was the result of precipitation of unknown solids during the treatment of sewage sludge.

Sediment and Soil. Thallium may partition from water to soils and sediments. Mathis and Kevern (1975) presented indirect evidence that thallium was adsorbed by lake sediments. Furthermore, thallium may be adsorbed by micaceous clays in solution (Frantz and Carlson 1987). In a study that evaluated the adsorption of thallium for three soils, K_d values of 768.3, 809.4, and 760.3 were determined (Kim et al. 2016).

Other Media. Partition coefficients such as adsorption constants describe the tendency of a chemical to partition to solid phases from water. Adsorption constants for inorganic ions such as Tl^+ cannot be predicted *a priori* but must be measured for each adsorbent. Thallium adsorption data in Magorian et al. (1974) for a hectorite clay (a rare montmorillonite clay mineral) at pH 8.1 suggest that an adsorption constant for this specific system may be approximately 19 L/g. No other information on the adsorption of thallium by earth materials was located.

Thallium may be bioconcentrated by organisms from water. A bioconcentration factor (BCF) relates the concentration of a chemical in the tissues of aquatic animals or plants to the concentration of the chemical in the water in which they live. Experimentally measured BCF values have been reported: 18.2 for clams and 11.7 for mussels (Zitko and Carson 1975). More recent data from Lin et al. (2001) measured a BCF of 10,000 in lake trout in Lake Michigan, significantly higher than an experimentally determined BCF of 27–1,430 in juvenile Atlantic salmon (Lin et al. 2001; Zitko et al. 1975). The maximum BCF for bluegill sunfish was 34 in the study of Barrows et al. (1978). Thallium is absorbed by plants from soil and thereby enters the terrestrial food chain (Ewers 1988; Sharma et al. 1986). Cataldo and Wildung (1983) demonstrated that thallium could be absorbed by the roots of higher plants from the rhizosphere.

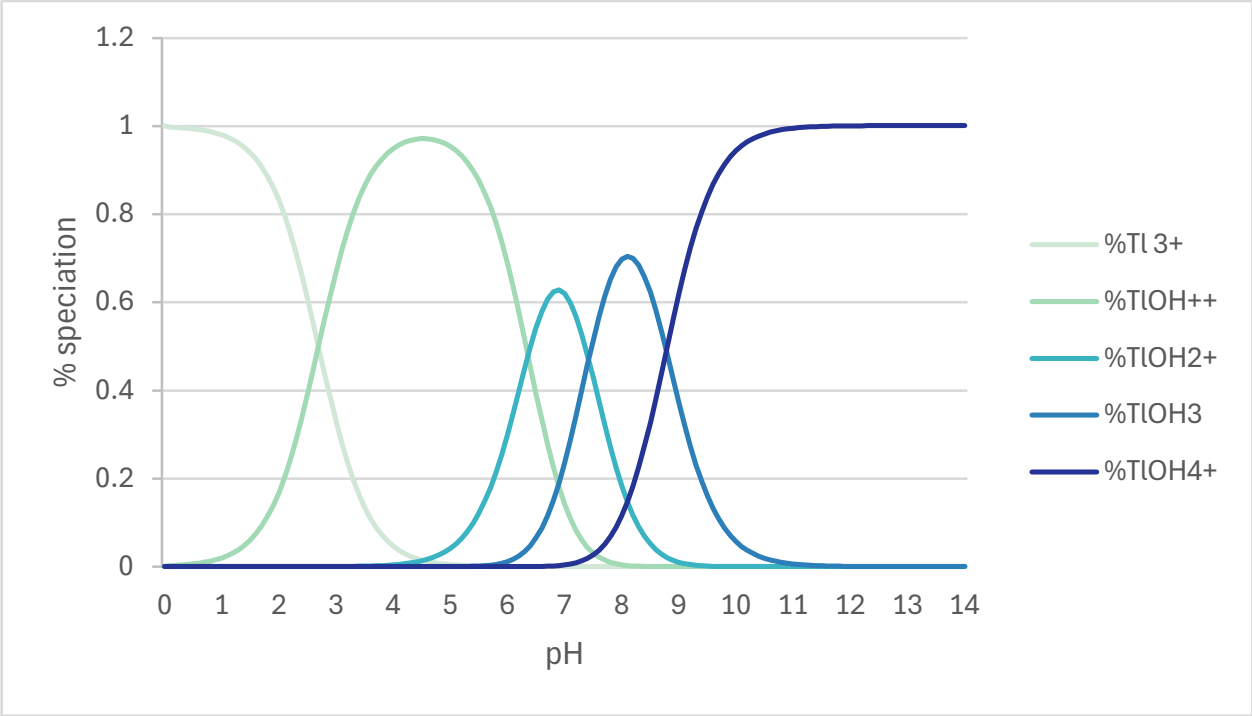
5.4.2 Transformation and Degradation

Air. Metallic thallium oxidizes slowly in air (O'Neil 2001), and thallous chloride is photosensitive (Cotton and Wilkinson 1980). However, there was no evidence that thallium is transformed significantly by photochemical reactions in the atmosphere (EPA 1979).

Water. The hydrolysis of thallium is an important acid-base reaction for the generation of hydroxy complexes in the aqueous environment. At pH <7, thallium III was converted to $Tl(OH)^{2+}$, to $Tl(OH)_3$ at pH 7.4–8.8, and $Tl(OH)_4^-$ at pH 8.8 (Lin and Nriagu 1998); see Figure 5-2. The oxidation state of thallium in water is dependent upon the redox potential. In strongly reducing conditions, it is typically in

the monovalent form; however, it can transform to the trivalent form under oxidizing and alkaline conditions.

Figure 5-2. Thallium III Speciation Curve



Source: Created in Excel using data from Lin and Nriagu (1998).

In natural waters at pH 7, thallium (I) is the predominant species (Kaplan and Mattigod 1998). Speciation calculations for thallium (I) in natural waters are discussed in Kaplan and Mattigod (1998). In seawater, 52% of total thallium (I) would exist in free ionic form, 36% would be complexed with chloride, and 11% would be complexed with sulfate ligands. Under typical pH conditions found in groundwater, river water, and eutrophic lake water, free thallium (I) exists predominantly in free ionic form (90.4% in groundwater, 82.7% in river water, and 76.8% in eutrophic lake water). In highly acidic bog water, only 32.4% of thallium (I) exists in free ionic form, with the remaining 67.6% bound to organic species. Based on these data, bound thallium (I) will predominate in waters with low pH and high levels of dissolved inorganic/ organic ligands.

Sediment and Soil. EPA (1979) concluded that there was no evidence that thallium is biotransformed in the environment. No other information was located.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to thallium depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of thallium in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on thallium levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-5 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-6.

Table 5-5. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air (nmol/m^3)	0.04	Karbowska 2016
Drinking water (ppb)	0.014	EPA 1994
Surface water and groundwater (ppb)	0.014	EPA 1994
Soil (ppb)	0.014	EPA 1994
Sediment (ppb)	0.014	EPA 1994
Whole blood (ppb)	0.037	Karbowska 2016

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-6. Summary of Environmental Levels of Thallium

Media	Low	High	For more information
Outdoor air (ppbv)	0.02	15.4	Section 5.5.1
Indoor air (ppbv)	0.02	22	Section 5.5.1
Surface water (ppb)	0.014	1,100	Section 5.5.2
Ground water (ppb)	0.014	3,810	Section 5.5.2
Drinking water (ppb)	0.014	79.5	Section 5.5.2
Ocean water (pg/L	0.014	14	Section 5.5.2
Food (ppb)	2	338,000	Section 5.5.4
Soil		171,000	Section 5.5.2

Detections of thallium in air, water, and soil at NPL sites are summarized in Table 5-7.

Table 5-7. Thallium Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	11	12.5	10.2	118	70
Soil (ppb)	3,810	5,960	9.33	142	80
Air (ppbv)	0.0065	0.0082	8.95	5	4

[a]Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

There are limited U.S. air monitoring data for thallium. The following data are 30-40 years old and may not be representative of current thallium levels. In six U.S. cities, the thallium concentrations ranged from 0.02 to 0.1 ng/m^3, with a typical concentration of 0.04 ng/m^3 (EPA 1980, 1988). Concentrations of thallium in Chadron, Nebraska reportedly ranged from 0.04 to 0.48 ng/m^3 (EPA 1980, 1988), and geometric mean concentrations measured during 1985–1986 in Genoa, Italy were about 0.015 µg/m^3 (Valerio et al. 1988). The estimated thallium concentration near a coal-burning power plant was 0.7 µg/m^3 (EPA 1988).

Some more recent monitoring data are available from China. Air particulate thallium was measured in three large cities and four remote locations with values of 2.52–15.4 ppbv ($PM_{2.5}$), 1.82–14.4 ppbv (PM_{10}) in cities and 1.52–2.12 ppb ($PM_{2.5}$) and 1.37–2.10 ppbv (PM_{10}) in remote locations (Belzile and Chen 2017).

Thallium levels were measured in workplace air in the past. Marcus (1985) reported maximum thallium levels in workplace air at 0.014 and 0.022 mg/m^3 during machining and alloying operations, respectively, of a magnesium alloy used in batteries at a plant in England. Air samples in two cement plants and two foundries in Italy had thallium concentrations of <1 µg /m^3 (Apostoli et al. 1988).

5.5.2 Water

The Water Quality Portal (WQP) is a source of discrete water-quality data in the United States and beyond. This cooperative service integrates publicly available water-quality data from the USGS, EPA, and over 400 state, federal, tribal, and local agencies. Analysis of compiled data from the WQP that spans 4 decades (1981–2023) indicates that thallium is a common surface water pollutant. Of 446,053 samples analyzed, thallium was detected in 115,741 (25.9% of samples). Of those 115,741 samples, only 2312 had values >10 µg/L. The highest value for sediment was 171,000 ppb, the highest value for groundwater was 3810 ppb, and the highest value for surface water was 1,100 ppb (WQP 2024).

Since thallium is a naturally occurring element, it may be present in ambient waters in trace amounts. However, monitoring data indicate elevated thallium concentrations near industrial and commercial sources and hazardous waste sites. The USGS conducted groundwater monitoring studies for radon and trace minerals from 1992 to 2003 on 51 of the nation's river basins and aquifers (USGS 2011). For 867 samples tested, thallium levels were all <1 ppb. Thallium and arsenic levels were monitored in groundwater wells from 1994 to 1999 at the Charleston Naval Complex located in North Charleston, South Carolina (USGS 2002). Mean thallium concentrations in water from all wells were <1.6–32.6 ppb in water samples from the upper surficial aquifer and <1.6–67.7 ppb in water samples from the lower surficial aquifer. Mean thallium concentrations ≥10 ppb were present in water samples from 21 of 604 wells.

The National tap water database indicates that thallium has been detected in tap water in >30 states (EWG 2019). Drinking water concentrations have been reported as high as 7.2 ng/mL (Harrington et al. 2022). Thallium was detected in 10% of urban stormwater runoff samples at concentrations of 1–14 µg/L (Cole et al. 1984). Thallium has been measured in seawater at 10–20 ng/L (Migaszewski and Gałuszka 2021; Sharma et al. 1986). Contaminated waters in Michigan contained 21 and 2,621 ng/L thallium. Levels of dissolved thallium in the Great Lakes ranged from 1.2 to 14.2 ng/L, with the lowest levels detected in Lake Superior and the highest levels detected in Lake Michigan (Cheam 2001).

5.5.3 Sediment and Soil

Thallium naturally occurs in the Earth's crust and is likely to be present in soils and sediments. The USGS reported thallium levels in U.S. soils (upper 5 cm) ranging of ~0.05–5 ppm, with a median value of about 0.5 ppm (USGS 2024); however, it exists mostly in association with potassium minerals in clays, granites, and soils. Thallium levels in U.S. soils tend to be lowest in the southeast (North Carolina, South Carolina, Georgia, Florida, and Alabama), while the highest levels tend to occur in western Pennsylvania, Ohio, and various locations in the western United States (USGS 2014). The limited data available indicate that soil thallium levels may be increased near thallium-emitting industrial sources and at hazardous waste sites. In the 1980s, measured thallium concentrations in lake sediments ranged from 0.13–0.27 µg/g in four remote Rocky Mountain lakes (Heit et al. 1984) to 2.1–23.1 mg/kg (mean value 13.1 mg/kg) in a Michigan lake reportedly polluted by airborne particulate matter (EPA 1988). Up to 5 mg/kg thallium was reported in stream sediments near metal industry runoff areas (Wallwork-Barber et al. 1985). Thallium concentrations in marine sediments were measured at approximately 0.08–5 mg/kg (Migaszewski and Gałuszka 2021).

5.5.4 Other Media

In the latest U.S. Food and Drug Administration (FDA) Total Diet Study (TDS) (fiscal years 2018–2020), thallium was only tested for in bottled water/spring water and it was not detected in any of the 27 samples tested (FDA 2022). The TDS monitors levels of chemicals such as pesticides, contaminants, and nutrients in foods consumed by the U.S. general population. The TDS collects commercially available regional foods in each of six U.S. regions (West, North Central, Northeast, Mid-Atlantic, Southeast, and Southwest).

Thallium has been found to accumulate by food crops, including green cabbage, rapeseed, and brassicaceous plants. In an experiment in which 12 commonly grown food crops were grown in soil containing 0.7 mg thallium/kg, the following thallium levels were detected: beetroot 8.75 mg/kg; green cabbage 7.85 mg/kg; *Iberis intermedia* 60.9 mg/kg; lettuce 3.1 mg/kg; onion 1.42 mg/kg; pea 1.82 mg/kg; radish 10.4 mg/kg; spinach 15.9 mg/kg; tomato 0.53 mg/kg; turnip 7.8 mg/kg; and watercress 84.4 mg/kg (LaCoste et al. 2001).

A study of lake trout from Lake Michigan reported thallium levels ranging from 9.8 to 496.9 ng/g, with an average concentration of 140.8 ng/g (Lin et al. 2001).

In a survey of Italian populations, thallium levels were measured in different foods with values as follows: cereals and cereal products, 0.055 mg/kg; legumes, 0.256 mg/kg; potatoes 0.002 mg/kg; fresh fruits; 0.046 mg/kg; and dry fruits, nuts, and seeds, 0.648 mg/kg (Doulgeridou et al. 2020). In a thallium-rich sulfide mineralization area in China, the following levels were found: green cabbage, 338 mg/kg; carrot, 22.1 mg/kg; and shelled rice, 2.4 mg/kg (Doulgeridou et al. 2020).

Data on thallium content of specific foods grown and consumed in the United States were not located. A 1980s study of the thallium content of food in the United Kingdom reported levels of thallium in meat, fish, fats, and green vegetables (Sherlock and Smart 1986).

5.6 GENERAL POPULATION EXPOSURE

Human exposure to thallium may occur by inhalation, ingestion, or dermal absorption. Recent data on the potential for general population exposure to thallium are limited. In the 1980s, the frequent source of exposure for the general population was ingestion of thallium-containing foods (EPA 1980, 1988; Ewers 1988). From the very limited data available, EPA estimated daily intakes for the general adult population from drinking water, air, and food of ≤6 µg/day (EPA 1980). A study from the United Kingdom also suggested that dietary intake from foods, particularly green vegetables, is the primary route of human exposure (Sherlock and Smart 1986). The same study from 1986 estimated 2 µg intake from water, 3.4 ng intake from air, and 5 µg intake from food. A more recent study estimated a daily intake in Northern Italy of 0.53 µg thallium/day, mostly derived from vegetables (mainly cabbage and root vegetables), meat, cereals, and fruit (particularly citrus fruits) (Filippini et al. 2020).

Urinary thallium levels are considered the most reliable indicator of thallium exposure. The geometric mean and selected percentiles of urinary levels of thallium for the general U.S. general population for select age and demographic groups from the NHANES are presented in Tables 5-8 and 5-9 (CDC 2023). The urinary thallium geometric mean levels for the most recent survey year (2017–2018) ranged from 0.154 to 0.180 µg/L for the different sex, age, and ethnicity groups and the 95th percentile levels rarely exceeded 0.5 µg/L (CDC 2023). The urinary thallium levels have remained fairly stable over time (1999–2000 to 2017–2018).

Table 5-8. Urinary Thallium Concentrations (in µg/L) in the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

Survey years	Geometric mean (95% confidence interval)[a]	Percentiles (95% confidence interval)[a]				Sample size
		50th	75th	90th	95th	
Total						
1999–2000	0.176 (0.162–0.192)	0.200 (0.180–0.220)	0.290 (0.270–0.330)	0.400 (0.370–0.420)	0.450 (0.430–0.480)	2,413
2001–2002	0.165 (0.154–0.177)	0.190 (0.180–0.200)	0.280 (0.260–0.290)	0.370 (0.350–0.390)	0.440 (0.410–0.470)	2,653
2003–2004	0.155 (0.145–0.165)	0.170 (0.160–0.180)	0.270 (0.250–0.290)	0.370 (0.340–0.400)	0.440 (0.410–0.490)	2,558
2005–2006	0.158 (0.151–0.165)	0.180 (0.170–0.190)	0.270 (0.260–0.280)	0.360 (0.350–0.390)	0.430 (0.410–0.460)	2,576
2007–2008	0.146 (0.139–0.153)	0.160 (0.150–0.170)	0.250 (0.230–0.260)	0.330 (0.320–0.360)	0.400 (0.390–0.420)	2,627
2009–2010	0.144 (0.137–0.152)	0.160 (0.150–0.170)	0.240 (0.230–0.250)	0.340 (0.310–0.360)	0.410 (0.380–0.440)	2,848
2011–2012	0.149 (0.138–0.160)	0.157 (0.144–0.169)	0.255 (0.232–0.278)	0.361 (0.334–0.377)	0.434 (0.379–0.521)	2,504
2013–2014	0.141 (0.132–0.150)	0.154 (0.139–0.163)	0.248 (0.228–0.266)	0.349 (0.338–0.370)	0.421 (0.414–0.438)	2,664
2015–2016	0.153 (0.143–0.163)	0.161 (0.149–0.177)	0.255 (0.234–0.275)	0.362 (0.330–0.385)	0.435 (0.403–0.466)	3,061
2017–2018	0.164 (0.155–0.174)	0.177 (0.165–0.187)	0.271 (0.254–0.287)	0.393 (0.366–0.421)	0.473 (0.436–0.509)	2,808
Age group[b]						
3–5 years						
2015–2016	0.150 (0.137–0.163)	0.159 (0.142–0.178)	0.251 (0.218–0.275)	0.347 (0.315–0.388)	0.432 (0.353–0.500)	486
2017–2018	0.174 (0.154–0.198)	0.183 (0.153–0.220)	0.289 (0.251–0.324)	0.389 (0.353–0.430)	0.463 (0.398–0.483)	403
6–11 years						
1999–2000	0.201 (0.167–0.243)	0.210 (0.150–0.280)	0.310 (0.250–0.350)	0.410 (0.330–0.450)	0.450 (0.350–0.590)	336
2001–2002	0.172 (0.147–0.202)	0.200 (0.160–0.220)	0.290 (0.230–0.330)	0.350 (0.340–0.370)	0.390 (0.360–0.430)	362
2003–2004	0.191 (0.170–0.215)	0.190 (0.170–0.230)	0.300 (0.250–0.370)	0.430 (0.360–0.500)	0.510 (0.430–0.690)	290
2005–2006	0.174 (0.158–0.192)	0.190 (0.170–0.210)	0.280 (0.250–0.300)	0.380 (0.320–0.430)	0.430 (0.400–0.480)	355
2007–2008	0.166 (0.150–0.185)	0.170 (0.150–0.200)	0.250 (0.230–0.270)	0.350 (0.310–0.410)	0.420 (0.360–0.470)	394
2009–2010	0.161 (0.147–0.176)	0.170 (0.150–0.200)	0.280 (0.230–0.310)	0.360 (0.330–0.410)	0.440 (0.400–0.460)	378
2011–2012	0.157 (0.143–0.172)	0.157 (0.136–0.195)	0.272 (0.232–0.308)	0.365 (0.330–0.474)	0.509 (0.372–0.629)	399
2013–2014	0.149 (0.131–0.170)	0.163 (0.146–0.173)	0.259 (0.221–0.282)	0.364 (0.331–0.400)	0.438 (0.367–0.577)	402
2015–2016	0.168 (0.151–0.186)	0.172 (0.150–0.209)	0.276 (0.234–0.306)	0.363 (0.314–0.420)	0.452 (0.369–0.574)	379
2017–2018	0.172 (0.154–0.193)	0.178 (0.158–0.202)	0.299 (0.256–0.322)	0.394 (0.361–0.493)	0.497 (0.405–0.522)	333

Table 5-8. Urinary Thallium Concentrations (in µg/L) in the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

