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.

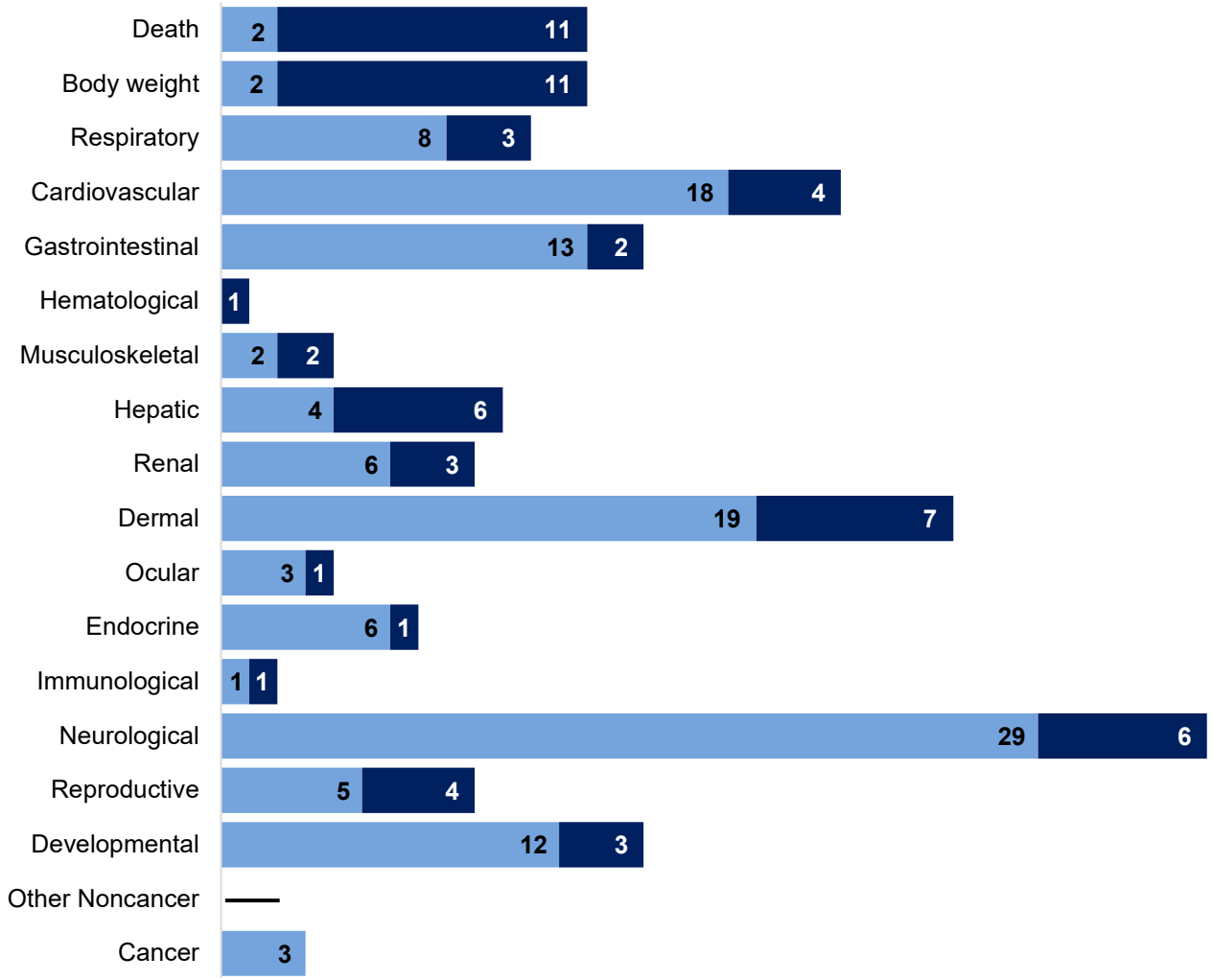
An overview of the types of studies and endpoints examined is presented in Figure 2-1. For this figure, case reports were treated as acute-duration oral exposure studies and most epidemiological studies were treated as chronic-duration oral studies, with the exception of occupational exposure studies 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.

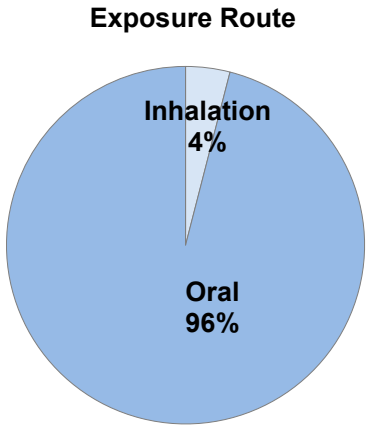
The human and animal studies suggest several sensitive targets of thallium toxicity: skin, gastrointestinal system, cardiovascular system, and neurological system. Of these endpoints, only dermal effects had sufficient data to undergo systemic review (see Appendix C for details).