Survey years	Geometric mean (95% confidence interval)[a]	Percentiles (95% confidence interval)[a]				Sample size
		50th	75th	90th	95th	
12–19 years						
1999–2000	0.202 (0.181–0.225)	0.220 (0.200–0.240)	0.300 (0.270–0.340)	0.410 (0.390–0.430)	0.470 (0.430–0.510)	697
2001–2002	0.200 (0.182–0.220)	0.220 (0.190–0.250)	0.310 (0.290–0.320)	0.370 (0.350–0.420)	0.470 (0.400–0.500)	746
2003–2004	0.201 (0.185–0.218)	0.220 (0.210–0.240)	0.310 (0.290–0.320)	0.410 (0.360–0.470)	0.500 (0.420–0.560)	725
2005–2006	0.182 (0.165–0.200)	0.210 (0.190–0.230)	0.290 (0.270–0.310)	0.370 (0.350–0.400)	0.430 (0.390–0.480)	701
2007–2008	0.172 (0.155–0.190)	0.180 (0.160–0.210)	0.270 (0.230–0.300)	0.330 (0.310–0.350)	0.390 (0.340–0.420)	376
2009–2010	0.150 (0.137–0.163)	0.160 (0.150–0.180)	0.250 (0.240–0.270)	0.340 (0.290–0.380)	0.400 (0.350–0.430)	451
2011–2012	0.155 (0.131–0.184)	0.169 (0.141–0.196)	0.288 (0.240–0.301)	0.376 (0.320–0.403)	0.447 (0.387–0.545)	390
2013–2014	0.160 (0.136–0.188)	0.170 (0.154–0.191)	0.274 (0.224–0.334)	0.400 (0.324–0.507)	0.495 (0.384–0.562)	451
2015–2016	0.168 (0.150–0.187)	0.186 (0.163–0.203)	0.248 (0.221–0.300)	0.368 (0.295–0.428)	0.437 (0.368–0.515)	402
2017–2018	0.176 (0.160–0.194)	0.192 (0.169–0.221)	0.289 (0.253–0.315)	0.388 (0.332–0.428)	0.442 (0.383–0.551)	364
≥20 years						
1999–2000	0.170 (0.157–0.183)	0.190 (0.180–0.210)	0.290 (0.260–0.320)	0.400 (0.370–0.420)	0.450 (0.420–0.480)	1,380
2001–2002	0.159 (0.147–0.173)	0.190 (0.170–0.200)	0.270 (0.250–0.290)	0.380 (0.350–0.400)	0.440 (0.410–0.490)	1,545
2003–2004	0.145 (0.134–0.156)	0.160 (0.150–0.170)	0.250 (0.240–0.270)	0.360 (0.330–0.390)	0.420 (0.390–0.460)	1,543
2005–2006	0.152 (0.144–0.161)	0.170 (0.160–0.180)	0.260 (0.240–0.270)	0.360 (0.340–0.390)	0.440 (0.400–0.470)	1,520
2007–2008	0.140 (0.133–0.148)	0.150 (0.140–0.160)	0.240 (0.230–0.250)	0.330 (0.310–0.360)	0.400 (0.380–0.440)	1,857
2009–2010	0.142 (0.133–0.150)	0.160 (0.150–0.170)	0.240 (0.220–0.250)	0.330 (0.310–0.360)	0.410 (0.370–0.440)	2,019
2011–2012	0.147 (0.136–0.159)	0.155 (0.142–0.167)	0.247 (0.223–0.274)	0.356 (0.324–0.377)	0.431 (0.375–0.520)	1,715
2013–2014	0.137 (0.129–0.146)	0.150 (0.136–0.161)	0.241 (0.222–0.262)	0.340 (0.326–0.364)	0.417 (0.398–0.426)	1,811
2015–2016	0.149 (0.140–0.160)	0.157 (0.144–0.173)	0.255 (0.234–0.268)	0.358 (0.328–0.379)	0.433 (0.395–0.464)	1,794
2017–2018	0.161 (0.151–0.172)	0.174 (0.162–0.185)	0.263 (0.247–0.280)	0.395 (0.364–0.421)	0.473 (0.434–0.510)	1,708
Gender						
Males						
1999–2000	0.197 (0.179–0.217)	0.220 (0.200–0.240)	0.320 (0.280–0.350)	0.400 (0.370–0.440)	0.450 (0.420–0.520)	1,200
2001–2002	0.184 (0.173–0.196)	0.210 (0.200–0.230)	0.290 (0.280–0.300)	0.380 (0.360–0.400)	0.430 (0.400–0.470)	1,313
2003–2004	0.167 (0.156–0.178)	0.190 (0.180–0.200)	0.280 (0.260–0.300)	0.370 (0.340–0.400)	0.430 (0.400–0.480)	1,281
2005–2006	0.171 (0.163–0.179)	0.190 (0.180–0.200)	0.270 (0.260–0.280)	0.370 (0.360–0.390)	0.430 (0.410–0.470)	1,271

Table 5-8. Urinary Thallium Concentrations (in µg/L) in the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

Survey years	Geometric mean (95% confidence interval)[a]	Percentiles (95% confidence interval)[a]				Sample size
		50th	75th	90th	95th	
2007–2008	0.154 (0.148–0.161)	0.170 (0.160–0.180)	0.250 (0.240–0.270)	0.340 (0.320–0.360)	0.390 (0.380–0.440)	1,327
2009–2010	0.152 (0.140–0.164)	0.170 (0.150–0.180)	0.250 (0.240–0.270)	0.330 (0.310–0.360)	0.410 (0.360–0.440)	1,398
2011–2012	0.165 (0.150–0.181)	0.173 (0.151–0.195)	0.272 (0.239–0.301)	0.369 (0.343–0.387)	0.431 (0.381–0.524)	1,262
2013–2014	0.147 (0.136–0.159)	0.161 (0.151–0.171)	0.258 (0.231–0.274)	0.356 (0.325–0.381)	0.422 (0.400–0.455)	1,318
2015–2016	0.163 (0.155–0.172)	0.181 (0.168–0.195)	0.267 (0.248–0.288)	0.366 (0.334–0.394)	0.440 (0.394–0.477)	1,524
2017–2018	0.175 (0.164–0.187)	0.185 (0.172–0.198)	0.271 (0.253–0.283)	0.387 (0.328–0.427)	0.465 (0.406–0.545)	1,381
Females						
1999–2000	0.159 (0.145–0.175)	0.180 (0.150–0.200)	0.270 (0.250–0.300)	0.390 (0.350–0.420)	0.460 (0.410–0.490)	1,213
2001–2002	0.149 (0.137–0.163)	0.160 (0.150–0.180)	0.260 (0.230–0.290)	0.370 (0.330–0.400)	0.440 (0.400–0.500)	1,340
2003–2004	0.144 (0.133–0.156)	0.160 (0.140–0.170)	0.250 (0.230–0.280)	0.370 (0.330–0.410)	0.450 (0.410–0.510)	1,277
2005–2006	0.146 (0.138–0.155)	0.160 (0.150–0.180)	0.260 (0.240–0.270)	0.360 (0.350–0.380)	0.440 (0.400–0.460)	1,305
2007–2008	0.139 (0.129–0.148)	0.150 (0.130–0.160)	0.240 (0.220–0.260)	0.330 (0.300–0.390)	0.410 (0.380–0.430)	1,300
2009–2010	0.137 (0.129–0.146)	0.150 (0.140–0.160)	0.230 (0.210–0.250)	0.340 (0.310–0.360)	0.410 (0.380–0.450)	1,450
2011–2012	0.135 (0.122–0.148)	0.141 (0.131–0.155)	0.237 (0.208–0.260)	0.348 (0.304–0.376)	0.434 (0.367–0.522)	1,242
2013–2014	0.135 (0.125–0.145)	0.143 (0.127–0.160)	0.241 (0.214–0.262)	0.348 (0.328–0.373)	0.421 (0.398–0.443)	1,346
2015–2016	0.143 (0.131–0.156)	0.146 (0.132–0.163)	0.236 (0.208–0.262)	0.352 (0.311–0.385)	0.432 (0.388–0.470)	1,537
2017–2018	0.154 (0.139–0.170)	0.165 (0.148–0.184)	0.272 (0.245–0.302)	0.398 (0.364–0.447)	0.486 (0.428–0.521)	1,427
Race						
Mexican American						
1999–2000	0.172 (0.150–0.196)	0.200 (0.160–0.230)	0.270 (0.250–0.300)	0.370 (0.320–0.420)	0.450 (0.370–0.520)	861
2001–2002	0.160 (0.148–0.173)	0.180 (0.160–0.200)	0.260 (0.240–0.270)	0.340 (0.310–0.360)	0.400 (0.350–0.440)	675
2003–2004	0.171 (0.160–0.183)	0.200 (0.170–0.220)	0.280 (0.260–0.310)	0.360 (0.340–0.420)	0.450 (0.390–0.480)	618
2005–2006	0.158 (0.149–0.167)	0.180 (0.170–0.190)	0.250 (0.240–0.270)	0.330 (0.300–0.360)	0.400 (0.360–0.440)	652
2007–2008	0.151 (0.140–0.164)	0.170 (0.150–0.180)	0.250 (0.220–0.270)	0.330 (0.310–0.360)	0.380 (0.350–0.390)	515
2009–2010	0.147 (0.139–0.155)	0.160 (0.150–0.180)	0.240 (0.210–0.260)	0.310 (0.290–0.320)	0.390 (0.320–0.430)	613
2011–2012	0.142 (0.135–0.150)	0.162 (0.143–0.174)	0.231 (0.210–0.248)	0.298 (0.268–0.321)	0.344 (0.306–0.381)	317
2013–2014	0.139 (0.127–0.154)	0.157 (0.137–0.175)	0.247 (0.206–0.274)	0.324 (0.285–0.387)	0.414 (0.324–0.511)	453
2015–2016	0.162 (0.145–0.181)	0.180 (0.150–0.210)	0.270 (0.247–0.288)	0.349 (0.309–0.406)	0.419 (0.349–0.492)	585

Table 5-8. Urinary Thallium Concentrations (in µg/L) in the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

Survey years	Geometric mean (95% confidence interval)[a]	Percentiles (95% confidence interval)[a]				Sample size
		50th	75th	90th	95th	
2017–2018	0.165 (0.157–0.173)	0.178 (0.170–0.193)	0.261 (0.246–0.276)	0.374 (0.345–0.398)	0.466 (0.391–0.521)	435
Non-Hispanic Black						
1999–2000	0.217 (0.197–0.239)	0.230 (0.220–0.260)	0.350 (0.300–0.390)	0.450 (0.400–0.520)	0.550 (0.460–0.630)	561
2001–2002	0.202 (0.187–0.218)	0.220 (0.200–0.230)	0.300 (0.270–0.340)	0.410 (0.380–0.440)	0.520 (0.440–0.590)	657
2003–2004	0.185 (0.167–0.206)	0.190 (0.170–0.220)	0.290 (0.250–0.330)	0.410 (0.330–0.490)	0.490 (0.410–0.640)	723
2005–2006	0.188 (0.169–0.210)	0.210 (0.180–0.230)	0.300 (0.270–0.320)	0.390 (0.360–0.440)	0.500 (0.430–0.530)	692
2007–2008	0.171 (0.160–0.182)	0.180 (0.170–0.190)	0.270 (0.250–0.290)	0.350 (0.330–0.390)	0.430 (0.390–0.460)	589
2009–2010	0.162 (0.148–0.177)	0.180 (0.160–0.200)	0.270 (0.250–0.280)	0.350 (0.330–0.400)	0.450 (0.390–0.510)	544
2011–2012	0.176 (0.150–0.206)	0.184 (0.158–0.214)	0.294 (0.244–0.364)	0.431 (0.370–0.503)	0.524 (0.429–0.657)	669
2013–2014	0.172 (0.156–0.189)	0.190 (0.170–0.213)	0.271 (0.241–0.301)	0.356 (0.325–0.380)	0.415 (0.375–0.433)	581
2015–2016	0.170 (0.156–0.186)	0.183 (0.171–0.197)	0.279 (0.260–0.296)	0.364 (0.338–0.393)	0.443 (0.414–0.494)	671
2017–2018	0.179 (0.169–0.191)	0.201 (0.178–0.213)	0.280 (0.259–0.297)	0.378 (0.338–0.399)	0.438 (0.406–0.501)	639
Non-Hispanic White						
1999–2000	0.170 (0.153–0.188)	0.200 (0.170–0.220)	0.290 (0.260–0.330)	0.400 (0.360–0.420)	0.450 (0.420–0.480)	801
2001–2002	0.159 (0.147–0.172)	0.180 (0.170–0.200)	0.270 (0.250–0.290)	0.360 (0.330–0.390)	0.430 (0.390–0.460)	1,114
2003–2004	0.146 (0.135–0.158)	0.160 (0.150–0.170)	0.260 (0.240–0.280)	0.360 (0.330–0.380)	0.410 (0.380–0.460)	1,074
2005–2006	0.150 (0.140–0.160)	0.170 (0.160–0.180)	0.260 (0.240–0.270)	0.350 (0.320–0.380)	0.420 (0.390–0.450)	1,041
2007–2008	0.138 (0.130–0.147)	0.150 (0.130–0.160)	0.240 (0.220–0.260)	0.320 (0.300–0.360)	0.390 (0.350–0.440)	1,095
2009–2010	0.139 (0.130–0.149)	0.150 (0.140–0.170)	0.240 (0.210–0.250)	0.330 (0.300–0.360)	0.400 (0.360–0.430)	1,225
2011–2012	0.143 (0.133–0.155)	0.149 (0.135–0.166)	0.245 (0.218–0.277)	0.353 (0.322–0.372)	0.412 (0.367–0.522)	820
2013–2014	0.132 (0.120–0.145)	0.139 (0.121–0.161)	0.235 (0.203–0.265)	0.340 (0.318–0.370)	0.419 (0.392–0.440)	985
2015–2016	0.143 (0.132–0.155)	0.151 (0.139–0.166)	0.236 (0.209–0.259)	0.336 (0.298–0.379)	0.414 (0.369–0.459)	924
2017–2018	0.160 (0.146–0.175)	0.172 (0.159–0.186)	0.270 (0.238–0.295)	0.398 (0.338–0.456)	0.484 (0.412–0.551)	918

Table 5-8. Urinary Thallium Concentrations (in µg/L) in the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

Survey years	Geometric mean (95% confidence interval)[a]	Percentiles (95% confidence interval)[a]				Sample size
		50th	75th	90th	95th	
All Hispanic						
2011–2012	0.145 (0.134–0.157)	0.158 (0.148–0.169)	0.237 (0.219–0.257)	0.305 (0.289–0.340)	0.381 (0.326–0.438)	573
2013–2014	0.144 (0.130–0.160)	0.160 (0.138–0.178)	0.251 (0.220–0.272)	0.340 (0.291–0.382)	0.417 (0.365–0.473)	701
2015–2016	0.159 (0.148–0.170)	0.174 (0.157–0.197)	0.263 (0.248–0.280)	0.351 (0.319–0.394)	0.419 (0.388–0.466)	982
2017–2018	0.169 (0.161–0.178)	0.181 (0.171–0.194)	0.264 (0.252–0.282)	0.393 (0.372–0.441)	0.469 (0.436–0.556)	676
Non–Hispanic Asian						
2011–2012	0.177 (0.160–0.197)	0.183 (0.163–0.214)	0.292 (0.255–0.319)	0.417 (0.372–0.489)	0.541 (0.431–0.664)	353
2013–2014	0.154 (0.140–0.169)	0.159 (0.134–0.184)	0.268 (0.239–0.310)	0.414 (0.368–0.438)	0.502 (0.421–0.662)	292
2015–2016	0.190 (0.175–0.206)	0.213 (0.189–0.241)	0.348 (0.306–0.371)	0.483 (0.413–0.543)	0.551 (0.514–0.595)	332
2017–2018	0.180 (0.166–0.196)	0.198 (0.178–0.207)	0.299 (0.260–0.323)	0.438 (0.379–0.467)	0.511 (0.460–0.583)	365

[a]Limits of detection in µg/L (survey years) were: 0.020 (1999–2000), 0.020 (2001–2002), 0.020 (2003–2004), 0.015 (2005–2006), 0.015 (2007–2008), 0.015 (2009–2010), 0.020 (2011–2012), 0.018 (2013–2014), 0.018 (2015–2016), and 0.018 (2017–2018).
[b]Participants were ≥6 years old in survey years through 2014; beginning with survey years 2015–2016, participants included those ≥3 years old.

Source: CDC 2023

Table 5-9. Creatinine-Corrected Urinary Thallium Concentrations (in µg/g of Creatinine) in the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

Survey years	Geometric mean (95% confidence interval)	Percentiles (95% confidence interval)				Sample size
		50th	75th	90th	95th	
Total						
1999–2000	0.166 (0.159–0.173)	0.168 (0.162–0.176)	0.224 (0.217–0.233)	0.297 (0.273–0.319)	0.366 (0.338–0.387)	2,413
2001–2002	0.156 (0.151–0.162)	0.156 (0.148–0.164)	0.215 (0.208–0.222)	0.287 (0.278–0.300)	0.349 (0.337–0.365)	2,652
2003–2004	0.154 (0.149–0.158)	0.153 (0.146–0.160)	0.214 (0.203–0.222)	0.286 (0.274–0.304)	0.350 (0.328–0.369)	2,558
2005–2006	0.155 (0.149–0.162)	0.150 (0.140–0.160)	0.210 (0.200–0.220)	0.300 (0.290–0.320)	0.370 (0.350–0.390)	2,576
2007–2008	0.152 (0.147–0.158)	0.150 (0.140–0.160)	0.210 (0.200–0.220)	0.290 (0.280–0.310)	0.370 (0.350–0.380)	2,627
2009–2010	0.153 (0.145–0.162)	0.150 (0.140–0.160)	0.220 (0.200–0.230)	0.300 (0.280–0.320)	0.370 (0.350–0.400)	2,848
2011–2012	0.168 (0.157–0.180)	0.167 (0.156–0.178)	0.235 (0.216–0.253)	0.337 (0.310–0.365)	0.425 (0.369–0.497)	2,502
2013–2014	0.162 (0.155–0.171)	0.161 (0.151–0.169)	0.236 (0.228–0.245)	0.338 (0.321–0.351)	0.429 (0.405–0.444)	2,663
2015–2016	0.171 (0.163–0.181)	0.169 (0.158–0.180)	0.243 (0.226–0.270)	0.348 (0.321–0.384)	0.432 (0.402–0.471)	3,058
2017–2018	0.179 (0.170–0.189)	0.174 (0.167–0.183)	0.251 (0.238–0.266)	0.380 (0.339–0.407)	0.472 (0.445–0.521)	2,806
Age group[a]						
3–5 years						
2015–2016	0.344 (0.330–0.358)	0.342 (0.328–0.358)	0.474 (0.436–0.507)	0.643 (0.587–0.717)	0.850 (0.682–0.972)	485
2017–2018	0.360 (0.333–0.389)	0.368 (0.335–0.397)	0.500 (0.465–0.559)	0.660 (0.564–0.777)	0.793 (0.687–0.914)	403
6–11 years						
1999–2000	0.221 (0.197–0.248)	0.222 (0.196–0.236)	0.297 (0.229–0.356)	0.375 (0.318–0.469)	0.424 (0.356–0.600)	336
2001–2002	0.211 (0.198–0.226)	0.207 (0.198–0.221)	0.286 (0.260–0.321)	0.370 (0.333–0.402)	0.412 (0.389–0.456)	362
2003–2004	0.223 (0.208–0.238)	0.216 (0.198–0.229)	0.306 (0.280–0.346)	0.412 (0.346–0.458)	0.458 (0.400–0.532)	290
2005–2006	0.215 (0.200–0.231)	0.210 (0.190–0.250)	0.310 (0.270–0.320)	0.360 (0.320–0.410)	0.430 (0.360–0.510)	355
2007–2008	0.217 (0.201–0.234)	0.220 (0.210–0.240)	0.310 (0.270–0.340)	0.410 (0.370–0.440)	0.470 (0.410–0.540)	394
2009–2010	0.219 (0.199–0.241)	0.220 (0.200–0.260)	0.300 (0.280–0.340)	0.400 (0.350–0.440)	0.500 (0.390–0.600)	378
2011–2012	0.223 (0.209–0.238)	0.216 (0.200–0.241)	0.301 (0.275–0.336)	0.395 (0.371–0.440)	0.486 (0.422–0.568)	398
2013–2014	0.222 (0.199–0.249)	0.227 (0.215–0.255)	0.318 (0.279–0.360)	0.429 (0.386–0.458)	0.502 (0.457–0.537)	402
2015–2016	0.238 (0.223–0.253)	0.232 (0.216–0.257)	0.335 (0.312–0.359)	0.450 (0.418–0.496)	0.524 (0.485–0.593)	379
2017–2018	0.240 (0.223–0.259)	0.243 (0.227–0.268)	0.328 (0.293–0.363)	0.435 (0.391–0.459)	0.621 (0.446–0.645)	332

Table 5-9. Creatinine-Corrected Urinary Thallium Concentrations (in µg/g of Creatinine) in the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

Survey years	Geometric mean (95% confidence interval)	Percentiles (95% confidence interval)				Sample size
		50th	75th	90th	95th	
12–19 years						
1999–2000	0.153 (0.146–0.160)	0.154 (0.146–0.162)	0.205 (0.191–0.219)	0.258 (0.231–0.278)	0.321 (0.265–0.364)	697
2001–2002	0.143 (0.137–0.150)	0.145 (0.135–0.152)	0.196 (0.184–0.207)	0.272 (0.250–0.289)	0.312 (0.299–0.333)	746
2003–2004	0.143 (0.135–0.152)	0.146 (0.131–0.155)	0.194 (0.179–0.208)	0.254 (0.234–0.280)	0.304 (0.271–0.327)	725
2005–2006	0.140 (0.133–0.147)	0.140 (0.130–0.150)	0.190 (0.170–0.200)	0.240 (0.220–0.270)	0.290 (0.250–0.310)	701
2007–2008	0.134 (0.124–0.145)	0.140 (0.120–0.150)	0.190 (0.180–0.220)	0.260 (0.220–0.300)	0.300 (0.250–0.370)	376
2009–2010	0.140 (0.127–0.155)	0.140 (0.120–0.160)	0.190 (0.170–0.220)	0.260 (0.220–0.310)	0.310 (0.260–0.370)	451
2011–2012	0.149 (0.134–0.165)	0.147 (0.130–0.169)	0.200 (0.180–0.218)	0.276 (0.235–0.321)	0.339 (0.268–0.500)	390
2013–2014	0.145 (0.133–0.158)	0.141 (0.131–0.160)	0.213 (0.182–0.231)	0.276 (0.237–0.301)	0.315 (0.283–0.361)	451
2015–2016	0.157 (0.145–0.169)	0.161 (0.144–0.175)	0.222 (0.191–0.244)	0.290 (0.262–0.329)	0.351 (0.289–0.410)	402
2017–2018	0.159 (0.151–0.167)	0.158 (0.153–0.174)	0.221 (0.195–0.241)	0.282 (0.252–0.304)	0.312 (0.282–0.354)	364
≥20 years						
1999–2000	0.162 (0.153–0.171)	0.167 (0.155–0.176)	0.218 (0.207–0.230)	0.286 (0.271–0.300)	0.364 (0.325–0.389)	1,380
2001–2002	0.153 (0.147–0.159)	0.153 (0.144–0.161)	0.210 (0.200–0.217)	0.278 (0.263–0.293)	0.343 (0.313–0.362)	1,544
2003–2004	0.148 (0.144–0.153)	0.149 (0.141–0.156)	0.206 (0.192–0.215)	0.273 (0.258–0.289)	0.333 (0.306–0.353)	1,543
2005–2006	0.152 (0.145–0.159)	0.150 (0.140–0.160)	0.210 (0.200–0.210)	0.290 (0.270–0.310)	0.370 (0.350–0.400)	1,520
2007–2008	0.149 (0.143–0.156)	0.150 (0.140–0.160)	0.210 (0.200–0.220)	0.280 (0.270–0.300)	0.350 (0.330–0.380)	1,857
2009–2010	0.150 (0.142–0.157)	0.150 (0.140–0.160)	0.210 (0.200–0.220)	0.290 (0.270–0.320)	0.370 (0.330–0.400)	2,019
2011–2012	0.166 (0.155–0.179)	0.164 (0.154–0.175)	0.233 (0.212–0.250)	0.333 (0.298–0.367)	0.436 (0.365–0.510)	1,714
2013–2014	0.160 (0.153–0.168)	0.157 (0.148–0.165)	0.229 (0.222–0.241)	0.333 (0.313–0.352)	0.429 (0.394–0.457)	1,810
2015–2016	0.163 (0.153–0.174)	0.159 (0.148–0.173)	0.231 (0.207–0.256)	0.323 (0.288–0.362)	0.400 (0.358–0.444)	1,792
2017–2018	0.171 (0.160–0.182)	0.168 (0.159–0.178)	0.235 (0.218–0.254)	0.348 (0.314–0.388)	0.456 (0.386–0.516)	1,707
Gender						
Males						
1999–2000	0.154 (0.147–0.161)	0.156 (0.149–0.164)	0.202 (0.192–0.214)	0.269 (0.254–0.297)	0.338 (0.300–0.364)	1,200
2001–2002	0.146 (0.140–0.153)	0.148 (0.142–0.157)	0.192 (0.184–0.204)	0.260 (0.246–0.278)	0.307 (0.291–0.342)	1,312
2003–2004	0.140 (0.135–0.146)	0.142 (0.134–0.149)	0.188 (0.180–0.198)	0.264 (0.235–0.286)	0.317 (0.287–0.350)	1,281
2005–2006	0.140 (0.134–0.147)	0.140 (0.130–0.140)	0.190 (0.180–0.200)	0.270 (0.240–0.300)	0.320 (0.300–0.340)	1,271

Table 5-9. Creatinine-Corrected Urinary Thallium Concentrations (in µg/g of Creatinine) in the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

Survey years	Geometric mean (95% confidence interval)	Percentiles (95% confidence interval)				Sample size
		50th	75th	90th	95th	
2007–2008	0.138 (0.131–0.145)	0.130 (0.130–0.140)	0.190 (0.180–0.210)	0.270 (0.250–0.290)	0.330 (0.300–0.360)	1,327
2009–2010	0.138 (0.129–0.148)	0.130 (0.130–0.150)	0.190 (0.170–0.210)	0.270 (0.240–0.300)	0.330 (0.290–0.360)	1,398
2011–2012	0.154 (0.142–0.167)	0.155 (0.144–0.165)	0.211 (0.197–0.233)	0.292 (0.258–0.326)	0.353 (0.312–0.385)	1,261
2013–2014	0.147 (0.137–0.158)	0.141 (0.133–0.150)	0.206 (0.194–0.222)	0.295 (0.272–0.315)	0.368 (0.341–0.414)	1,317
2015–2016	0.155 (0.145–0.166)	0.150 (0.138–0.167)	0.220 (0.199–0.247)	0.322 (0.298–0.348)	0.396 (0.358–0.449)	1,524
2017–2018	0.163 (0.154–0.173)	0.157 (0.145–0.168)	0.230 (0.212–0.244)	0.353 (0.310–0.391)	0.433 (0.380–0.542)	1,380
Females						
1999–2000	0.178 (0.167–0.189)	0.182 (0.169–0.197)	0.244 (0.226–0.259)	0.317 (0.281–0.366)	0.380 (0.333–0.462)	1,213
2001–2002	0.167 (0.158–0.176)	0.167 (0.153–0.180)	0.233 (0.217–0.250)	0.313 (0.282–0.348)	0.378 (0.348–0.402)	1,340
2003–2004	0.167 (0.162–0.173)	0.166 (0.157–0.177)	0.235 (0.222–0.243)	0.313 (0.286–0.333)	0.368 (0.340–0.412)	1,277
2005–2006	0.171 (0.162–0.181)	0.170 (0.160–0.180)	0.230 (0.220–0.250)	0.330 (0.300–0.360)	0.430 (0.370–0.490)	1,305
2007–2008	0.167 (0.163–0.173)	0.170 (0.160–0.180)	0.230 (0.230–0.240)	0.320 (0.300–0.340)	0.390 (0.360–0.430)	1,300
2009–2010	0.170 (0.161–0.178)	0.170 (0.160–0.180)	0.230 (0.220–0.250)	0.340 (0.310–0.370)	0.420 (0.370–0.470)	1,450
2011–2012	0.183 (0.172–0.195)	0.180 (0.168–0.193)	0.261 (0.240–0.286)	0.382 (0.349–0.420)	0.480 (0.422–0.510)	1,241
2013–2014	0.179 (0.172–0.187)	0.180 (0.171–0.190)	0.264 (0.248–0.274)	0.374 (0.352–0.402)	0.439 (0.416–0.482)	1,346
2015–2016	0.188 (0.179–0.199)	0.187 (0.175–0.199)	0.265 (0.243–0.283)	0.379 (0.339–0.408)	0.458 (0.418–0.517)	1,534
2017–2018	0.195 (0.185–0.207)	0.191 (0.177–0.206)	0.268 (0.252–0.289)	0.400 (0.365–0.455)	0.504 (0.465–0.571)	1,426
Race						
Mexican American						
1999–2000	0.158 (0.147–0.170)	0.160 (0.148–0.176)	0.213 (0.200–0.237)	0.282 (0.266–0.304)	0.343 (0.306–0.389)	861
2001–2002	0.156 (0.145–0.169)	0.155 (0.145–0.167)	0.204 (0.191–0.221)	0.286 (0.250–0.317)	0.361 (0.301–0.424)	674
2003–2004	0.159 (0.148–0.170)	0.157 (0.143–0.172)	0.211 (0.187–0.241)	0.293 (0.273–0.324)	0.369 (0.326–0.422)	618
2005–2006	0.149 (0.139–0.158)	0.150 (0.140–0.160)	0.200 (0.180–0.210)	0.270 (0.240–0.290)	0.320 (0.280–0.370)	652
2007–2008	0.151 (0.143–0.160)	0.160 (0.130–0.170)	0.200 (0.190–0.220)	0.270 (0.250–0.280)	0.320 (0.290–0.370)	515
2009–2010	0.154 (0.141–0.167)	0.150 (0.140–0.170)	0.210 (0.180–0.230)	0.280 (0.250–0.330)	0.360 (0.310–0.430)	613
2011–2012	0.160 (0.150–0.170)	0.163 (0.141–0.175)	0.222 (0.198–0.245)	0.295 (0.276–0.326)	0.359 (0.302–0.440)	317
2013–2014	0.159 (0.151–0.168)	0.151 (0.142–0.162)	0.218 (0.194–0.230)	0.313 (0.282–0.350)	0.409 (0.350–0.457)	453
2015–2016	0.178 (0.165–0.192)	0.178 (0.158–0.199)	0.241 (0.217–0.278)	0.369 (0.316–0.403)	0.455 (0.406–0.513)	584

Table 5-9. Creatinine-Corrected Urinary Thallium Concentrations (in µg/g of Creatinine) in the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

Survey years	Geometric mean (95% confidence interval)	Percentiles (95% confidence interval)				Sample size
		50th	75th	90th	95th	
2017–2018	0.178 (0.165–0.192)	0.178 (0.164–0.194)	0.242 (0.221–0.264)	0.343 (0.306–0.389)	0.435 (0.377–0.486)	433
Non-Hispanic Black						
1999–2000	0.142 (0.133–0.152)	0.140 (0.129–0.151)	0.200 (0.184–0.214)	0.278 (0.244–0.307)	0.383 (0.286–0.462)	561
2001–2002	0.138 (0.128–0.150)	0.136 (0.125–0.146)	0.194 (0.170–0.212)	0.256 (0.238–0.278)	0.328 (0.271–0.387)	657
2003–2004	0.133 (0.122–0.145)	0.128 (0.119–0.143)	0.185 (0.171–0.200)	0.255 (0.237–0.269)	0.323 (0.267–0.377)	723
2005–2006	0.137 (0.128–0.145)	0.130 (0.130–0.140)	0.190 (0.180–0.200)	0.240 (0.220–0.290)	0.320 (0.270–0.370)	692
2007–2008	0.125 (0.118–0.132)	0.130 (0.120–0.130)	0.170 (0.160–0.180)	0.230 (0.210–0.260)	0.280 (0.250–0.330)	589
2009–2010	0.128 (0.120–0.137)	0.120 (0.110–0.130)	0.180 (0.160–0.210)	0.250 (0.230–0.280)	0.310 (0.270–0.350)	544
2011–2012	0.137 (0.119–0.157)	0.137 (0.113–0.159)	0.208 (0.174–0.244)	0.284 (0.248–0.334)	0.348 (0.293–0.406)	669
2013–2014	0.131 (0.125–0.137)	0.126 (0.117–0.138)	0.181 (0.171–0.189)	0.254 (0.232–0.276)	0.324 (0.265–0.421)	581
2015–2016	0.135 (0.126–0.145)	0.130 (0.119–0.138)	0.194 (0.181–0.212)	0.304 (0.270–0.339)	0.369 (0.333–0.412)	669
2017–2018	0.135 (0.127–0.145)	0.135 (0.128–0.144)	0.190 (0.179–0.206)	0.267 (0.245–0.308)	0.335 (0.300–0.368)	639
Non-Hispanic White						
1999–2000	0.169 (0.160–0.179)	0.173 (0.167–0.181)	0.227 (0.215–0.240)	0.300 (0.272–0.329)	0.364 (0.333–0.377)	801
2001–2002	0.161 (0.155–0.167)	0.161 (0.153–0.171)	0.222 (0.214–0.231)	0.292 (0.278–0.304)	0.348 (0.330–0.383)	1,114
2003–2004	0.154 (0.148–0.160)	0.153 (0.143–0.162)	0.214 (0.200–0.223)	0.283 (0.271–0.304)	0.333 (0.313–0.363)	1,074
2005–2006	0.156 (0.148–0.164)	0.150 (0.140–0.160)	0.210 (0.200–0.230)	0.300 (0.280–0.320)	0.360 (0.330–0.400)	1,041
2007–2008	0.154 (0.146–0.164)	0.160 (0.140–0.170)	0.220 (0.210–0.230)	0.300 (0.280–0.320)	0.370 (0.340–0.390)	1,095
2009–2010	0.155 (0.145–0.166)	0.150 (0.140–0.170)	0.220 (0.200–0.240)	0.310 (0.280–0.330)	0.380 (0.340–0.410)	1,225
2011–2012	0.173 (0.161–0.186)	0.171 (0.161–0.181)	0.235 (0.213–0.261)	0.337 (0.309–0.373)	0.453 (0.357–0.521)	818
2013–2014	0.163 (0.151–0.176)	0.163 (0.149–0.176)	0.242 (0.226–0.255)	0.338 (0.309–0.362)	0.430 (0.390–0.482)	984
2015–2016	0.169 (0.157–0.182)	0.168 (0.154–0.180)	0.239 (0.213–0.276)	0.336 (0.300–0.369)	0.404 (0.371–0.450)	924
2017–2018	0.185 (0.172–0.198)	0.179 (0.168–0.191)	0.254 (0.236–0.280)	0.386 (0.338–0.433)	0.477 (0.420–0.559)	918

Table 5-9. Creatinine-Corrected Urinary Thallium Concentrations (in µg/g of Creatinine) in the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

Survey years	Geometric mean (95% confidence interval)	Percentiles (95% confidence interval)				Sample size
		50th	75th	90th	95th	
All Hispanic						
2011–2012	0.162 (0.150–0.176)	0.158 (0.142–0.174)	0.221 (0.198–0.250)	0.304 (0.278–0.347)	0.370 (0.316–0.440)	573
2013–2014	0.161 (0.153–0.170)	0.154 (0.145–0.164)	0.222 (0.208–0.238)	0.318 (0.294–0.344)	0.386 (0.350–0.432)	701
2015–2016	0.180 (0.170–0.190)	0.178 (0.167–0.190)	0.241 (0.225–0.266)	0.366 (0.332–0.389)	0.444 (0.424–0.509)	981
2017–2018	0.183 (0.171–0.195)	0.178 (0.164–0.189)	0.249 (0.229–0.280)	0.377 (0.333–0.435)	0.498 (0.454–0.622)	674
Non–Hispanic Asian						
2011–2012	0.237 (0.219–0.256)	0.228 (0.206–0.250)	0.337 (0.297–0.367)	0.526 (0.442–0.586)	0.663 (0.557–0.830)	353
2013–2014	0.242 (0.221–0.264)	0.237 (0.216–0.268)	0.352 (0.304–0.382)	0.456 (0.417–0.529)	0.570 (0.460–0.857)	292
2015–2016	0.259 (0.242–0.278)	0.254 (0.234–0.279)	0.368 (0.333–0.406)	0.536 (0.492–0.603)	0.663 (0.572–0.742)	332
2017–2018	0.236 (0.221–0.252)	0.229 (0.203–0.252)	0.330 (0.309–0.355)	0.453 (0.392–0.520)	0.595 (0.507–0.707)	365

[a]Participants were ≥6 years old in survey years through 2014; beginning with survey years 2015–2016, participants included those ≥3 years old.

Source: CDC 2023

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Occupational exposure to thallium may be significant for workers in smelters, power plants, cement factories, and other industries that produce or use thallium compounds or alloys. Exposure may occur by dermal absorption from handling thallium-containing compounds, ores, limestone, or cement or by inhalation of workplace air (Ewers 1988; Marcus 1985; Schaller et al. 1980).

No recent data were located for U.S. workplaces. Although data on exposure levels in workplace air are rare, studies associating workplace exposure and elevated urinary thallium confirm the occurrence of industrial exposures in Europe (Apostoli et al. 1988; Marcus 1985; Schaller et al. 1980; Staff et al. 2014). A 2014 study of workers in the United Kingdom reported a median urinary thallium level of 0.41 µg/L (Staff et al. 2014). The urinary thallium levels were higher than levels measured in general workers (0.20 µg/L) or non-occupational exposed people (0.11 µg/L) (Staff et al. 2014).

Populations with potentially high exposures are those living near coal-burning power plants, metal smelters, or cement plants (Sharma et al. 1986). The airborne particulate emissions from these plants may have high thallium levels, especially on the small-diameter, respirable particles (Davison et al. 1974; Ewers 1988). Human populations living in the vicinity of these plants may be exposed by inhalation or by ingestion of fruits and vegetables home-grown in contaminated soils (Brockhaus et al. 1980, 1981; EPA 1988; Sharma et al. 1986).

Limited data suggest that smokers may have potentially higher exposure to thallium than nonsmokers. Although authoritative evaluations of cigarette smoke constituents do not include thallium, thallium was detected at 0.057–0.170 µg/g in cigar stubs and 0.024 µg/g in cigarette tobacco (EPA 1980). A more recent study reported an average thallium concentration of 0.0089 µg/g in tobacco samples collected from a commercial cigarette brand in Poland (Karbowska and Zembrzuski 2016). One study indicates that the urinary excretion of thallium in smokers is about twice that of nonsmokers (EPA 1980). A recent study showed that illicit opioid users were a high-risk group for thallium toxicity. In the studied group, the median (interquartile range) concentrations of thallium in urine, blood, and hair were 54.8, 14.5, and 5.4 µg/g, respectively, as compared to respective levels 4.8, 2.4, and 1.4 µg/g in the control group (Molavi et al. 2020).

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

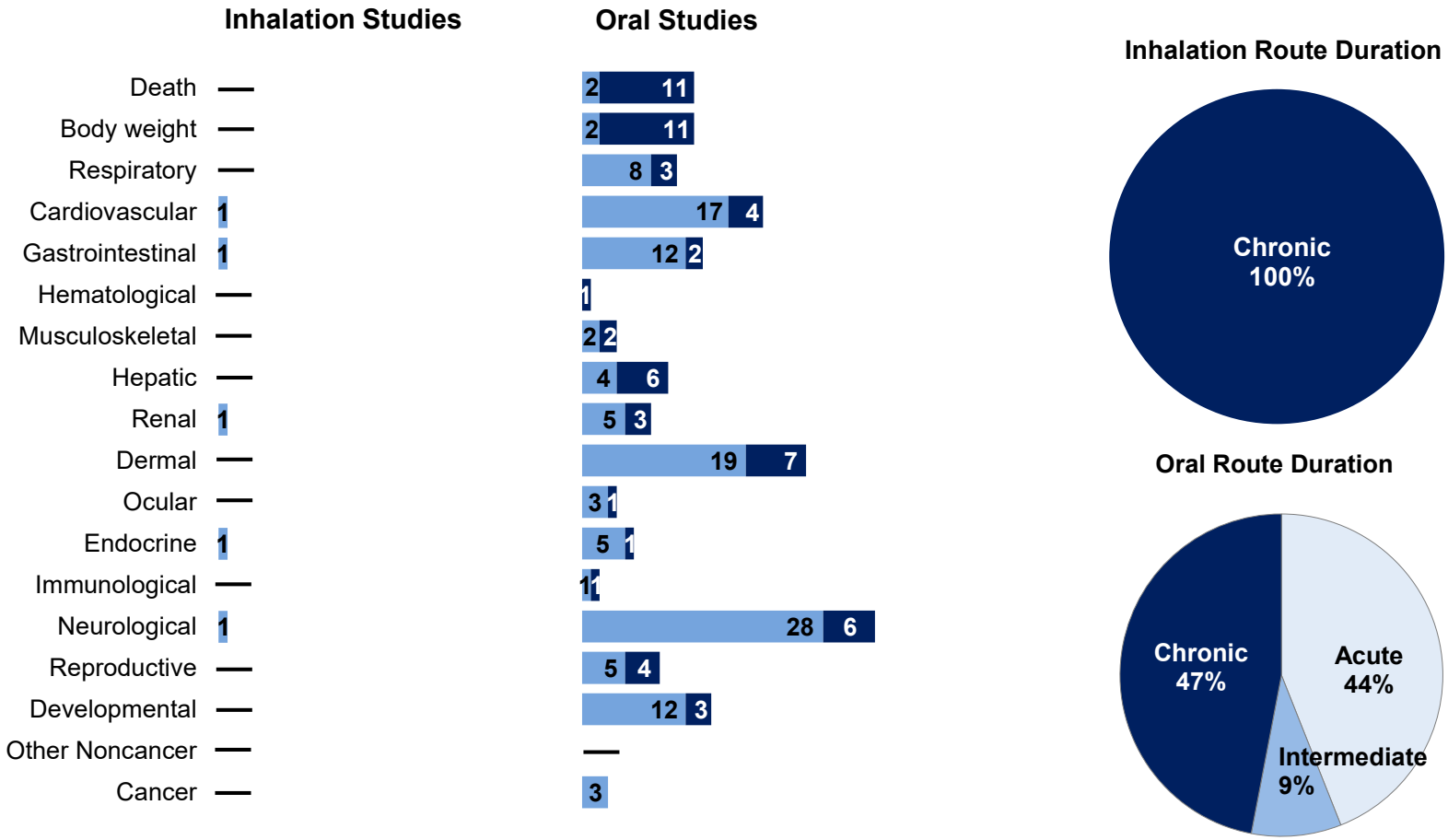
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to thallium that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of thallium. The number of human and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

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding thallium in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. No MRLs were derived for thallium; see Appendix A for detailed information.

Table 7-1. Regulations and Guidelines Applicable to Thallium

Agency	Description	Information	Reference
	Air		
EPA	RfC		IRIS 2009
	Thallium(I) soluble salts	Value(s) not derived	
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	Thallium		
	1-Day health advisory (10-kg child)	0.007 mg/L	
	10-Day health advisory (10-kg child)	0.007 mg/L	
	National primary drinking water regulations		EPA 2009b
	Thallium		
	MCL	0.002 mg/L	
	MCLG	0.0005 mg/L	
	RfD		IRIS 2009
	Thallium(I) soluble salts	Value(s) not derived	
	Provisional peer reviewed toxicity values		
	Thallium and compounds	Provisional screening values only	EPA 2012
WHO	Drinking water quality guidelines	Not listed	WHO 2022
FDA	Substances added to food (formerly EAFUS)[a]	Not listed	FDA 2023b
	Allowable level in bottled water	0.002 mg/L	FDA 2023a
	Cancer		
HHS	Carcinogenicity classification	Not evaluated	NTP 2021
EPA	Carcinogenicity classification	Inadequate information to assess carcinogenic potential	IRIS 2009

Table 7-1. Regulations and Guidelines Applicable to Thallium

Agency	Description	Information	Reference
IARC	Carcinogenicity classification	Not evaluated	IARC 2023
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction		OSHA 2021a, 2021b, 2021c
	Thallium, soluble compounds (as Tl)	0.1 mg/m^3 [a]	
NIOSH	REL (up to 10-hour TWA)		NIOSH 2019
	Thallium, soluble compounds (as Tl)	0.1 mg/m^3 [a]	
	Emergency Criteria		
NIOSH	IDLH		NIOSH 1994
	Thallium, soluble compounds (as Tl)	15 mg/m^3	
EPA	AEGLs-air	Not listed	EPA 2018b
DOE	PACs-air		DOE 2018a
	Thallium		
	PAC-1[b]	0.06 mg/m^3	
	PAC-2[b]	3.3 mg/m^3	
	PAC-3[b]	20 mg/m^3	
	Thallium chloride		
	PAC-1[b]	0.18 mg/m^3	
	PAC-2[b]	2 mg/m^3	
	PAC-3[b]	23 mg/m^3	
	Thallium hydroxide		
	PAC-1[b]	0.065 mg/m^3	
	PAC-2[b]	3.7 mg/m^3	
	PAC-3[b]	22 mg/m^3	
	Thallium nitrite		
	PAC-1[b]	0.074 mg/m^3	
	PAC-2[b]	4.2 mg/m^3	
	PAC-3[b]	25 mg/m^3	
	Thallium oxide		
	PAC-1[b]	0.062 mg/m^3	
	PAC-2[b]	3.5 mg/m^3	
	PAC-3[b]	21 mg/m^3	
	Thallium sulfate		
	PAC-1[b]	0.18 mg/m^3	
	PAC-2[b]	2 mg/m^3	
	PAC-3[b]	21 mg/m^3	
	Thallium(I) acetate		
	PAC-1[b]	0.077 mg/m^3	
	PAC-2[b]	4.3 mg/m^3	
	PAC-3[b]	26 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Thallium

Agency	Description	Information	Reference
	Thallium(I) carbonate (2:1)		
	PAC-1[b]	0.18mg/m^3	
	PAC-2[b]	2 mg/m^3	
	PAC-3[b]	23 mg/m^3	
	Thallium(I) sulfate		
	PAC-1[b]	0.18 mg/m^3	
	PAC-2[b]	2 mg/m^3	
	PAC-3[b]	25 mg/m^3	
	Thallium(III) oxide		
	PAC-1[b]	0.18 mg/m^3	
	PAC-2[b]	2 mg/m^3	
	PAC-3[b]	8.7 mg/m^3	
	Thallous nitrate		
	PAC-1[b]	0.078 mg/m^3	
	PAC-2[b]	4.3 mg/m^3	
	PAC-3[b]	26 mg/m^3	

[a]Skin notation
[b]Definitions of PAC terminology are available from DOE (2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

Adams JB, Audhya T, McDonough-Means S, et al. 2013. Toxicological status of children with autism vs. neurotypical children and the association with autism severity. Biol Trace Elem Res 151(2):171-180. https://doi.org/10.1007/s12011-012-9551-1.

Adams J, Howsmon DP, Kruger U, et al. 2017. Significant association of urinary toxic metals and autism-related symptoms-a nonlinear statistical analysis with cross validation. PLoS One 12(1):e0169526. https://doi.org/10.1371/journal.pone.0169526.

Al Hammouri F, Darwazeh G, Said A, et al. 2011. Acute thallium poisoning: series of ten cases. J Med Toxicol 7(4):306-311. https://doi.org/10.1007/s13181-011-0165-3.

Almassri I, Sekkarie M. 2018. Cases of thallium intoxication in Syria: A diagnostic and a therapeutic challenge. Avicenna J Med 8(3):78-81. https://doi.org/10.4103/ajm.AJM_17_18.

Andersen ME, Krishnan K. 1994. Relating in vitro to in vivo exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, replacement. New York, NY: Marcel Dekker, Inc., 9-25.

Andre T, Ullberg S, Winqvist G. 1960. The accumulation and retention of thallium in tissues of the mouse. Acta Pharmacol Toxicol 16:229-234. https://doi.org/10.1111/j.1600-0773.1960.tb01207.x.

Anschutz M, Herken R, Neubert D. 1981. Studies on embryo toxic effects of thallium using the whole embryo culture technique. In: Neubert D, Merker H, eds. Culture techniques: Applicability for studies on prenatal differentiation and toxicity: 5th symposium on prenatal development, May 1981, Berlin. Berlin, West Germany: Walter de Gruyter, 57-66.

Apostoli P, Maranelli G, Minoia C, et al. 1988. Urinary thallium: Critical problems, reference values and preliminary results of an investigation in workers with suspected industrial exposure. Sci Total Environ 71(3):513-518. https://doi.org/10.1016/0048-9697(88)90226-4.

ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Agency for Toxic Substances and Disease Registry. Fed Reg 54(174):37618-37634. https://www.govinfo.gov/content/pkg/FR-1989-09-11/pdf/FR-1989-09-11.pdf. October 4, 2023.

ATSDR. 2022. Thallium. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/SPL/resources/index.html. January 8, 2024.

Bailey MR, Ansoborlo E, Guilmette RA, et al. 2007. Updating the ICRP human respiratory tract model. Radiat Prot Dosimetry 127(1-4):31-34. https://doi.org/10.1093/rpd/ncm249.

Barclay RK, Peacock WC, Karnofsky DA. 1953. Distribution and excretion of radioactive thallium in the chick embryo, rat, and man. J Pharmacol Exp Ther 107(2):178-187.

Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8(4):471-486. https://doi.org/10.1016/0273-2300(88)90047-5.

Barrows ME, Petrocelli SR, Macek KJ, et al. 1978. Bioconcentration and elimination of selected water pollutants by bluegill sunfish. In: Haque R, ed. Dynamics, exposure and hazard assessment of toxic chemicals. Ann Arbor, MI: Ann Arbor Science Publishers, Inc., 379-392.

Belzile N, Chen Y. 2017. Thallium in the environment: A critical review focused on natural waters, soils, sediments and airborne particles. Appl Geochem 84:218-243. https://doi.org/10.1016/j.apgeochem.2017.06.013.

Bloom MS, Buck Louis GM, Sundaram R, et al. 2015. Birth outcomes and background exposures to select elements, the Longitudinal Investigation of Fertility and the Environment (LIFE). Environ Res 138:118-129. https://doi.org/10.1016/j.envres.2015.01.008.

Bornhausen M, Hagen U. 1984. Operant behavior performance changes in rat after prenatal and postnatal exposure to heavy metals. IRCS Med Sci 12(9-10):805-806.

Brockhaus A, Dolgner R, Ewers U, et al. 1980. Excessive thallium absorption among a population living near a thallium emitting cement plant. Dev Toxicol Environ Sci 8:565-568.

8. REFERENCES

Brockhaus A, Dolgner R, Ewers U, et al. 1981. Intake and health effects of thallium among a population living in the vicinity of a cement plant emitting thallium containing dust. Int Arch Occup Environ Health 48:375-389. https://doi.org/10.1007/BF00378686.

Brown DR, Callahan BG, Cleaves MA, et al. 1985. Thallium induced changes in behavioral patterns: correlation with altered lipid peroxidation and lysosomal enzyme activity in brain regions of male rats. Toxicol Ind Health 1(1):81-98. https://doi.org/10.1177/074823378500100109.

Cao HM, Yang YZ, Huang BY, et al. 2023. A cross-sectional study of the association between heavy metals and pan-cancers associated with sex hormones in NHANES 1999-2018. Environ Sci Pollut Res Int 30(21):61005-61017. https://doi.org/10.1007/s11356-023-26828-2.

Casto BC, Meyers J, DiPaolo JA. 1979. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res 39(1):193-198.

Cataldo DA, Wildung RE. 1983. The role of soil and plant metabolic processes in controlling trace element behavior and bioavailability to animals. Sci Total Environ 28:159-168. https://doi.org/10.1016/s0048-9697(83)80015-1.

Cavanagh JB, Fuller NH, Johnson HR, et al. 1974. The effects of thallium salts, with particular reference to the nervous system changes. A report of three cases. Q J Med 43(170):293-319. https://doi.org/10.1093/oxfordjournals.qjmed.a067389.

CDC. 2023. Urinary thallium. Biomonitoring data tables for environmental chemicals. Centers for Disease Control and Prevention. https://www.cdc.gov/exposurereport/data_tables.html. January 12, 2024.

Cheam V. 2001. Thallium contamination of water in Canada. Water Qual Res J 36(4):851-877. https://doi.org/10.2166/wqrj.2001.046.

Clewell HJ. 1995. The application of physiologically based pharmacokinetic modeling in human health risk assessment of hazardous substances. Toxicol Lett 79(1-3):207-217. https://doi.org/10.1016/0378-4274(95)03372-r.

Cole RH, Frederick RE, Healy RG, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the nationwide urban runoff program. J Water Pollut Control Fed 56(7):898-908.

Cotton FA, Wilkinson G. 1980. Thallium. In: Advanced inorganic chemistry: A comprehensive text. 4th ed. New York, NY: John Wiley & Sons, 349.

Cvjetko P, Cvjetko I, Pavlica M. 2010. Thallium toxicity in humans. Arh Hig Rada Toksikol 61(1):111-119. https://doi.org/10.2478/10004-1254-61-2010-1976.

Dai J, Wu X, Bai Y, et al. 2019. Effect of thallium exposure and its interaction with smoking on lung function decline: A prospective cohort study. Environ Int 127:181-189. https://doi.org/10.1016/j.envint.2019.03.034.

Dai-xing Z, Ding-nan L. 1985. Chronic thallium poisoning in a rural area of Guizhou Province, China. J Environ Health 48(1):14-18.

Davis LE, Standefer JC, Kornfeld M, et al. 1981. Acute thallium poisoning: toxicological and morphological studies of the nervous system. Ann Neurol 10(1):38-44. https://doi.org/10.1002/ana.410100108.

Davison RL, Natusch DF, Wallace JR, et al. 1974. Trace elements in fly ash: Dependence of concentration on particle size. Environ Sci Technol 8(13):1107-1113. https://doi.org/10.1021/es60098a003.

de Groot G, van Leusen R, van HAN. 1985. Thallium concentrations in body fluids and tissues in a fatal case of thallium poisoning. Vet Hum Toxicol 27(2):115-119.

Desenclos JC, Wilder MH, Coppenger GW, et al. 1992. Thallium poisoning: an outbreak in Florida, 1988. South Med J 85(12):1203-1206. https://doi.org/10.1097/00007611-199212000-00012.

DOE. 2018a. Table 2: Protective action criteria (PAC) rev. 29a based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed in alphabetical order. June 2018. U.S. Department of Energy. https://edms3.energy.gov/pac/docs/Revision_29A_Table2.pdf. March 15, 2023.

DOE. 2018b. Protective action criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29A, June 2018. U.S. Department of Energy. https://edms3.energy.gov/pac/. July 6, 2022.

Dolgner R, Brockhaus A, Ewers U, et al. 1983. Repeated surveillance of exposure to thallium in a population living in the vicinity of a cement plant emitting dust containing thallium. Int Arch Occup Environ Health 52(1):79-94. https://doi.org/10.1007/BF00380610.

Dou Y, Yin Y, Li Z, et al. 2022. Maternal exposure to metal mixtures during early pregnancy and fetal growth in the Jiangsu Birth Cohort, China. Environ Res 215(Pt 2):114305. https://doi.org/10.1016/j.envres.2022.114305.

Doulgeridou A, Amlund H, Sloth JJ, et al. 2020. Review of potentially toxic rare earth elements, thallium and tellurium in plant-based foods. EFSA J 18(Suppl 1):e181101. https://doi.org/10.2903/j.efsa.2020.e181101.

Downs WL, Scott JK, Steadman LT, et al. 1960. Acute and sub-acute toxicity studies of thallium compounds. Am Ind Hyg Assoc J 21(5):399-406. https://doi.org/10.1080/00028896009344093.

Ducket S, Hiller D, Ballas S. 1983. Quantitation and localization of thallium-204 in the central and peripheral nervous system of adult and young rats. Neurotoxicology 4(2):227-234.

El-Masri HA, Mumtaz MM, Yushak ML. 2004. Application of physiologically-based pharmacokinetic modeling to investigate the toxicological interaction between chlorpyrifos and parathion in the rat. Environ Toxicol Pharmacol 16(1-2):57-71. https://doi.org/10.1016/j.etap.2003.10.002.

EPA. 1979. Water-related environmental fate of 129 priority pollutants. Vol I. Introduction and technical background, metals and inorganics, pesticides and PCBs. Washington, DC: U.S. Environmental Protection Agency. PB80204373. EPA440479029a. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100K7FH.txt. January 10, 2024.

EPA. 1980. Ambient water quality criteria for thallium. Washington, DC: U.S. Environmental Protection Agency. PB81117848. EPA440580074. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=2000LNGQ.txt. January 10, 2024.

EPA. 1983. Treatability manual. Volume 1: Treatability data. Washington, DC: U.S. Environmental Protection Agency. EPA600282001a. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=30005R3P.txt. January 10, 2024.

EPA. 1985. Suspended, cancelled and restricted pesticides. Washington, DC: U.S. Environmental Protection Agency. EPA740K85001. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=91017N0P.txt. January 10, 2024.

EPA. 1986. Subchronic (90 day) toxicity of thallium (I) sulfate in Sprague-Dawley rats. Unpublished report to U.S. Environmental Protection Agency by Midwest Research Institute.

EPA. 1988. Health and environmental effects document for thallium and compounds. Cincinnati, OH: U.S. Environmental Protection Agency. ECAO-CIN-G031. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9100RH6Z.txt. February 19, 2024.

EPA. 1994. Method 200.8: Determination of trace elements in waters and wastes by inductively coupled plasma-mass spectrometry. Cincinnati, OH: U.S. Environmental Protection Agency. https://www.epa.gov/sites/default/files/2015-06/documents/epa-200.8.pdf. January 10, 2024.

EPA. 2009a. Toxicological review of thallium and compounds (CAS No. 7440-28-0). Washington, DC: U.S. Environmental Protection Agency. PB2010101623. EPA635R08001F. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB2010101623.xhtml. December 12, 2023.

EPA. 2009b. National primary drinking water regulations. U.S. Environmental Protection Agency. EPA816F090004. https://www.epa.gov/sites/default/files/2016-06/documents/npwdr_complete_table.pdf. September 7, 2017.

EPA. 2012. Provisional peer reviewed toxicity values for thallium and compounds: metallic thallium (7440-28-0), thallium (I) acetate (563-68-8), thallium (I) carbonate (6533-73-9), thallium (I) chloride (7791-12-0), thallium (I) nitrate (10102-45-1), and thallium (I) sulfate (7446-18-6). Cincinnati, OH: U.S. Environmental Protection Agency. EPA690R12026F. https://cfpub.epa.gov/ncea/pprtv/documents/ThalliumSolubleSalts.pdf. January 8, 2024.

EPA. 2018a. 2018 Edition of the drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency. EPA822F18001. https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf. June 15, 2022.

EPA. 2018b. Compiled AEGL values. U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2018-08/documents/compiled_aegls_update_27jul2018.pdf. April 12, 2020.

EPA. 2022. Toxic chemical release inventory reporting forms and instructions: Revised 2021 version. U.S. Environmental Protection Agency. EPA740B22002. https://ordspub.epa.gov/ords/guideme_ext/guideme_ext/guideme/file/ry_2021_rfi.pdf. August 22, 2023.

Ewers U. 1988. Environmental exposure to thallium. Sci Total Environ 71(3):285-292. https://doi.org/10.1016/0048-9697(88)90199-4.

EWG. 2019. Thallium. EWG's tap water database. Environmental Working Group. https://www.ewg.org/tapwater/contaminant.php?contamcode=1085. January 12, 2024.

Fan Y, Tao C, Li Z, et al. 2023. Association of endocrine-disrupting chemicals with all-cause and cause-specific mortality in the U.S.: A prospective cohort study. Environ Sci Technol 57(7):2877-2886. https://doi.org/10.1021/acs.est.2c07611.

FDA. 2022. FDA total diet study (TDS) FY2018-FY2020 report supplement: Summary of analytical results. U.S. Food and Drug Administration. https://www.fda.gov/food/fda-total-diet-study-tds/fda-total-diet-study-tds-results. January 12, 2024.

FDA. 2023a. Subpart B - Requirements for specific standardized beverages. Bottled water. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 165.110. https://www.govinfo.gov/content/pkg/CFR-2023-title21-vol2/pdf/CFR-2023-title21-vol2-sec165-110.pdf. January 8, 2024.

FDA. 2023b. Substances added to food. U.S. Food and Drug Administration. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=FoodSubstances. May 28, 2023.

Filippini T, Tancredi S, Malagoli C, et al. 2020. Dietary estimated intake of trace elements: Risk assessment in an Italian population. Exp Health 12(4):641-655. https://doi.org/10.1007/s12403-019-00324-w.

Formigli L, Scelsi R, Poggi P, et al. 1986. Thallium-induced testicular toxicity in the rat. Environ Res 40(2):531-539. https://doi.org/10.1016/s0013-9351(86)80128-1.

Frantz G, Carlson RM. 1987. Division S-2-soil chemistry: Effects of rubidium, cesium, and thallium on interlayer potassium release from transvaal vermiculite. Soil Sci Soc Am J 51:305-308. https://doi.org/10.2136/sssaj1987.03615995005100020008x.

Gastel B. 1978. Thallium poisoning. Johns Hopkins Med J 142:27-31.

Gehring PJ, Hammond PB. 1967. The interrelation between thallium and potassium in animals. J Pharmacol Exp Ther 155(1):187-201.

Gibson JE, Becker BA. 1970. Placental transfer, embryotoxicity, and teratogenicity of thallium sulfate in normal and potassium-deficient rats. Toxicol Appl Pharmacol 16(1):120-132. https://doi.org/10.1016/0041-008x(70)90168-7.

Gregotti C, Di Nucci A, Formigli L, et al. 1985. Altered testicular enzyme patterns in rats after long-term exposure to thallium sulphate. J Toxicol Clin Exp 5(4):265-271.

Gross P, Runne E, Wilson JW. 1948. Studies on the effect of thallium poisoning of the rat; the influence of cystine and methionine on alopecia and survival periods. J Invest Dermatol 10(3):119-134. https://doi.org/10.1038/jid.1948.20.

Grunfeld O, Hinostroza G. 1964. Thallium poisoning. Arch Intern Med 114:132-138. https://doi.org/10.1001/archinte.1964.03860070178025.

Grunfeld O, Battilana G, Aldana L, et al. 1963. Electrocardiographic changes in experimental thallium poisoning. Am J Vet Res 24:1291-1296.

Guo X, Li N, Wang H, et al. 2022. Combined exposure to multiple metals on cardiovascular disease in NHANES under five statistical models. Environ Res 215(Pt 3):114435. https://doi.org/10.1016/j.envres.2022.114435.

Hantson P, Desoir R, Léonard ED, et al. 1997. Cytogenetic observations following thallium poisoning. J Toxicol Environ Health 50(2):97-100. https://doi.org/10.1080/009841097160500.

Harrington JM, Poitras EP, Weber FX, et al. 2022. Validation of analytical method for determination of thallium in rodent plasma and tissues by inductively coupled plasma-mass spectrometry (ICP-MS). Anal Lett 55(8):1269-1280. https://doi.org/10.1080/00032719.2021.1993876.

Hasan M, Bajpai VK, Shipstone AC. 1977b. Electron microscope study of thallium-induced alterations in the oligodendrocytes of the rat area postrema. Exp Pathol 13(6):338-345. https://doi.org/10.1016/s0014-4908(77)80021-5.

Hasan M, Ashraf I, Bajpai VK. 1978. Electron microscopic study of the effects of thallium poisoning on the rat cerebellum. Forensic Sci 11(2):139-146. https://doi.org/10.1016/s0379-0738(78)80008-5.

Hasan M, Chandra SV, Dua PR, et al. 1977a. Biochemical and electrophysiologic effects of thallium poisoning on the rat corpus striatum. Toxicol Appl Pharmacol 41(2):353-359. https://doi.org/10.1016/0041-008x(77)90036-9.

Heit M, Klusek CS, Baron J. 1984. Evidence of deposition of anthropogenic pollutants in remote Rocky Mountain lakes. Water Air Soil Pollut 22:403-416. https://doi.org/10.1007/BF00282611.

Hoffman RS, Hoffman R. 2000. Thallium poisoning during pregnancy: a case report and comprehensive literature review. J Toxicol Clin Toxicol 38(7):767-775. https://doi.org/10.1081/clt-100102390.

IARC. 2023. Agents classified by the IARC Monographs, volumes 1–135. International Agency for Research on Cancer. https://monographs.iarc.fr/list-of-classifications. January 8, 2024.

ICRP. 1994. Human respiratory tract model for radiological protection. International Commission on Radiological Protection. ICRP Publication 66. https://journals.sagepub.com/doi/pdf/10.1177/ANIB_24_1-3. December 6, 2023.

ICRP. 1995. Age-dependent doses to members of the public from intake of radionuclides: part 4 inhalation dose coefficients. International Commission on Radiological Protection. ICRP Publication 71. https://www.icrp.org/publication.asp?id=ICRP%20Publication%2071. May 16, 2024.

ICRP. 2022. Thallium (Z=81). Occupational intakes of radionuclides: Part 5. International Commission on Radiological Protection. 343-353. ICRP Publication 151.

IRIS. 2009. Thallium (I), soluble salts; CASRN various. Integrated Risk Information System. U.S. Environmental Protection Agency. https://iris.epa.gov/static/pdfs/1012_summary.pdf. January 8, 2024.

Jha S, Kumar R, Kumar R. 2006. Thallium poisoning presenting as paresthesias, paresis, psychosis and pain in abdomen. J Assoc Physicians India 54:53-55.

Kanematsu N, Hara M, Kada T. 1980. Rec assay and mutagenicity studies on metal compounds. Mutat Res 77(2):109-116. https://doi.org/10.1016/0165-1218(80)90127-5.

Kaplan DI, Mattigod SV. 1998. Aqueous geochemistry of thallium. In: Nriagu JO, ed. Thallium in the environment. New York, NY: Wiley, 15-29.

Karbowska B. 2016. Presence of thallium in the environment: sources of contaminations, distribution and monitoring methods. Environ Monit Assess 188(11):640. https://doi.org/10.1007/s10661-016-5647-y.

Karbowska B, Zembrzuski W. 2016. Determining thallium in a commercial tobacco brand available in Poland. Polish J Environ Stud 25(5):2217-2220. https://doi.org/10.15244/pjoes/61951.

Karlsson U. 2006. Environmental levels of thallium – Influence of redox properties and anthropogenic sources. In: Örebro studies in chemistry 5. Gothenburg, Sweden: Universitetsbiblioteket, 1-34. https://urn.kb.se/resolve?urn=urn:nbn:se:oru:diva-356. February 21, 2024.

Kim DJ, Shin HJ, Ahn BK, et al. 2016. Competitive adsorption of thallium in different soils as influenced by selected counter heavy metals. Appl Biol Chem 59(5):695-701. https://doi.org/10.1007/s13765-016-0215-2.

Kuo HC, Huang CC, Tsai YT, et al. 2005. Acute painful neuropathy in thallium poisoning. Neurology 65(2):302-304. https://doi.org/10.1212/01.wnl.0000169021.26172.f8.

LaCoste C, Robinson B, Brooks R. 2001. Uptake of thallium by vegetables: Its significance for human health, phytoremediation, and phytomining. J Plant Nutr 24(8):1205-1215. https://doi.org/10.1081/pln-100106976.

Lameijer W, van Zwieten PA. 1977. Kinetic behavior of thallium in the rat. Accelerated elimination of thallium owing to treatment with potent diuretic agents. Arch Toxicol 37(4):265-273. https://doi.org/10.1007/BF00330818.

Lameijer W, van Zwieten PA. 1978. Accelerated elimination of thallium in the rat due to subchronic treatment with furosemide. Arch Toxicol 40:7-16. https://doi.org/10.1007/BF00353275.

Leloux MS, Nguyen PL, Claude JR. 1987. Experimental studies on thallium toxicity in rats. I-Localization and elimination of thallium after oral acute and sub-acute intoxication. J Toxicol Clin Exp 7(4):247-257.

Li JM, Wang W, Lei S, et al. 2014. Misdiagnosis and long-term outcome of 13 patients with acute thallium poisoning in China. Clin Toxicol 52(3):181-186. https://doi.org/10.3109/15563650.2014.892123.

Li D, Yao H, Du L, et al. 2022a. Thallium(I and III) exposure leads to liver damage and disorders of fatty acid metabolism in mice. Chemosphere 307(Pt 1):135618. https://doi.org/10.1016/j.chemosphere.2022.135618.

Li D, Yao H, Zhu X, et al. 2022b. Thallium(I) exposure perturbs the gut microbiota and metabolic profile as well as the regional immune function of C57BL/6 J mice. Environ Sci Pollut Res Int 29(60):90495-90508. https://doi.org/10.1007/s11356-022-22145-2.

Li D, Li L, Yao H, et al. 2023a. Thallium exposure induces changes in B and T cell generation in mice. Toxicology 492:153532. https://doi.org/10.1016/j.tox.2023.153532.

Li X, Zhang D, Zhao Y, et al. 2023b. Correlation of heavy metals' exposure with the prevalence of coronary heart disease among US adults: findings of the US NHANES from 2003 to 2018. Environ Geochem Health 45:6745-6759. https://doi.org/10.1007/s10653-023-01670-0.

Liang C, Luo G, Cao Y, et al. 2022. Environmental thallium exposure and the risk of early embryonic arrest among women undergoing in vitro fertilization: thallium exposure and polymorphisms of mtDNA gene interaction and potential cause exploring. Environ Sci Pollut Res Int 29(41):62648-62661. https://doi.org/10.1007/s11356-022-19978-2.

Lide DR. 2005. [Thallium]. In: CRC Handbook of chemistry and physics. CRC Press LLC, 4-31, 34-89.

Lie R, Thomas RG, Scott JK. 1960. The distribution and excretion of thallium-204 in the rat, with suggested MPC's and a bio-assay procedure. Health Phys 2:334-340. https://doi.org/10.1097/00004032-195910000-00004.

Limos LC, Ohnishi A, Suzuki N, et al. 1982. Axonal degeneration and focal muscle fiber necrosis in human thallotoxicosis: Histopathological studies of nerve and muscle. Muscle Nerve 5(9):698-706. https://doi.org/10.1002/mus.880050906.

Lin TS, Nriagu J. 1998. Revised hydrolysis constants for thallium(I) and thallium(III) and the environmental implications. J Air Waste Manag Assoc 48(2):151-156. https://doi.org/10.1080/10473289.1998.10463658.

Lin TS, Nriagu J, Wang XQ. 2001. Thallium concentration in lake trout from Lake Michigan. Bull Environ Contam Toxicol 67(6):921-925. https://doi.org/10.1007/s001280209.

Liu H, Liao G. 2021. Long-term misdiagnosis and neurologic outcomes of thallium poisoning: A case report and literature review. Brain Behav 11(3):e02032. https://doi.org/10.1002/brb3.2032.

Liu M, Song J, Jiang Y, et al. 2021. A case-control study on the association of mineral elements exposure and thyroid tumor and goiter. Ecotoxicol Environ Saf 208:111615. https://doi.org/10.1016/j.ecoenv.2020.111615.

Lu CI, Huang CC, Chang YC, et al. 2007. Short-term thallium intoxication: dermatological findings correlated with thallium concentration. Arch Dermatol 143(1):93-98. https://doi.org/10.1001/archderm.143.1.93.

Ludolph A, Elger CE, Sennhenn R, et al. 1986. Chronic thallium exposure in cement plant workers: Clinical and electrophysiological data. Trace Elem Med 3(3):121-125.

Lund A. 1956a. Distribution of thallium in the organism and its elimination. Acta Pharmacol Toxicol 12(3):251-259. https://doi.org/10.1111/j.1600-0773.1956.tb01385.x.

Lund A. 1956b. The effect of various substances on the excretion and the toxicity of thallium in the rat. Acta Pharmacol Toxicol 12(3):260-268. https://doi.org/10.1111/j.1600-0773.1956.tb01386.x.

Ma X, Pan W, Zhu Z, et al. 2022. A case-control study of thallium exposure with the risk of premature ovarian insufficiency in women. Arch Environ Occup Health 77(6):468-477. https://doi.org/10.1080/19338244.2021.1931797.

Magorian TR, Wood KG, Michalovic JG, et al. 1974. Abundance and distribution of thallium. Water pollution by thallium and related metals. 145-160. PB253333.

Manzo L, Scelsi R, Moglia A, et al. 1983. Long-term toxicity of thallium in the rat. In: Chemical toxicology and clinical chemistry of metals. London, England: Academic Press, 401-405.

Marcus RL. 1985. Investigation of a working population exposed to thallium. J Soc Occup Med 35(1):4-9. https://doi.org/10.1093/occmed/35.1.4.

Mathis BJ, Kevern NR. 1975. Distribution of mercury, cadmium, lead and thallium in a enthropic lake. Hydrobiologia 46(2-3):207-222. https://doi.org/10.1007/BF00043141.

Meggs WJ, Hoffman RS, Shih RD, et al. 1994. Thallium poisoning from maliciously contaminated food. J Toxicol Clin Toxicol 32(6):723-730. https://doi.org/10.3109/15563659409017979.

Migaszewski ZM, Gałuszka A. 2021. Abundance and fate of thallium and its stable isotopes in the environment. Rev Environ Sci Bio/Technol 20(1):5-30. https://doi.org/10.1007/s11157-020-09564-8.

Migliore L, Cocchi L, Nesti C, et al. 1999. Micronuclei assay and FISH analysis in human lymphocytes treated with six metal salts. Environ Mol Mutagen 34(4):279-284. https://doi.org/10.1002/(sici)1098-2280(1999)34:4<279::aid-em8>3.0.co;2-7.

Misra UK, Kalita J, Yadav RK, et al. 2003. Thallium poisoning: emphasis on early diagnosis and response to haemodialysis. Postgrad Med J 79(928):103-105. https://doi.org/10.1136/pmj.79.928.103.

Moeschlin S. 1980. Thallium poisoning. Clin Toxicol 17(1):133-146. https://doi.org/10.3109/15563658008985073.

Molavi N, Ghaderi A, Banafshe HR. 2020. Determination of thallium in urine, blood, and hair in illicit opioid users in Iran. Hum Exp Toxicol 39(6):808-815. https://doi.org/10.1177/0960327120903487.

Mourelle M, Favari L, Amezcua JL. 1988. Protection against thallium hepatotoxicity by silymarin. J Appl Toxicol 8(5):351-354. https://doi.org/10.1002/jat.2550080503.

Mumtaz MM, Ray M, Crowell SR, et al. 2012a. Translational research to develop a human PBPK models tool kit-volatile organic compounds (VOCs). J Toxicol Environ Health A 75(1):6-24. https://doi.org/10.1080/15287394.2012.625546.

Mumtaz M, Fisher J, Blount B, et al. 2012b. Application of physiologically based pharmacokinetic models in chemical risk assessment. J Toxicol 2012:904603. https://doi.org/10.1155/2012/904603.

NAS/NRC. 2006. Human biomonitoring for environmental chemicals. Washington, DC: The National Academies Press, National Research Council. https://nap.nationalacademies.org/catalog/11700/human-biomonitoring-for-environmental-chemicals. August 23, 2023.

Navas-Acien A, Silbergeld EK, Sharrett R, et al. 2005. Metals in urine and peripheral arterial disease. Environ Health Perspect 113(2):164-169. https://doi.org/10.1289/ehp.7329.

NIOSH. 1994. Thallium (soluble compounds, as Tl). Immediately dangerous to life or health (IDLH) values. National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/idlh/thallium.html. January 8, 2024.

NIOSH. 2019. Thallium (soluble compounds, as Tl). NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/npg/npgd0608.html. January 8, 2024.

NLM. 2024. PubChem compound summary: Thallium. U.S. National Library of Medicine. https://pubchem.ncbi.nlm.nih.gov/compound/5359464. January 12, 2024.

NTP. 2013. Draft OHAT approach for systematic review and evidence integration for literature-based health assessments - February 2013. National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/draftohatapproach_february2013.pdf. October 4, 2023.

NTP. 2015. OHAT risk of bias rating tool for human and animal studies. National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf. March 19, 2019.

NTP. 2021. CASRN index. Report on carcinogens. National Toxicology Program. https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#P. January 10, 2022.

Nuvolone D, Petri D, Aprea MC, et al. 2021. Thallium contamination of drinking water: Health implications in a residential cohort study in Tuscany (Italy). Int J Environ Res Public Health 18(8):4058. https://doi.org/10.3390/ijerph18084058.

Olsen I, Jonsen J. 1982. Whole-body autoradiography of 204Tl in embryos, fetuses and placentas of mice. Toxicology 23:353-358. https://doi.org/10.1016/0300-483x(82)90073-7.

O'Neil MJ. 2001. Thallium. In: The Merck index - An encyclopedia of chemicals, drugs, and biologicals. 13th ed. Whitehouse Station, NJ: Merck and Co., Inc., 1650-1651.

OSHA. 2021a. Occupational safety and health standards. Subpart Z - Toxic and hazardous substances. Air contaminants. Table Z-1. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. https://www.govinfo.gov/content/pkg/CFR-2021-title29-vol6/pdf/CFR-2021-title29-vol6-sec1910-1000.pdf. August 28, 2022.

OSHA. 2021b. Occupational safety and health standards for shipyard employment. Subpart Z - Toxic and hazardous substances. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. https://www.govinfo.gov/content/pkg/CFR-2021-title29-vol7/pdf/CFR-2021-title29-vol7-sec1915-1000.pdf. August 28, 2022.

OSHA. 2021c. Safety and health regulations for construction. Subpart D - Occupational health and environment controls. Gases, vapors, fumes, dusts, and mists. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55. https://www.govinfo.gov/content/pkg/CFR-2021-title29-vol8/pdf/CFR-2021-title29-vol8-sec1926-55.pdf. August 28, 2022.

Padilla MA, Elobeid M, Ruden DM, et al. 2010. An examination of the association of selected toxic metals with total and central obesity indices: NHANES 99-02. Int J Environ Res Public Health 7(9):3332-3347. https://doi.org/10.3390/ijerph7093332.

Pedro A, Lehmann PA, Favari L. 1985. Acute thallium intoxication: Kinetic study of the relative efficacy of several antidotal treatments in rats. Arch Toxicol 57:56-60. https://doi.org/10.1007/BF00286576.

Peng S, Lu T, Liu Y, et al. 2022. Short-term exposure to fine particulate matter and its constituents may affect renal function via oxidative stress: A longitudinal panel study. Chemosphere 293:133570. https://doi.org/10.1016/j.chemosphere.2022.133570.

Peter AL, Viraraghavan T. 2005. Thallium: a review of public health and environmental concerns. Environ Int 31(4):493-501. https://doi.org/10.1016/j.envint.2004.09.003.

Pino MTL, Marotte C, Verstraeten SV. 2017. Epidermal growth factor prevents thallium(I)- and thallium(III)-mediated rat pheochromocytoma (PC12) cell apoptosis. Arch Toxicol 91(3):1157-1174. https://doi.org/10.1007/s00204-016-1793-9.

Qi J, Lai Y, Liang C, et al. 2019. Prenatal thallium exposure and poor growth in early childhood: A prospective birth cohort study. Environ Int 123:224-230. https://doi.org/10.1016/j.envint.2018.12.005.

Qiu L, Shen W, Ye C, et al. 2022. Association of exposure to PM2.5-bound metals with maternal thyroid function in early pregnancy. Sci Total Environ 810:151167. https://doi.org/10.1016/j.scitotenv.2021.151167.

Rade JE, Marafante E, Sabbioni E, et al. 1982. Placental transfer and retention of 201Tl thallium in the rat. Toxicol Lett 11:275-280. https://doi.org/10.1016/0378-4274(82)90161-8.

Rader ST, Maier RM, Barton MD, et al. 2019. Uptake and fractionation of thallium by Brassica juncea in a geogenic thallium-amended substrate. Environ Sci Technol 53(5):2441-2449. https://doi.org/10.1021/acs.est.8b06222.

Rahman HH, Niemann D, Munson-McGee SH. 2022a. Association between environmental toxic metals, arsenic and polycyclic aromatic hydrocarbons and chronic obstructive pulmonary disease in the US adult population. Environ Sci Pollut Res Int 29(36):54507-54517. https://doi.org/10.1007/s11356-022-19695-w.

Rahman HH, Niemann D, Munson-McGee SH. 2022b. Environmental exposure to metals and the risk of high blood pressure: a cross-sectional study from NHANES 2015-2016. Environ Sci Pollut Res Int 29(1):531-542. https://doi.org/10.1007/s11356-021-15726-0.

Rahman HH, Niemann D, Munson-McGee SH. 2022c. Urinary metals, arsenic, and polycyclic aromatic hydrocarbon exposure and risk of chronic bronchitis in the US adult population. Environ Sci Pollut Res Int 29(48):73480-73491. https://doi.org/10.1007/s11356-022-20982-9.

Rahman HH, Niemann D, Munson-McGee SH. 2022d. Urinary metals, arsenic, and polycyclic aromatic hydrocarbon exposure and risk of self-reported emphysema in the US adult population. Lung 200(2):237-249. https://doi.org/10.1007/s00408-022-00518-1.

Rao M, Raju G, Ramana KV, et al. 1993. Toxicological studies of thallium dicarboxylates. J Ind Chem Soc 70(8):727-729.

Rayisyan M, Zakharova N, Babaskina L. 2021. Complexions therapy and severe intoxication by thallium salts. J Environ Sci Health A Tox Hazard Subst Environ Eng 56(4):445-453. https://doi.org/10.1080/10934529.2021.1885905.

RePORTER. 2024. Thallium. Research Portfolio Online Reporting Tools. National Institutes of Health. https://reporter.nih.gov/. January 8, 2024.

Reyes-Rodríguez M, Santos-Cruz LF, García-Castro C, et al. 2021. Genotoxicity and cytotoxicity evaluation of two thallium compounds using the Drosophila wing somatic mutation and recombination test. Heliyon 7(5):e07087. https://doi.org/10.1016/j.heliyon.2021.e07087.

Rios C, Galvan-Arzate S, Tapia R. 1989. Brain regional thallium distribution in rats acutely intoxicated with Tl2S04. Arch Toxicol 63:34-37. https://doi.org/10.1007/BF00334631.

Riyaz R, Pandalai SL, Schwartz M, et al. 2013. A fatal case of thallium toxicity: challenges in management. J Med Toxicol 9(1):75-78. https://doi.org/10.1007/s13181-012-0251-1.

Roby DS, Fein AM, Bennett RH, et al. 1984. Cardiopulmonary effects of acute thallium poisoning. Chest 85(2):236-240. https://doi.org/10.1378/chest.85.2.236.

Rodríguez-Mercado JJ, Mosqueda-Tapia G, Altamirano-Lozano MA. 2017. Genotoxicity assessment of human peripheral lymphocytes induced by thallium(I) and thallium(III). Toxicol Environ Chem 99(5-6):987-998. https://doi.org/10.1080/02772248.2017.1307377.

Rodríguez-Mercado JJ, Hernández-de la Cruz H, Felipe-Reyes M, et al. 2015. Evaluation of cytogenetic and DNA damage caused by thallium(I) acetate in human blood cells. Environ Toxicol 30(5):572-580. https://doi.org/10.1002/tox.21934.

Rooney AA, Boyles AL, Wolfe MS, et al. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122(7):711-718. https://doi.org/10.1289/ehp.1307972.

Rossi F, Marrazzo R, Berrino L, et al. 1988. Prenatal and postnatal thallium exposure in rats: effect on development of vasomotor reactivity in pups. Teratog Carcinog Mutagen 8(1):13-23. https://doi.org/10.1002/tcm.1770080103.

Ruan F, Zhang J, Liu J, et al. 2022. Association between prenatal exposure to metal mixtures and early childhood allergic diseases. Environ Res 206:112615. https://doi.org/10.1016/j.envres.2021.112615.

Ruiz P, Ray M, Fisher J, et al. 2011. Development of a human physiologically based pharmacokinetic (PBPK) toolkit for environmental pollutants. Int J Mol Sci 12(11):7469-7480. https://doi.org/10.3390/ijms12117469.

Rusyniak DE, Kao LW, Nanagas KA, et al. 2003. Dimercaptosuccinic acid and Prussian Blue in the treatment of acute thallium poisoning in rats. J Toxicol Clin Toxicol 41(2):137-142. https://doi.org/10.1081/clt-120019129.

Sabbioni E, Marafante E, Rade J, et al. 1980. Metabolic patterns of low and toxic doses of thallium in the rat. Dev Toxicol Environ Sci 8:559-564.

Saha A, Sadhu HG, Karnik AB, et al. 2004. Erosion of nails following thallium poisoning: a case report. Occup Environ Med 61(7):640-642. https://doi.org/10.1136/oem.2003.009464.

Salehi S, Saljooghi AS, Badiee S, et al. 2017. Chelation of thallium (III) in rats using combined deferasirox and deferiprone therapy. Toxicol Res 33(4):299-304. https://doi.org/10.5487/tr.2017.33.4.299.

Sasaki N, Carpenter DO. 2022. Associations between metal exposures and cognitive function in American older adults. Int J Environ Res Public Health 19(4):2327. https://doi.org/10.3390/ijerph19042327.

Sax NI, Lewis RJ. 1987. Thallium. In: Hawley's condensed chemical dictionary. 11th ed. New York, NY: Van Nostrand Reinhold Company, 1142-1143.

Schaller KH, Manke G, Raithel HJ, et al. 1980. Investigations of thallium-exposed workers in cement factories. Int Arch Occup Environ Health 47(3):223-231. https://doi.org/10.1007/BF00381680.

Schoer J. 1984. Thallium. In: Hutzinger O, ed. The handbook of environmental chemistry: Anthropogenic compounds. Vol. 3. Part C. New York, NY: Springer-Verlag, 143-214.

Shan Q. 2022. Trend analysis of the association of urinary metals and obesity in children and adolescents. Chemosphere 307(Pt 1):135617. https://doi.org/10.1016/j.chemosphere.2022.135617.

Sharma J, Sharma RL, Singh HB, et al. 1986. Hazards and analysis of thallium-a review. Toxicol Environ Chem 11(2):93-116. https://doi.org/10.1080/02772248609357123.

Sherlock JC, Smart GA. 1986. Thallium in foods and the diet. Food Addit Contam 3(4):363-370. https://doi.org/10.1080/02652038609373603.

Shipkowski KA, Hubbard TD, Ryan K, et al. 2023. Short-term toxicity studies of thallium (I) sulfate administered in drinking water to Sprague Dawley rats and B6C3F1/N mice. Toxicol Rep 10:621-632. https://doi.org/10.1016/j.toxrep.2023.05.003.

Sojáková M, Žigrai M, Karaman A, et al. 2015. Thallium intoxication. Neuro Endocrinol Lett 36(4):311-315.

Staff JF, Cotton RJ, Warren ND, et al. 2014. Comparison of urinary thallium levels in non-occupationally exposed people and workers. Int Arch Occup Environ Health 87(3):275-284. https://doi.org/10.1007/s00420-013-0859-8.

Stephenson T, Lester JN. 1987a. Heavy metal behavior during the activated sludge process: I. Extent of soluble and insoluble metal removal. Sci Total Environ 63:199-214. https://doi.org/10.1016/0048-9697(87)90046-5.

Stephenson T, Lester JN. 1987b. Heavy metal behavior during the activated sludge process: II. Insoluble metal removal mechanisms. Sci Total Environ 63:215-230. https://doi.org/10.1016/0048-9697(87)90047-7.

Strauss HW, Miller DD, Wittry MD, et al. 2008. Procedure guideline for myocardial perfusion imaging 3.3. J Nucl Med Technol 36(3):155-161. https://doi.org/10.2967/jnmt.108.056465.

Sun TW, Xu QY, Zhang XJ, et al. 2012. Management of thallium poisoning in patients with delayed hospital admission. Clin Toxicol 50(1):65-69. https://doi.org/10.3109/15563650.2011.638926.

Sweeney LM, Gearhart JM. 2020. Examples of physiologically based pharmacokinetic modeling applied to risk assessment. In: Fisher JW, Gearhart JM, Lin Z, eds. Physiologically based pharmacokinetic

(PBPK) modeling. Academic Press: 281-299. https://doi.org/10.1016/B978-0-12-818596-4.00011-4.

Tabassum H, Alrashed M, Malik A, et al. 2022. A unique investigation of thallium, tellurium, osmium, and other heavy metals in recurrent pregnancy loss: A novel approach. Int J Gynaecol Obstet 160(3):790-796. https://doi.org/10.1002/ijgo.14390.

Tan YM, Chan M, Chukwudebe A, et al. 2020. PBPK model reporting template for chemical risk assessment applications. Regul Toxicol Pharmacol 115:104691. https://doi.org/10.1016/j.yrtph.2020.104691.

Tong J, Liang CM, Huang K, et al. 2020. Prenatal serum thallium exposure and 36-month-old children's attention-deficit/hyperactivity disorder symptoms: Ma'anshan birth cohort study. Chemosphere 244:125499. https://doi.org/10.1016/j.chemosphere.2019.125499.

Tong J, Liang C, Wu X, et al. 2022. Prenatal serum thallium exposure and cognitive development among preschool-aged children: A prospective cohort study in China. Environ Pollut 293:118545. https://doi.org/10.1016/j.envpol.2021.118545.

TRI22. 2024. Thallium. TRI explorer: release reports. Washington, DC: Toxics Release Inventory. U.S. Environmental Protection Agency. https://enviro.epa.gov/triexplorer/tri_release.chemical. January 11, 2024.

Tromme I, Van Neste D, Dobbelaere F, et al. 1998. Skin signs in the diagnosis of thallium poisoning. Br J Dermatol 138(2):321-325. https://doi.org/10.1046/j.1365-2133.1998.02083.x.

Tsai YT, Huang CC, Kuo HC, et al. 2006. Central nervous system effects in acute thallium poisoning. Neurotoxicology 27(2):291-295. https://doi.org/10.1016/j.neuro.2005.10.009.

U.S. Bureau of Mines. 1983. Thallium. Mineral commodity summaries. Washington, DC: U.S. Bureau of Mines.

U.S. Bureau of Mines. 1988. Thallium. Mineral commodity summaries. Washington, DC: U.S. Bureau of Mines.

USGS. 2002. Magnitude and extent of arsenic and thallium concentrations in ground water and sediments at the Charleston Naval Complex, North Charleston, South Carolina, 1994-99. Columbia, SC: U.S. Geological Survey. Water-Resources Investigations Report 02-4226. https://pubs.usgs.gov/wri/2002/4226/report.pdf. January 12, 2024.

USGS. 2011. Trace elements and radon in groundwater across the United States, 1992–2003. Reston, VA: U.S. Geological Survey. Scientific Investigations Report 2011–5059. https://pubs.usgs.gov/sir/2011/5059/pdf/sir2011-5059_report-covers_508.pdf. January 12, 2024.

USGS. 2014. Geochemical and mineralogical maps for soils of the conterminous United States. Reston, VA: U.S. Geological Survey. Open-File Report 2014–1082. https://doi.org/10.3133/ofr20141082.

USGS. 2023. Thallium. Mineral commodity summaries, January 2023. U.S. Geological Survey. https://pubs.usgs.gov/periodicals/mcs2023/mcs2023-thallium.pdf. January 11, 2024.

USGS. 2024. Thallium. Mineral commodity summaries, January 2024. U.S. Geological Survey. https://pubs.usgs.gov/periodicals/mcs2024/mcs2024.pdf. January 11, 2024.

Valerio F, Brescianini C, Mazzucotelli A, et al. 1988. Seasonal variation of thallium, lead, and chromium concentrations in airborne particulate matter collected in an urban area. Sci Total Environ 71(3):501-509. https://doi.org/10.1016/0048-9697(88)90224-0.

Villanueva E, Hernandez-Cueto C, Lachica E, et al. 1990. Poisoning by thallium. A study of five cases. Drug safety 5(5):384-389. https://doi.org/10.2165/00002018-199005050-00006.

Vrij AA, Cremers HM, Lustermans FA. 1995. Successful recovery of a patient with thallium poisoning. Neth J Med 47(3):121-126. https://doi.org/10.1016/0300-2977(95)00006-9.

Wallwork-Barber MK, Lyall K, Ferenbaugh RW. 1985. Thallium movement in a simple aquatic ecosystem. J Environ Sci Health 20(6):689-700. https://doi.org/10.1080/10934528509375252.

Wang Q, Huang X, Liu L. 2007. Analysis of nine cases of acute thallium poisoning. J Huazhong Univ Sci Technolog Med Sci 27(2):213-216. https://doi.org/10.1007/s11596-007-0229-4.

Wang YX, Sun Y, Huang Z, et al. 2016. Associations of urinary metal levels with serum hormones, spermatozoa apoptosis and sperm DNA damage in a Chinese population. Environ Int 94:177-188. https://doi.org/10.1016/j.envint.2016.05.022.

Wang X, Karvonen-Gutierrez CA, Herman WH, et al. 2020. Urinary metals and incident diabetes in midlife women: Study of Women's Health Across the Nation (SWAN). BMJ Open Diabetes Res Care 8(1):e001233. https://doi.org/10.1136/bmjdrc-2020-001233.

Wang TT, Wen B, Yu XN, et al. 2021. Early diagnosis, treatment, and outcomes of five patients with acute thallium poisoning. World J Clin Cases 9(19):5082-5091. https://doi.org/10.12998/wjcc.v9.i19.5082.

Wang S, Sun J, Tang C, et al. 2022a. Association between urinary thallium exposure and cardiovascular disease in U.S. adult population. Chemosphere 294:133669. https://doi.org/10.1016/j.chemosphere.2022.133669.

Wang X, Xiao P, Wang R, et al. 2022b. Relationships between urinary metals concentrations and cognitive performance among U.S. older people in NHANES 2011-2014. Front Public Health 10:985127. https://doi.org/10.3389/fpubh.2022.985127.

Wang X, Karvonen-Gutierrez CA, Herman WH, et al. 2022c. Metals and risk of incident metabolic syndrome in a prospective cohort of midlife women in the United States. Environ Res 210:112976. https://doi.org/10.1016/j.envres.2022.112976.

Wang W, Xiang LY, Ma YC, et al. 2023. The association between heavy metal exposure and erectile dysfunction in the United States. Asian J Androl 25(2):271-276. https://doi.org/10.4103/aja202237.

Weaver VM, Vargas GG, Silbergeld EK, et al. 2014. Impact of urine concentration adjustment method on associations between urine metals and estimated glomerular filtration rates (eGFR) in adolescents. Environ Res 132:226-232. https://doi.org/10.1016/j.envres.2014.04.013.

WHO. 1996. Thallium. Environmental health criteria 182. Geneva: World Health Organization. https://www.inchem.org/documents/ehc/ehc/ehc182.htm. January 10, 2024.

WHO. 2010. WHO guidelines for indoor air quality: Selected pollutants. World Health Organization. https://www.who.int/publications/i/item/9789289002134. April 25, 2012.

WHO. 2022. Guidelines for drinking-water quality. Fourth edition incorporating the first and second addenda. Geneva: World Health Organization. https://www.who.int/publications/i/item/9789240045064. September 18, 2023.

Wick S, Baeyens B, Marques Fernandes M, et al. 2020. Thallium sorption and speciation in soils: Role of micaceous clay minerals and manganese oxides. Geochim Cosmochim Acta 288:83-100. https://doi.org/10.1016/j.gca.2020.07.037.

WQP. 2024. Thallium. Water quality portal Advisory Committee on Water Information (ACWI); Agricultural Research Service (ARS); Environmental Protection Agency (EPA); National Water Quality Monitoring Council (NWQMC); United States Geological Survey (USGS). https://www.waterqualitydata.us/portal/. January 1, 2024.

Wu M, Shu Y, Wang Y. 2022. Exposure to mixture of heavy metals and muscle strength in children and adolescents: a population-based study. Environ Sci Pollut Res Int 29(40):60269-60277. https://doi.org/10.1007/s11356-022-19916-2.

Wu Y, Zeng F, Li J, et al. 2023. Sex-specific relationships between prenatal exposure to metal mixtures and birth weight in a Chinese birth cohort. Ecotoxicol Environ Saf 262:115158. https://doi.org/10.1016/j.ecoenv.2023.115158.

Xia W, Du X, Zheng T, et al. 2016. A case-control study of prenatal thallium exposure and low birth weight in China. Environ Health Perspect 124(1):164-169. https://doi.org/10.1289/ehp.1409202.

Xie Z, Aimuzi R, Si M, et al. 2023. Associations of metal mixtures with metabolic-associated fatty liver disease and non-alcoholic fatty liver disease: NHANES 2003-2018. Front Public Health 11:1133194. https://doi.org/10.3389/fpubh.2023.1133194.

Yao L, Liu L, Dong M, et al. 2022. Trimester-specific prenatal heavy metal exposures and sex-specific postpartum size and growth. J Expo Sci Environ Epidemiol 33(6):895-902. https://doi.org/10.1038/s41370-022-00443-8.

8. REFERENCES

Yorita Christensen KL. 2013. Metals in blood and urine, and thyroid function among adults in the United States 2007-2008. Int J Hyg Environ Health 216(6):624-632. https://doi.org/10.1016/j.ijheh.2012.08.005.

Yu YJ, Li ZC, Zhou Y, et al. 2023. Associations between trace level thallium and multiple health effects in rural areas: Chinese Exposure and Response Mapping Program (CERMP). Sci Total Environ 862:160466. https://doi.org/10.1016/j.scitotenv.2022.160466.

Zasukhina GD, Vasilyeva IM, Sdirkova NI, et al. 1983. Mutagenic effect of thallium and mercury salts on rodent cells with different repair activities. Mutat Res 124(2):163-173. https://doi.org/10.1016/0165-1218(83)90176-3.

Zavaliy LB, Petrikov SS, Simonova AY, et al. 2021. Diagnosis and treatment of persons with acute thallium poisoning. Toxicol Rep 8:277-281. https://doi.org/10.1016/j.toxrep.2021.01.013.

Zhang HT, Qiao BP, Liu BP, et al. 2014. Study on the treatment of acute thallium poisoning. Am J Med Sci 347(5):377-381. https://doi.org/10.1097/MAJ.0b013e318298de9c.

Zhao G, Ding M, Zhang B, et al. 2008. Clinical manifestations and management of acute thallium poisoning. Eur Neurol 60(6):292-297. https://doi.org/10.1159/000157883.

Zhou H, Sun X, Wang Y, et al. 2021a. The mediating role of placental weight change in the association between prenatal exposure to thallium and birth weight: A prospective birth cohort study. Front Public Health 9:679406. https://doi.org/10.3389/fpubh.2021.679406.

Zhou TT, Hu B, Meng XL, et al. 2021b. The associations between urinary metals and metal mixtures and kidney function in Chinese community-dwelling older adults with diabetes mellitus. Ecotoxicol Environ Saf 226:112829. https://doi.org/10.1016/j.ecoenv.2021.112829.

Zhu B, Liang C, Yan S, et al. 2019. Association between serum thallium in early pregnancy and risk of gestational diabetes mellitus: The Ma'anshan birth cohort study. J Trace Elem Med Biol 52:151-156. https://doi.org/10.1016/j.jtemb.2018.12.011.

Zitko V, Carson WV. 1975. Accumulation of thallium in clams and mussels. Bull Environ Contam Toxicol 14(5):530-533. https://doi.org/10.1007/BF01683366.

Zitko V, Carson WV, Carson WG. 1975. Thallium: occurrence in the environment and toxicity to fish. Bull Environ Contam Toxicol 13(1):23-30. https://doi.org/10.1007/BF01684859.

Zou P, Li M, Chen W, et al. 2022. Association between trace metals exposure and hearing loss. Front Public Health 10:973832. https://doi.org/10.3389/fpubh.2022.973832.

APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Thallium compounds
CAS Numbers: Various CAS numbers
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: An acute-duration inhalation MRL was not derived for thallium due to the lack of acute-duration inhalation studies.

Rationale for Not Deriving an MRL: No acute-duration inhalation studies were identified for thallium.

Agency Contact (Chemical Manager): Fahim Atif

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Thallium compounds
CAS Numbers: Various CAS numbers
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: An intermediate-duration inhalation MRL was not derived for thallium due to the lack of intermediate-duration inhalation studies.

Rationale for Not Deriving an MRL: No intermediate-duration inhalation studies were identified for thallium.

Agency Contact (Chemical Manager): Fahim Atif

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Thallium compounds
CAS Numbers: Various CAS numbers
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: A chronic-duration inhalation MRL was not derived for thallium due to the limitations in the small number of chronic-duration exposure studies.

Rationale for Not Deriving an MRL: Several studies have evaluated the toxicity of airborne thallium in humans (Ludolph et al. 1986; Marcus 1985; Peng et al. 2022; Qiu et al. 2022). A study in workers reported paresthesia (Ludolph et al. 1986); another study found no cardiovascular effects and a lower incidence of gastrointestinal effects (Marcus 1985). In studies examining the relationship between the thallium content of $PM_{2.5}$ and adverse health effects, alterations in parameters of renal function (Peng et al. 2022) or no effect on thyroid hormone levels (Qiu et al. 2022) were reported. None of the available studies evaluated a wide range of potential health effects and poorly characterized exposure characteristics. Therefore, studies were not considered suitable for MRL derivation. No chronic-duration inhalation studies in animals were identified for thallium.

Agency Contact (Chemical Manager): Fahim Atif

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Thallium compounds
CAS Numbers: Various CAS numbers
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: The available database was considered inadequate for derivation of an acute-duration oral MRL for thallium. Studies on the acute oral toxicity of thallium in humans are limited to case reports, most of which did not report doses. A small number of limited-scope acute oral studies in animals have been identified; however, these studies do not allow for identification of sensitive targets of toxicity and the lowest dose tested resulted in increases in mortality.

Rationale for Not Deriving an MRL: Information on the toxicity of thallium following acute oral exposure comes from numerous case reports of intentional or accidental poisonings and a small number of animal studies. Although a wide variety of effects have been reported in individuals acutely ingesting thallium, the most consistently reported effects are cardiovascular (e.g., tachycardia, hypertension, EKG alterations), gastrointestinal (e.g., abdominal pain, nausea/vomiting, constipation), dermal (e.g., alopecia), and neurological (peripheral neuropathy resulting in paresthesia, hyperalgesia, and weakness) effects. In a small number of case reports, dose information was provided; however, case reports are not considered suitable for derivation of an MRL because they typically only involve one person and there is no control group.

A small number of studies in animals have evaluated the acute oral toxicity. Increases in lethality were observed in rats at ≥15 mg thallium/kg following a single-dose exposure (Downs et al. 1960; Leloux et al. 1987) and at 0.77 mg thallium/kg/day following a 4-day exposure (Leloux et al. 1987). In mice and rabbits, deaths were observed at 2.5 and 61 mg thallium/kg, respectively (Grunfeld et al. 1963; Rao et al. 1993). Other observed effects include body weight decreases, diarrhea, alopecia, and decreases in spontaneous activity. Effects observed at doses that did not cause deaths in the study are summarized in Table A-1. In addition to the effects listed in Table A-1, there is some evidence of neurodevelopmental and hepatic effects. Bornhausen and Hagen (1984) reported impaired performance on an operant behavior test in the offspring of rat dams administered thallium I sulfate on GDs 6–9. However, poor reporting of the methods and results precludes an independent evaluation of the study. Li et al. (2022a) reported hepatic sinus congestion and necrosis in mice exposed to thallium I nitrate (1.2 mg thallium/kg/day) or thallium III nitrate (0.7 mg thallium/kg/day) for 2 weeks; however, no incidence data were provided to evaluate whether the incidence was significantly different from controls. The study also reported alterations in the levels of hepatic fatty acids in mice exposed to 1.2 mg thallium/kg/day as thallium I nitrate or to 0.7 mg thallium/kg/day as thallium III nitrate (Li et al. 2022a). However, the toxicological significance of these alterations is not known.

Table A-1. Summary of NOAEL and LOAEL Values in Animals Following Acute Oral Exposure to Thallium

Species, duration	Effect	Compound	NOAEL (mg Tl/kg/day)	LOAEL (mg Tl/kg/day)	Reference
Mouse, 2 weeks	Decreased terminal body weight (11–16%)	Thallium I sulfate	0.4 (M) 0.7 (F)	0.9 (M) 1.5 (F)	Shipkowski et al. 2023

Table A-1. Summary of NOAEL and LOAEL Values in Animals Following Acute Oral Exposure to Thallium

Species, duration	Effect	Compound	NOAEL (mg Tl/kg/day)	LOAEL (mg Tl/kg/day)	Reference
Mouse, 1 week	Decreased terminal body weight (21%)	Thallium I nitrate		8 (serious LOAEL)	Li et al. 2023a
Mouse, 1 week	Decreased relative thymus weight, decreased B cell frequency in bone marrow, blood, and spleen	Thallium I nitrate		8	Li et al. 2023a
Rat, 1 day	Diarrhea	Thallium I sulfate		18.2	Rusyniak et al. 2003
Rat, 1 day	Alopecia	Thallium I sulfate		18.2	Rusyniak et al. 2003
Rat, 1 day	Decreased spontaneous activity	Thallium I sulfate		18.2	Rusyniak et al. 2003

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

None of the available studies identified a reliable LOAEL that was lower than the lowest dose associated with lethality (0.77 mg thallium/kg/day as thallium I nitrate). Thus, an acute-duration oral MRL is not derived.

Agency Contact (Chemical Manager): Fahim Atif

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Thallium compounds
CAS Numbers: Various CAS numbers
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: The database was not considered adequate for derivation of an intermediate-duration oral MRL for thallium due to uncertainty of whether the alopecia observed at the lowest LOAEL was related to thallium exposure.

Rationale for Not Deriving an MRL: No human studies have evaluated the toxicity of thallium following intermediate-duration oral exposure; nine animal studies have been identified, the results of these studies are summarized in Table A-2. Alopecia is the most consistently reported effect reported in intermediate-duration oral studies. Alopecia is also commonly reported in humans acutely exposed to thallium and typically occurs 1–3 weeks after exposure.

Table A-2. Summary of NOAEL and LOAEL Values in Animals Following Intermediate Oral Exposure to Thallium

Species, duration	Effect	Compound	NOAEL (mg Tl/kg/day)	LOAEL (mg Tl/kg/day)	Reference
Rat, 90 days	Alopecia	Thallium I sulfate		0.2[a]	EPA 1986
Rat, 9–15 weeks	Alopecia	Thallium I acetate	0.4	1.1	Downs et al. 1960
Rat, 30 or 60 days	Irritability	Thallium I sulfate		1.2	Gregotti et al. 1985
Rat, 60 days	Decreased sperm motility	Thallium I sulfate		1.3	Formigli et al. 1986
Rat, 36 weeks	Alopecia	Thallium I sulfate		1.5[b]	Manzo et al. 1983
Rat, 36 weeks	Decreased motor and sensory action potentials	Thallium I sulfate		1.5[b]	Manzo et al. 1983
Rat, 9–15 weeks	Alopecia	Thallium I oxide		1.6	Downs et al. 1960
Rat, 21 weeks	Alopecia	Thallium I acetate		2[b]	Gross et al. 1948
Rat, GD 6–PND 28	Alopecia in dams and pups	Thallium I sulfate	1	2.2	Shipkowski et al. 2023

Table A-2. Summary of NOAEL and LOAEL Values in Animals Following Intermediate Oral Exposure to Thallium

Species, duration	Effect	Compound	NOAEL (mg Tl/kg/day)	LOAEL (mg Tl/kg/day)	Reference
Rat, GD 6–PND 28	Decreased pup body weight	Thallium I sulfate	1	2.2	Shipkowski et al. 2023

[a]There is uncertainty whether this dose is a LOAEL, see text for additional information.
[b]Increased mortality was also observed at this dose level.

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PND = postnatal day

The lowest dose associated with an adverse effect is 0.20 mg thallium/kg/day reported in the EPA (1986) rat study. The incidence of alopecia in this study (as presented in EPA 2009a) was observed in 2/20, 1/20, 4/20, 9/20, and 4/20 male rats and 4/20, 1/20, 4/20, 9/20, and 12/20 female rats in the untreated controls, vehicle controls, and 0.008, 0.04, and 0.20 mg thallium/kg/day groups, respectively. However, some of the alopecia was attributed to barbering behavior (defined as abnormal whisker or fur plucking behavior). In the 0.20 mg thallium/kg/day female rats, five instances of alopecia were not attributed to barbering behavior; this incidence is significantly higher than controls. Atrophy of hair follicles was also observed in two of the females in the 0.20 mg thallium/kg/day group with alopecia; this effect was not observed in the males at this dose level or in the male or female vehicle controls. The study investigators did not consider the alopecia to be toxicologically significant and attributed it to the cyclic pattern of hair growth in rats. Although there is some uncertainty, ATSDR considered alopecia to be a thallium-related and adverse effect. This consideration is supported by the findings of alopecia in several other intermediate-duration animal studies (Downs et al. 1960; Manzo et al. 1983; Shipkowski et al. 2023) and in humans acutely exposed to thallium (for example, Al Hammouri et al. 2011; Almassri and Sekkarie 2018; Desenclos et al. 1992; Sun et al. 2012; Villanueva et al. 1990; Wang et al. 2007; Zavaliy et al. 2021; Zhang et al. 2014). However, the uncertainty of the interpretation of the EPA (1986) findings precludes identifying a LOAEL and using the study as the basis of an intermediate-duration oral MRL. The Downs et al. (1960) study of thallium I acetate was not considered suitable for MRL derivation due to the high mortality in the control group (two of five males and two of five females died after 12 and 8 weeks of exposure, respectively) and the uncertainty in whether basing an MRL of a NOAEL of 0.4 mg thallium/kg/day would be protective for alopecia given the possible LOAEL of 0.2 mg thallium/kg/day identified in the EPA (1986) study.

Agency Contact (Chemical Manager): Fahim Atif

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Thallium compounds
CAS Numbers: Various CAS numbers
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: The database was considered inadequate for derivation of a chronic-duration oral MRL for thallium. Although a number of epidemiological studies have been identified, they were not considered suitable for MRL derivation due to inconsistent or unsupported findings and lack of a pharmacokinetic model to convert urinary (or blood) thallium levels to intakes.

Rationale for Not Deriving an MRL: A number of epidemiological studies have evaluated possible associations between thallium exposure and adverse effects; the majority of the studies were cross-sectional in design and were conducted in the general population with no known source of elevated thallium exposure. Interpretation of the results of these studies is limited by the lack of consistent findings. In addition, many outcomes were only examined in one or two studies. Another limitation of the epidemiological studies is that none of the studies reported external doses; exposure was assessed using biomarkers of exposure, typically urinary thallium levels or blood thallium levels, or did not provide exposure information. However, pharmacokinetic models relating urinary or blood thallium levels to thallium intake have not been identified. The lack of consistent or supported findings and the lack of pharmacokinetic models to estimate doses preclude using the epidemiological studies as the basis of an MRL. No chronic-duration oral animal studies were identified.

Agency Contact (Chemical Manager): Fahim Atif

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR THALLIUM

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to thallium.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for thallium. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of thallium have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of thallium are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the 1992 toxicological profile for thallium; thus, the literature search was restricted to studies published between January 1990 and July 2023. The following main databases were searched in July 2023:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for thallium. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to thallium were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
07/2023	((("Thallium/toxicity"[mh] OR "Thallium/adverse effects"[mh] OR "Thallium/poisoning"[mh] OR "Thallium/pharmacokinetics"[mh]) OR ("Thallium"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Thallium"[mh] AND toxicokinetics[mh:noexp]) OR ("Thallium/blood"[mh] OR "Thallium/cerebrospinal fluid"[mh] OR "Thallium/urine"[mh]) OR ("Thallium"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Thallium"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Thallium/antagonists and inhibitors"[mh]) OR ("Thallium/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Thallium/pharmacology"[majr])) OR ("Thallium"[mh] AND ("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR "thallium acetate"[nm] OR ("Bithallium trisulfate"[tw] OR "Dithallium oxide"[tw] OR "dithallium trioxide"[tw] OR "Dithallium tris(sulphate)"[tw] OR "Dithalloxane-1,3-dione"[tw] OR "KRS-5"[tw] OR "Nitric acid, thallium salt"[tw] OR "Nitric acid, thallium(3+) salt"[tw] OR "Sulfuric acid, thallium(2+) salt"[tw] OR "Sulfuric acid, thallium(3+) salt"[tw] OR "Thallic nitrate"[tw] OR "Thallic oxide"[tw] OR "Thallic sulfate"[tw] OR "thallium bromide"[tw] OR "Thallium fluoride"[tw] OR "Thallium iodide"[tw] OR "Thallium monobromide"[tw] OR "Thallium monofluoride"[tw] OR "thallium monoiodide"[tw] OR "Thallium oxide"[tw] OR "Thallium peroxide"[tw] OR "Thallium sesquioxide"[tw] OR "Thallium tribromide"[tw] OR "Thallium trichloride"[tw] OR "Thallium trifluoride"[tw] OR "Thallium triiodide"[tw] OR "Thallium trinitrate"[tw] OR "Thallium

Table B-2. Database Query Strings

Database search date	Query string
	trioxide"[tw] OR "Thallium(1+) bromide"[tw] OR "Thallium(1+) iodide"[tw] OR "Thallium(1+) lambda 1 -thallanolate"[tw] OR "Thallium(1+) oxide"[tw] OR "Thallium(1+) thallium(3+) sulfate"[tw] OR "Thallium(3+) oxide"[tw] OR "Thallium(3+) sulfate"[tw] OR "Thallium(3+) tribromide"[tw] OR "Thallium(3+) trichloride"[tw] OR "Thallium(3+) trifluoride"[tw] OR "Thallium(3+) triiodide"[tw] OR "Thallium(3+) trinitrate"[tw] OR "Thallium(I) bromide"[tw] OR "Thallium(I) fluoride"[tw] OR "Thallium(I) iodide"[tw] OR "Thallium(I) oxide"[tw] OR "Thallium(II) sulfate"[tw] OR "Thallium(III) bromide"[tw] OR "Thallium(III) chloride"[tw] OR "Thallium(III) iodide"[tw] OR "Thallium(III) oxide"[tw] OR "Thallium(III) sulfate"[tw] OR "Thallous bromide"[tw] OR "Thallous fluoride"[tw] OR "Thallous iodide"[tw] OR "Thallous oxide"[tw]) OR (("thallium"[tw] OR "dithallium"[tw] OR "thallic"[tw] OR "thallous"[tw] OR "Bithallium trisulfate"[tw] OR "Bonide antzix"[tw] OR "Carbonic acid, dithallium(1+) salt"[tw] OR "Dithalloxane-1,3-dione"[tw] OR "Eccothal"[tw] OR "KRS-5"[tw] OR "Ramor"[tw] OR "Ratox"[tw] OR "Tharattin"[tw] OR "Th-Universal"[tw] OR "Triacetatothallium(III)"[tw] OR "Tris(acetato)thallium"[tw] OR "Zelio"[tw] OR "thallium208"[tw] OR "208thallium"[tw] OR "tl-208"[tw] OR "tl208"[tw] OR "208tl"[tw] OR "208-tl"[tw] OR "thallium201"[tw] OR "201thallium"[tw] OR "tl-201"[tw] OR "tl201"[tw] OR "201tl"[tw] OR "201-tl"[tw] OR "thallium199"[tw] OR "199thallium"[tw] OR "tl-199"[tw] OR "tl199"[tw] OR "199tl"[tw] OR "199-tl"[tw] OR "thallium200"[tw] OR "200thallium"[tw] OR "tl-200"[tw] OR "tl200"[tw] OR "200tl"[tw] OR "200-tl"[tw] OR "thallium202"[tw] OR "202thallium"[tw] OR "tl-202"[tw] OR "tl202"[tw] OR "202tl"[tw] OR "202-tl"[tw] OR "thallium204"[tw] OR "204thallium"[tw] OR "tl-204"[tw] OR "tl204"[tw] OR "204tl"[tw] OR "204-tl"[tw] OR "thallium210"[tw] OR "210thallium"[tw] OR "tl-210"[tw] OR "tl210"[tw] OR "210tl"[tw] OR "210-tl"[tw]) NOT medline[sb]) OR ("Thallium Radioisotopes/toxicity"[mh] OR "Thallium Radioisotopes/adverse effects"[mh] OR "Thallium Radioisotopes/poisoning"[mh] OR "Thallium Radioisotopes/pharmacokinetics"[mh]) OR ("Thallium Radioisotopes"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Thallium Radioisotopes"[mh] AND toxicokinetics[mh:noexp]) OR ("Thallium Radioisotopes/blood"[mh] OR "Thallium Radioisotopes/cerebrospinal fluid"[mh] OR "Thallium Radioisotopes/urine"[mh]) OR ("Thallium Radioisotopes"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Thallium Radioisotopes"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Thallium Radioisotopes/antagonists and inhibitors"[mh]) OR ("Thallium Radioisotopes/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Thallium Radioisotopes/pharmacology"[majr]) OR ("Thallium Radioisotopes"[mh] AND ("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR (("Thallium"[mh] OR "Thallium Radioisotopes"[mh]) AND (indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR "serum"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh]))) AND (2020/10/01:3000[mhda] OR 2020/10/01:3000[edat] OR 2020/10/01:3000[crdat])
11/2020	(((((("Thallium/toxicity"[mh] OR "Thallium/adverse effects"[mh] OR "Thallium/poisoning"[mh] OR "Thallium/pharmacokinetics"[mh]) OR ("Thallium"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Thallium"[mh] AND toxicokinetics[mh:noexp]) OR ("Thallium/blood"[mh] OR "Thallium/cerebrospinal fluid"[mh] OR "Thallium/urine"[mh]) OR ("Thallium"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Thallium"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Thallium/antagonists and inhibitors"[mh]) OR ("Thallium/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Thallium"[mh] AND cancer[sb]) OR ("Thallium/pharmacology"[majr]))) OR ("thallium acetate"[nm]) OR (("Bithallium trisulfate"[tw] OR "Dithallium oxide"[tw] OR "dithallium trioxide"[tw] OR "Dithallium tris(sulphate)"[tw] OR "Dithalloxane-1,3-dione"[tw] OR "KRS-5"[tw] OR "Nitric acid, thallium salt"[tw] OR "Nitric acid, thallium(3+) salt"[tw] OR "Sulfuric acid, thallium(2+) salt"[tw] OR "Sulfuric acid, thallium(3+) salt"[tw] OR "Thallic nitrate"[tw] OR "Thallic oxide"[tw] OR "Thallic sulfate"[tw] OR "thallium bromide"[tw] OR "Thallium fluoride"[tw] OR "Thallium iodide"[tw] OR "Thallium monobromide"[tw] OR "Thallium monofluoride"[tw] OR "thallium monoiodide"[tw] OR "Thallium oxide"[tw] OR "Thallium peroxide"[tw] OR "Thallium sesquioxide"[tw] OR "Thallium tribromide"[tw] OR "Thallium trichloride"[tw] OR "Thallium trifluoride"[tw] OR "Thallium triiodide"[tw] OR "Thallium trinitrate"[tw] OR "Thallium trioxide"[tw] OR "Thallium(1+) bromide"[tw] OR "Thallium(1+) iodide"[tw] OR "Thallium(1+) lambda 1 -thallanolate"[tw] OR "Thallium(1+) oxide"[tw] OR "Thallium(1+) thallium(3+) sulfate"[tw] OR "Thallium(3+) oxide"[tw] OR "Thallium(3+) sulfate"[tw] OR "Thallium(3+) tribromide"[tw] OR "Thallium(3+) trichloride"[tw] OR "Thallium(3+) trifluoride"[tw] OR "Thallium(3+) triiodide"[tw] OR "Thallium(3+) trinitrate"[tw] OR "Thallium(I) bromide"[tw] OR "Thallium(I) fluoride"[tw] OR "Thallium(I) iodide"[tw] OR "Thallium(I) oxide"[tw] OR "Thallium(II) sulfate"[tw] OR "Thallium(III) bromide"[tw] OR "Thallium(III) chloride"[tw] OR "Thallium(III) iodide"[tw] OR "Thallium(III) oxide"[tw] OR "Thallium(III) sulfate"[tw] OR "Thallous bromide"[tw] OR "Thallous fluoride"[tw] OR "Thallous iodide"[tw] OR "Thallous oxide"[tw])) OR ((thallium OR dithallium OR thallic OR thallous OR "Bithallium trisulfate"[tw] OR "Bonide antzix"[tw] OR "Carbonic acid, dithallium(1+) salt"[tw] OR "Dithalloxane-1,3-dione"[tw] OR "Eccothal"[tw] OR "KRS-5"[tw] OR "Ramor"[tw] OR "Ratox"[tw] OR "Tharattin"[tw] OR "Th-Universal"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"Triacetatothallium(III)"[tw] OR "Tris(acetato)thallium"[tw] OR "Zelio"[tw] OR "thallium208"[tw] OR "208thallium"[tw] OR "tl-208"[tw] OR "tl208"[tw] OR "208tl"[tw] OR "208-tl"[tw] OR "thallium201"[tw] OR "201thallium"[tw] OR "tl-201"[tw] OR "tl201"[tw] OR "201tl"[tw] OR "201-tl"[tw] OR "thallium199"[tw] OR "199thallium"[tw] OR "tl-199"[tw] OR "tl199"[tw] OR "199tl"[tw] OR "199-tl"[tw] OR "thallium200"[tw] OR "200thallium"[tw] OR "tl-200"[tw] OR "tl200"[tw] OR "200tl"[tw] OR "200-tl"[tw] OR "thallium202"[tw] OR "202thallium"[tw] OR "tl-202"[tw] OR "tl202"[tw] OR "202tl"[tw] OR "202-tl"[tw] OR "thallium204"[tw] OR "204thallium"[tw] OR "tl-204"[tw] OR "tl204"[tw] OR "204tl"[tw] OR "204-tl"[tw] OR "thallium210"[tw] OR "210thallium"[tw] OR "tl-210"[tw] OR "tl210"[tw] OR "210tl"[tw] OR "210-tl"[tw]) NOT medline[sb]) OR ((("Thallium Radioisotopes/toxicity"[mh] OR "Thallium Radioisotopes/adverse effects"[mh] OR "Thallium Radioisotopes/poisoning"[mh] OR "Thallium Radioisotopes/pharmacokinetics"[mh]) OR ("Thallium Radioisotopes"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Thallium Radioisotopes"[mh] AND toxicokinetics[mh:noexp]) OR ("Thallium Radioisotopes/blood"[mh] OR "Thallium Radioisotopes/cerebrospinal fluid"[mh] OR "Thallium Radioisotopes/urine"[mh]) OR ("Thallium Radioisotopes"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Thallium Radioisotopes"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Thallium Radioisotopes/antagonists and inhibitors"[mh]) OR ("Thallium Radioisotopes/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Thallium Radioisotopes"[mh] AND cancer[sb]) OR ("Thallium Radioisotopes/pharmacology"[majr]))))) AND (1990:3000[dp] OR 1990:3000[mhda] OR 1990:3000[crdt] OR 1990:3000[edat]))
NTRL	
07/2023	Date Published 1990 to 2023 "thallium" OR "dithallium" OR "thallic" OR "thallous" OR "Bithallium trisulfate" OR "Bonide antzix" OR "Carbonic acid, dithallium(1+) salt" OR "Dithalloxane-1,3-dione" OR "Eccothal" OR "KRS-5" OR "Ramor" OR "Ratox" OR "Tharattin" OR "Th-Universal" OR "Triacetatothallium(III)" OR "Tris(acetato)thallium" OR "Zelio" OR "thallium208" OR "208thallium" OR "tl-208" OR "tl208" OR "208tl" OR "208-tl" OR "thallium201" OR "201thallium" OR "tl-201" OR "tl201" OR "201tl" OR "201-tl" OR "thallium199" OR "199thallium" OR "tl-199" OR "tl199" OR "199tl" OR "199-tl" OR "thallium200" OR "200thallium" OR "tl-200" OR "tl200" OR "200tl" OR "200-tl" OR "thallium202" OR "202thallium" OR "tl-202" OR "tl202" OR "202tl" OR "202-tl" OR "thallium204" OR "204thallium" OR "tl-204" OR "tl204" OR "204tl" OR "204-tl" OR "thallium210" OR "210thallium" OR "tl-210" OR "tl210" OR "210tl" OR "210-tl"
Toxcenter	
07/2023	FILE 'TOXCENTER' ENTERED AT 10:46:34 ON 03 JUL 2023 L1 12931 SEA FILE=TOXCENTER 7440-28-0 OR 563-68-8 OR 2570-63-0 OR 15843-14-8 OR 13453-32-2 OR 7791-12-0 OR 10102-45-1 OR

Table B-2. Database Query Strings

Database search date	Query string
	1314-32-5 OR 1314-12-1 OR 7446-18-6 OR 10031-59-1 OR 6533-73-9 OR 29809-42-5 OR 7789-40-4 OR 7790-30-9 OR 7789-27-
	L2 373 SEA FILE=TOXCENTER 15230-71-4 OR 13746-98-0 OR 16901-76-1 OR 16222-66-5 OR 37475-01-7 OR 13701-90-1 OR 57232-83-4 OR 13453-37-7 OR 7783-57-5 OR 14627-67-9 OR 22537-56-0
	L3 1178 SEA FILE=TOXCENTER 14913-50-9 OR 15064-65-0 OR 15064-66-1 OR 15720-55-5 OR 15720-57-7 OR 13968-51-9 OR 13966-01-3
	L4 0 SEA FILE=TOXCENTER 55172â□□29â□□7
	L5 14345 SEA FILE=TOXCENTER L1 OR L2 OR L3
	L6 1582 SEA FILE=TOXCENTER L5 AND ED>=20201001
	L7 1582 SEA FILE=TOXCENTER L6 NOT TSCATS/FS
	L8 1395 SEA FILE=TOXCENTER L7 NOT PATENT/DT
	ACT TOXQUERY/Q

	L9 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L10 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L11 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L12 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L13 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L14 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L15 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L16 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L17 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L18 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L19 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L20 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L21 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L22 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L23 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L24 QUE (ENDOCRIN? AND DISRUPT?)
	L25 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L26 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L27 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)

Table B-2. Database Query Strings

Database search date	Query string
	L28 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L29 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L30 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L31 QUE (NEPHROTOX? OR HEPATOTOX?)
	L32 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L33 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L34 QUE L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33
	L35 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L36 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L37 QUE L34 OR L35 OR L36
	L38 QUE (NONHUMAN MAMMALS)/ORGN
	L39 QUE L37 OR L38
	L40 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L41 QUE L39 OR L40

	L42 819 SEA FILE=TOXCENTER L8 AND L41
	L43 97 SEA FILE=TOXCENTER L42 AND MEDLINE/FS
	L44 722 SEA FILE=TOXCENTER L42 NOT MEDLINE/FS
	L45 703 DUP REM L43 L44 (116 DUPLICATES REMOVED)
	L*** DEL 97 S L42 AND MEDLINE/FS
	L*** DEL 97 S L42 AND MEDLINE/FS
	L46 97 SEA FILE=TOXCENTER L45
	L*** DEL 722 S L42 NOT MEDLINE/FS
	L*** DEL 722 S L42 NOT MEDLINE/FS
	L47 606 SEA FILE=TOXCENTER L45
	L48 606 SEA FILE=TOXCENTER (L46 OR L47) NOT MEDLINE/FS D SCAN L48
	L49 0 SEA "55172â□□29â□□7"
11/2020	FILE 'TOXCENTER' ENTERED AT 13:47:07 ON 05 NOV 2020
	L1 11321 SEA FILE=TOXCENTER 7440-28-0 OR 563-68-8 OR 2570-63-0 OR 15843-14-8 OR 13453-32-2 OR 7791-12-0 OR 10102-45-1 OR 1314-32-5 OR 1314-12-1 OR 7446-18-6 OR 10031-59-1 OR 6533-73-9 OR 29809-42-5 OR 7789-40-4 OR 7790-30-9 OR 7789-27-7
	L2 332 SEA FILE=TOXCENTER 15230-71-4 OR 13746-98-0 OR 16901-76-1 OR 16222-66-5 OR 37475-01-7 OR 13701-90-1 OR 57232-83-4 OR 13453-37-7 OR 7783-57-5 OR 14627-67-9 OR 22537-56-0

Table B-2. Database Query Strings

Database search date	Query string
	L4 1082 SEA FILE=TOXCENTER 14913-50-9 OR 15064-65-0 OR 15064-66-1 OR 15720-55-5 OR 15720-57-7 OR 13968-51-9 OR 13966-01-3 OR 55172&#8208
	L5 12614 SEA FILE=TOXCENTER L1 OR L2 OR L4
	L6 8889 SEA FILE=TOXCENTER L5 AND PY>1989
	L8 8889 SEA FILE=TOXCENTER L6 NOT TSCATS/FS
	L9 7764 SEA FILE=TOXCENTER L8 NOT PATENT/DT
	ACT TOXQUERY/Q

	L10 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L11 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L12 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L13 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L14 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L15 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L16 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L17 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L18 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L19 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L20 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L21 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L22 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L23 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L24 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L25 QUE (ENDOCRIN? AND DISRUPT?)
	L26 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L27 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L28 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L29 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L30 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)

Table B-2. Database Query Strings

Database search date	Query string
	L31 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L32 QUE (NEPHROTOX? OR HEPATOTOX?) L33 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L34 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L35 QUE L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33 OR L34 L36 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L37 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L38 QUE L35 OR L36 OR L37 L39 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L40 QUE L38 OR L39 --------- L41 3673 SEA FILE=TOXCENTER L9 AND L40 L42 505 SEA FILE=TOXCENTER L41 AND MEDLINE/FS L43 3168 SEA FILE=TOXCENTER L41 NOT MEDLINE/FS L44 3157 DUP REM L42 L41 (1021 DUPLICATES REMOVED) ANSWERS '1-3157' FROM FILE TOXCENTER L*** DEL 3673 S L9 AND L40 L*** DEL 3673 S L9 AND L40 L45 2652 SEA FILE=TOXCENTER L44 L*** DEL 505 S L41 AND MEDLINE/FS L*** DEL 505 S L41 AND MEDLINE/FS L46 505 SEA FILE=TOXCENTER L44 L47 2652 SEA FILE=TOXCENTER (L45 OR L46) NOT MEDLINE/FS

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
07/2023	Compounds searched: 7440-28-0; 563-68-8; 2570-63-0; 15843-14-8; 13453-32-2; 7791-12-0; 15230-71-4; 10102-45-1; 13746-98-0; 16901-76-1; 1314-32-5; 1314-12-1; 7446-18-6; 10031-59-1; 16222-66-5; 37475-01-7; 6533-73-9; 29809-42-5; 7789-40-4; 13701-90-1; 7790-30-9; 57232-83-4; 13453-37-7; 7789-27-7; 7783-57-5; 14627-67-9; 22537-56-0; 14913-50-9; 15064-65-0; 15064-66-1; 15720-55-5; 15720-57-7; 13968-51-9; 13966-01-3; 55172-29-7

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
NTP	
07/2023	7440-28-0 563-68-8 2570-63-0 15843-14-8 13453-32-2 7791-12-0 15230-71-4 10102-45-1 13746-98-0 16901-76-1 1314-32-5 1314-12-1 7446-18-6 10031-59-1 16222-66-5 37475-01-7 6533-73-9 29809-42-5 7789-40-4 13701-90-1 7790-30-9 57232-83-4 13453-37-7 7789-27-7 7783-57-5 14627-67-9 22537-56-0 14913-50-9 15064-65-0 15064-66-1 15720-55-5 15720-57-7 13968-51-9 13966-01-3 55172-29-7 "thallium" "dithallium" "thallic" "thallous" "bithallium" "Ramor" "Ratox" "Zelio" "Eccothal" "Tharattin" "Triacetatothallium" "Tris(acetato)thallium" "thallium208" "208thallium" "tl-208" "tl208" "208tl" "208-tl" "thallium201" "201thallium" "tl-201" "tl201" "201tl" "201-tl" "thallium199" "199thallium" "tl-199" "tl199" "199tl" "199-tl" "thallium200" "200thallium" "tl-200" "tl200" "200tl" "200-tl" "thallium202" "202thallium" "tl-202" "tl202" "202tl" "202-tl" "thallium204" "204thallium" "tl-204" "tl204" "204tl" "204-tl" "thallium210" "210thallium" "tl-210" "tl210" "210tl" "210-tl"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
Regulations.gov	
07/2023	Limited to Notices, 1990-present "7440-28-0" "563-68-8" "2570-63-0" "15843-14-8" "13453-32-2" "7791-12-0" "15230-71-4" "10102-45-1" "13746-98-0" "16901-76-1" "1314-32-5" "1314-12-1" "7446-18-6" "10031-59-1" "16222-66-5" "37475-01-7" "6533-73-9" "29809-42-5" "7789-40-4" "13701-90-1" "7790-30-9" "57232-83-4" "13453-37-7" "7789-27-7" "7783-57-5" "14627-67-9 " "22537-56-0" "14913-50-9" "15064-65-0" "15064-66-1" "15720-55-5" "15720-57-7" "13968-51-9" "13966-01-3" "55172-29-7" thallium dithallium bithallium thallic thallous triacetatothallium
NIH RePORTER	
01/2024	Search Criteria Fiscal Year: Active Projects Text Search: "thallium" OR "dithallium" OR "thallic" OR "thallous" OR "Bithallium trisulfate" OR "Bonide antzix" OR "Carbonic acid, dithallium(1+) salt" OR "Dithalloxane-1,3-dione" OR "Eccothal" OR "KRS-5" OR "Ramor" OR "Ratox" OR "Tharattin" OR "Th-Universal" OR "Triacetatothallium(III)" OR "Tris(acetato)thallium" OR "Zelio" OR "thallium208" OR "208thallium" OR "tl-208" OR "tl208" OR "208tl" OR "208-tl" OR "thallium201" OR "201thallium" OR "tl-201" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"tl201" OR "201tl" OR "201-tl" OR "thallium199" OR "199thallium" OR "tl-199" OR "tl199" OR "199tl" OR "199-tl" OR "thallium200" OR "200thallium" OR "tl-200" OR "tl200" OR "200tl" OR "200-tl" OR "thallium202" OR "202thallium" OR "tl-202" OR "tl202" OR "202tl" OR "202-tl" OR "thallium204" OR "204thallium" OR "tl-204" OR "tl204" OR "204tl" OR "204-tl" OR "thallium210" OR "210thallium" OR "tl-210" OR "tl210" OR "210tl" OR "210-tl" OR "Bithallium trisulfate" OR "Dithallium oxide" OR "dithallium trioxide" OR "Dithallium tris(sulphate)" OR "Dithalloxane-1,3-dione" OR "KRS-5" OR "Nitric acid, thallium salt" OR "Nitric acid, thallium(3+) salt" OR "Sulfuric acid, thallium(2+) salt" OR "Sulfuric acid, thallium(3+) salt" OR "Thallic nitrate" OR "Thallic oxide" OR "Thallic sulfate" OR "thallium bromide" OR "Thallium fluoride" OR "Thallium iodide" OR "Thallium monobromide" OR "Thallium monofluoride" OR "thallium monoiodide" OR "Thallium oxide" OR "Thallium peroxide" OR "Thallium sesquioxide" OR "Thallium tribromide" OR "Thallium trichloride" OR "Thallium trifluoride" OR "Thallium triiodide" OR "Thallium trinitrate" OR "Thallium trioxide" OR "Thallium(1+) bromide" OR "Thallium(1+) iodide" OR "Thallium(1+) lambda 1 - thallanolate" OR "Thallium(1+) oxide" OR "Thallium(1+) thallium(3+) sulfate" OR "Thallium(3+) oxide" OR "Thallium(3+) sulfate" OR "Thallium(3+) tribromide" OR "Thallium(3+) trichloride" OR "Thallium(3+) trifluoride" OR "Thallium(3+) triiodide" OR "Thallium(3+) trinitrate" OR "Thallium(I) bromide" OR "Thallium(I) fluoride" OR "Thallium(I) iodide" OR "Thallium(I) oxide" OR "Thallium(II) sulfate" OR "Thallium(III) bromide" OR "Thallium(III) chloride" OR "Thallium(III) iodide" OR "Thallium(III) oxide" OR "Thallium(III) sulfate" OR "Thallous bromide" OR "Thallous fluoride" OR "Thallous iodide" OR "Thallous oxide" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2023 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 6,525
- Number of records identified from other strategies: 100
- Total number of records to undergo literature screening: 6,625

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on thallium:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

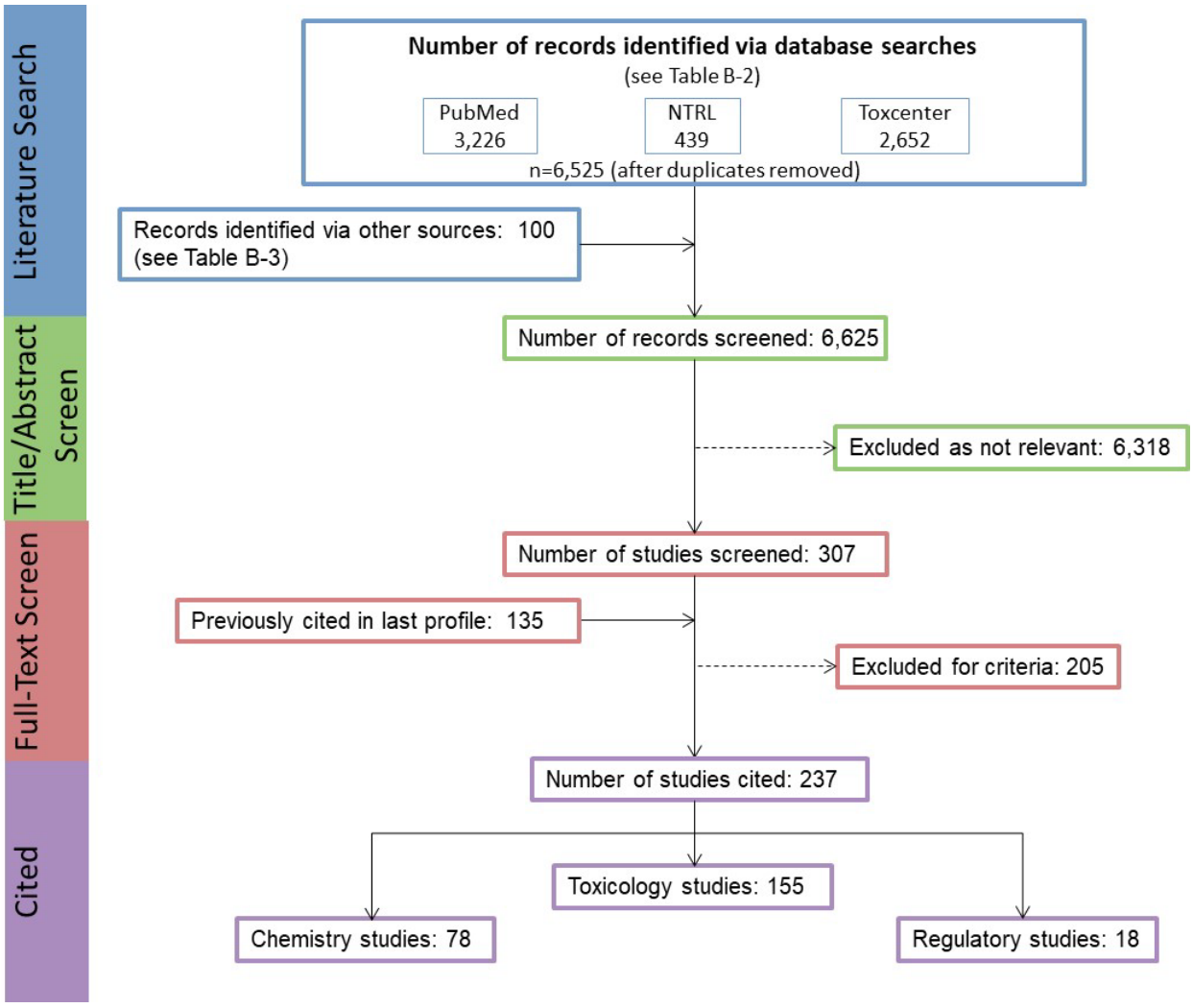
- Number of titles and abstracts screened: 6,625
- Number of studies considered relevant and moved to the next step: 307

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 307
- Number of studies cited in the pre-public draft of the toxicological profile: 135
- Total number of studies cited in the profile: 237

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. July 2023 Literature Search Results and Screen for Thallium



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR THALLIUM

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to thallium, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to thallium:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to thallium. The inclusion criteria used to identify relevant studies examining the health effects of thallium are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of thallium. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the 1992 toxicological profile for thallium; thus, the literature search was restricted to studies published between January 1990 and July 2023. See Appendix B for the databases searched and the search strategy.

A total of 6,625 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of thallium.

Title and Abstract Screen. In the Title and Abstract Screen step, 6,625 records were reviewed; 81 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 99 health effect documents (documents identified in the updated literature search and documents cited in older versions of the profile) was performed. From those 99 documents (101 studies), 6 documents (7 studies) were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for Thallium and overviews of the results of oral exposure studies (no inhalation or dermal exposure animals studies were identified) are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Table 2-2).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for thallium identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Available human studies include numerous case studies and case series reports, a small number of occupational exposure studies and studies of people living near a thallium point source, and general population studies evaluating possible associations between a biomarker of thallium exposure and adverse health outcomes. The general population studies provide limited information on health outcomes of concern due to the inconsistency of the findings and co-exposure to other compounds. When evaluated together, the case reports and case series reports suggest that the cardiovascular system, gastrointestinal system, skin, and peripheral nervous system are sensitive targets of thallium toxicity. A small number of animal studies have evaluated health outcomes following

acute- or intermediate-duration oral exposure. Alopecia was considered a sensitive outcome. Case studies and case-series reports were not included in the formal systematic review due to inherent high risk of bias and low confidence based on study design. However, consistent findings from numerous case studies were considered during the adjustment of the confidence rating. Animal studies have not adequately evaluated cardiovascular, gastrointestinal, or neurological endpoints (typically only examined in one study or did not evaluate function). Studies examining alopecia were carried through to Steps 4–8 of the systematic review. There were 7 studies (published in 6 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Thallium Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort			1 0	1 0									1 1				
Case control																	
Population																	
Case series																	
Oral studies																	
Cohort								1 1			1 1						
Case control																	
Population		1															
Case series		3 3	10 10	11 11		1 1	2 2	2 2	18 18	3 3			21 21		1 1		
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10	

Table C-4. Overview of the Health Outcomes for Thallium Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	
Oral studies																	
Acute-duration	5		1	1		1	3		1			1	3		1		
	3		1	1		0	2		1			1	3		1		
Intermediate-duration	6	3	3	1	1	1	3	3	6	1	1		3	4	2		
	3	0	0	0	0	0	0	0	6	0	0		2	1	2		
Chronic-duration																	
Dermal studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10	

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of thallium health effects studies (animal experimental studies) are presented in Table C-8.

Table C-8. Summary of Risk of Bias Assessment for Thallium—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Other bias: Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Alopecia										
Oral acute-duration exposure										
Rusyniak et al. 2003	–	+	+	+	+	+	+	+	+	First
Oral Intermediate-duration exposure										
Downs et al. 1960 (thallium acetate)	–	+	+	+	+	–	+	+	+	First
Downs et al. 1960 (thallium oxide)	–	+	+	+	+	–	+	+	+	First
Gross et al. 1948	–	+	+	+	+	–	+	+	+	First
Manzo et al. 1983	–	+	–	+	+	–	+	+	+	First
Shipkowski et al. 2023	–	+	+	+	+	–	+	+	+	First
EPA 1986	++	+	+	+	+	++	+	+	++	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to thallium and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to thallium and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-9, C-10, and C-11, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-9. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-10. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-11. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining alopecia observed in the animal experimental studies are presented in Table C-12.

Table C-12. Presence of Key Features of Study Design for Thallium—Experimental Animal Studies

	Key feature				
Reference	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Alopecia					
Oral acute-duration exposure					
Rusyniak et al. 2003	Yes	Yes	Yes	No	Moderate

Table C-12. Presence of Key Features of Study Design for Thallium—Experimental Animal Studies

Reference	Key feature				
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Oral intermediate-duration exposure					
Downs et al. 1960 (thallium acetate)	Yes	Yes	Yes	No	Moderate
Downs et al. 1960 (thallium oxide)	Yes	Yes	Yes	No	Moderate
Gross et al. 1948	No	Yes	Yes	No	Low
Manzo et al. 1983	Yes	Yes	Yes	No	Moderate
Shipkowski et al. 2023	Yes	Yes	Yes	Yes	High
EPA 1986	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-13. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-13.

Table C-13. Initial Confidence Rating for Thallium Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Alopecia		
Oral acute-duration		
Animal studies		
Rusyniak et al. 2003	Moderate	Moderate
Oral intermediate-duration		
Animal studies		
Downs et al. 1960 (thallium acetate)	Moderate	High
Downs et al. 1960 (thallium oxide)	Moderate	
Gross et al. 1948	Low	
Manzo et al. 1983	Moderate	
Shipkowski et al. 2023	High	
EPA 1986	High	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for alopecia are presented in Table C-14. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with thallium exposure is presented in Table C-15.

Table C-14. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Alopecia			
Human studies			
Animal studies	High	+1 Consistency of effect	High

Table C-15. Confidence in the Body of Evidence for Thallium

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Alopecia		High

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-5, C-6, and C-7). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
    - No downgrade if none of the factors are considered indirect
    - Downgrade one confidence level if one of the factors is considered indirect
    - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
    - No downgrade if there are no serious imprecisions
    - Downgrade one confidence level for serious imprecisions
    - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
    - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
    - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence of a monotonic dose-response gradient
    - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for thallium, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for thallium is presented in Table C-16.

Table C-16. Level of Evidence of Health Effects for Thallium

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Animal studies			
Alopecia	High	Effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

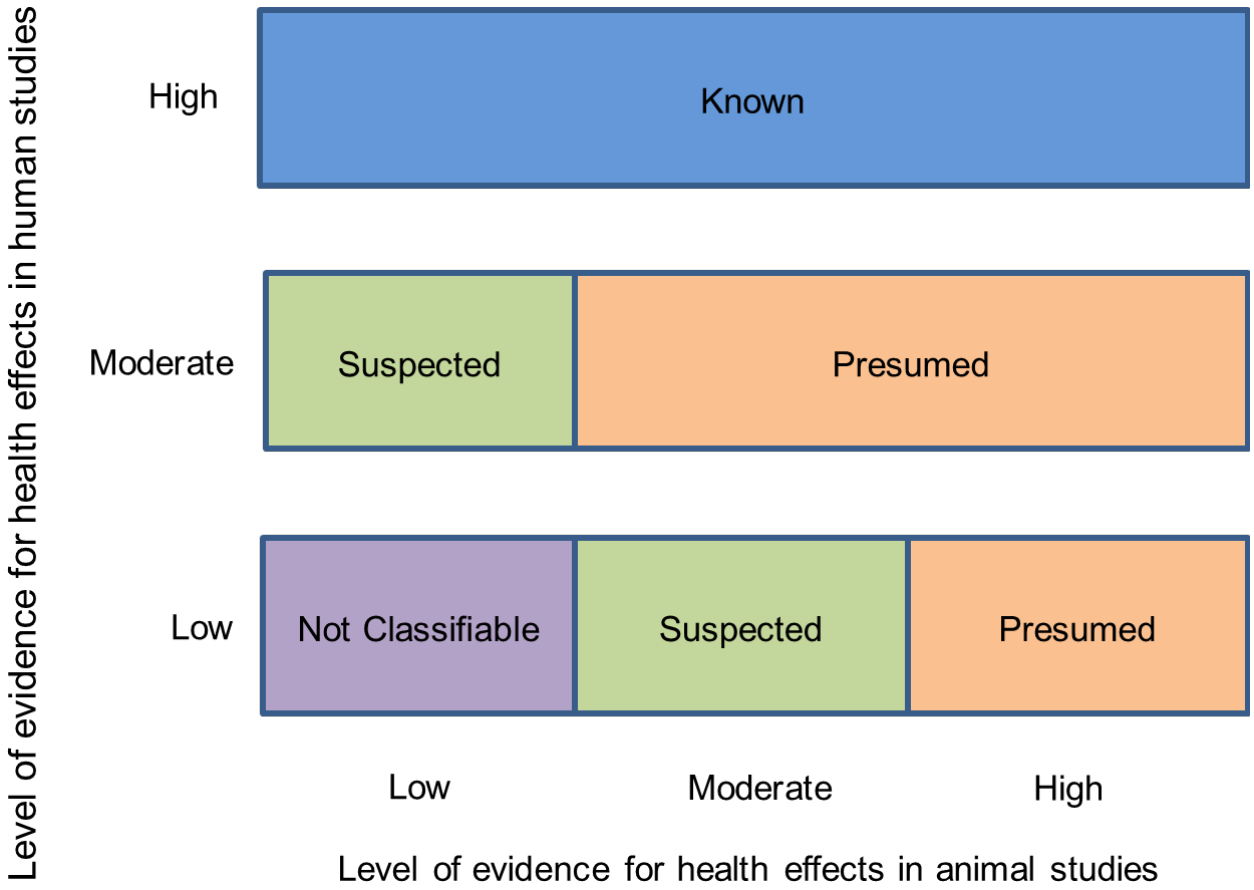
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for thallium are listed below and summarized in Table C-17.

Presumed Health Effects

- Alopecia
  - No experimental or reliable epidemiological studies evaluating alopecia in humans were identified.
  - High level of evidence in animals following acute- or intermediate-duration oral exposure (Downs et al. 1960; EPA 1986; Gross et al. 1948; Manzo et al. 1983; Rusyniak et al. 2003; Shipkowski et al. 2023).
  - Studies evaluating alopecia in humans are limited to case studies or case series reports. These studies provide consistent evidence of alopecia in humans following acute-duration oral exposure to thallium (for example, Al Hammouri et al. 2011; Almassri and Sekkarie 2018; Desenclos et al. 1992; Gastel 1978; Grunfeld and Hinostroza 1964; Lu et al. 2007; Meggs et al. 1994; Rayisyan et al. 2021; Sojáková et al. 2015; Sun et al. 2012; Villanueva et al. 1990; Wang et al. 2007, 2021; Zavaliy et al. 2021; Zhang et al. 2014; Zhao et al. 2008).

Table C-17. Hazard Identification Conclusions for Thallium

Outcome	Hazard identification
Alopecia	Presumed health effect

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

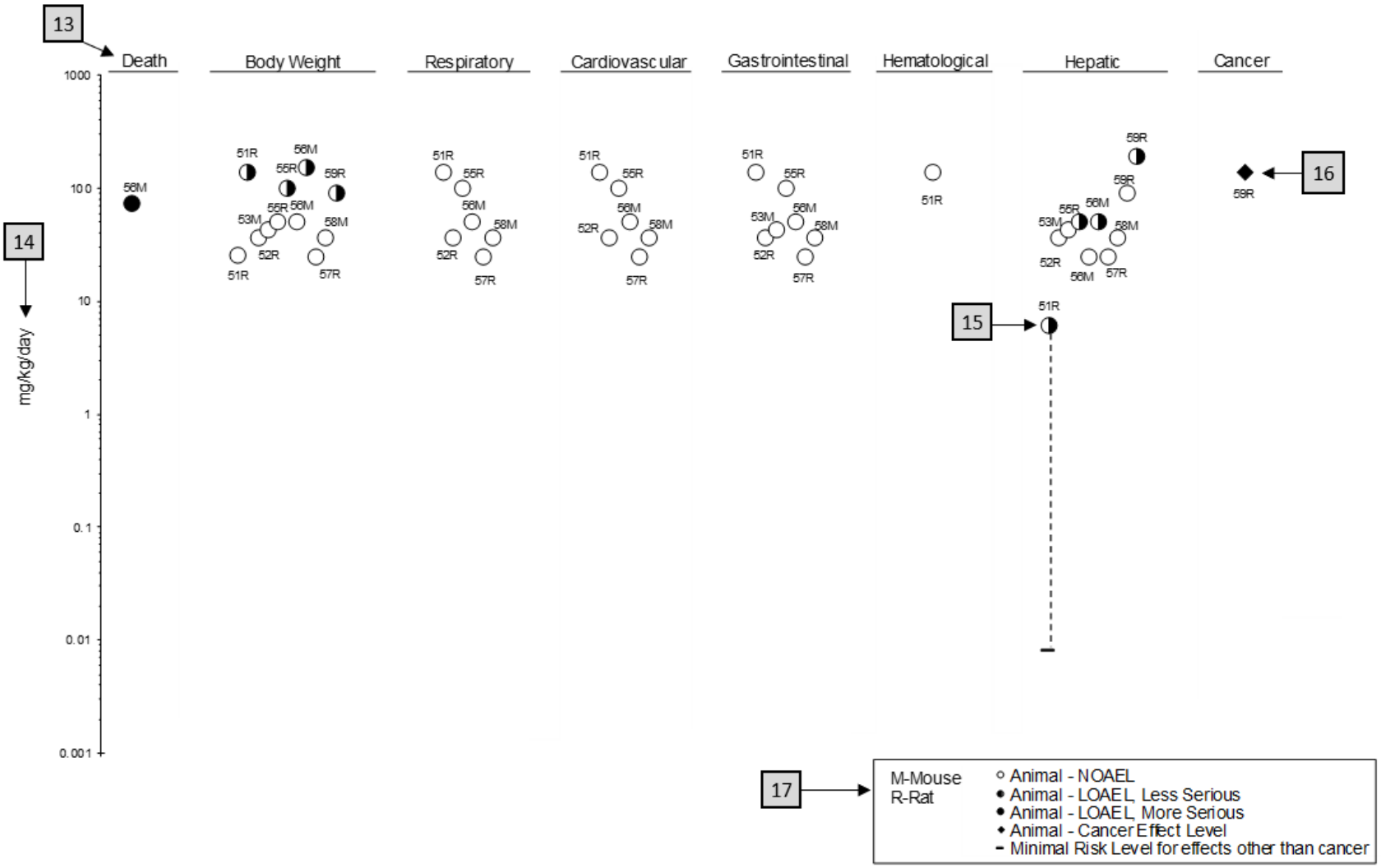
(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/clinician-briefs-overviews.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or malignant tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The exposure level of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this exposure level, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly 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.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission

VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result