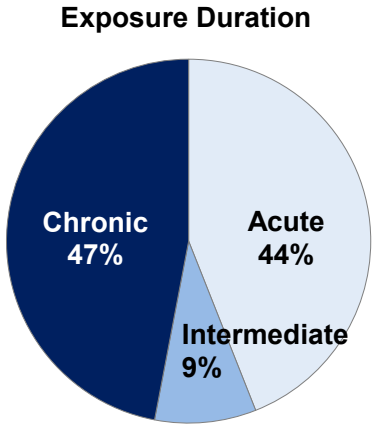
- **Dermal effects:** Alopecia is a presumed health effect in humans based on consistent evidence in humans acutely exposed to ingested thallium and a high level of evidence in animals orally exposed to thallium.
- **Gastrointestinal effects:** Symptoms of gastrointestinal effects including abdominal 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)

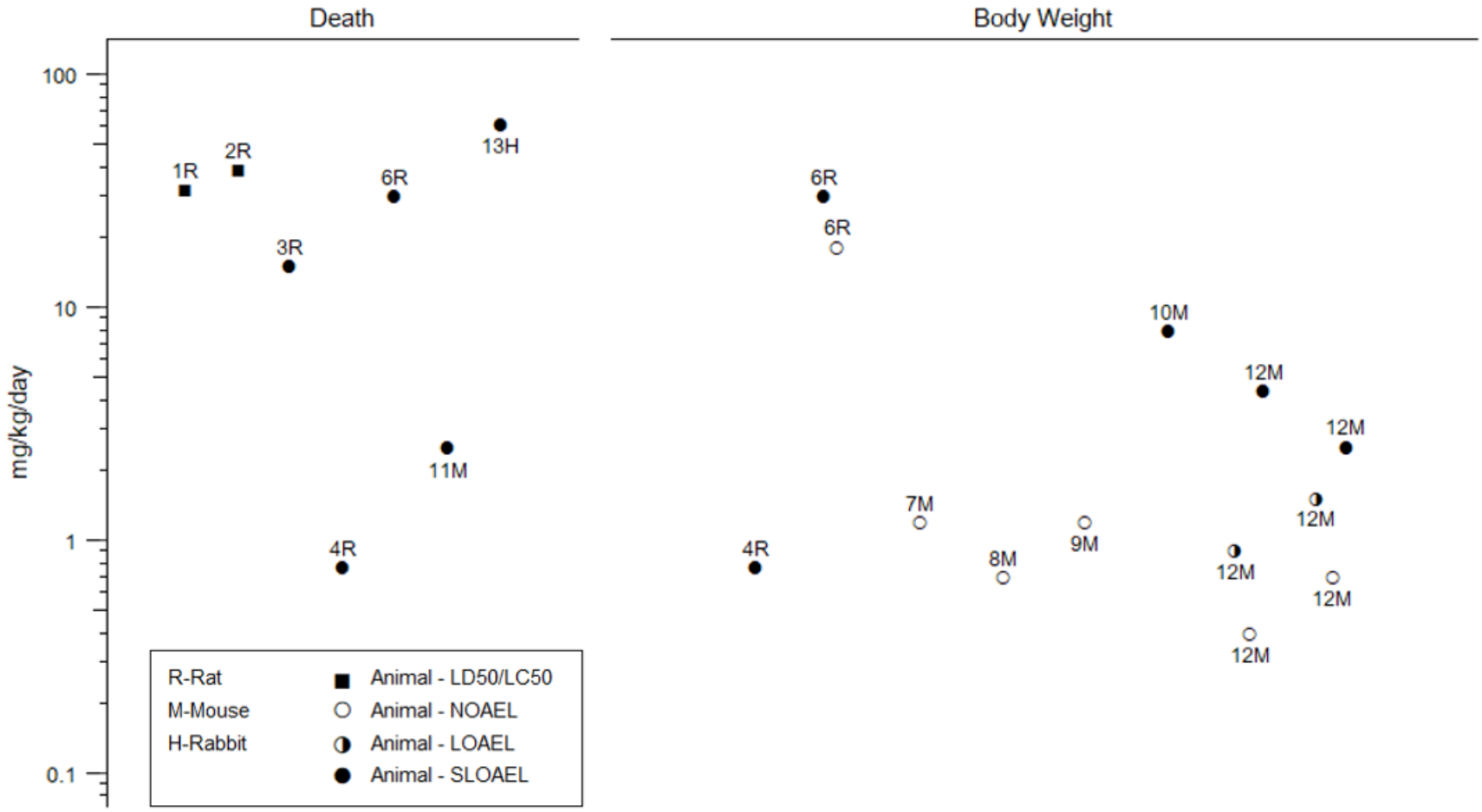


Figure 2-2. Levels of Significant Exposure to Thallium – Oral
Acute (≤14 days)

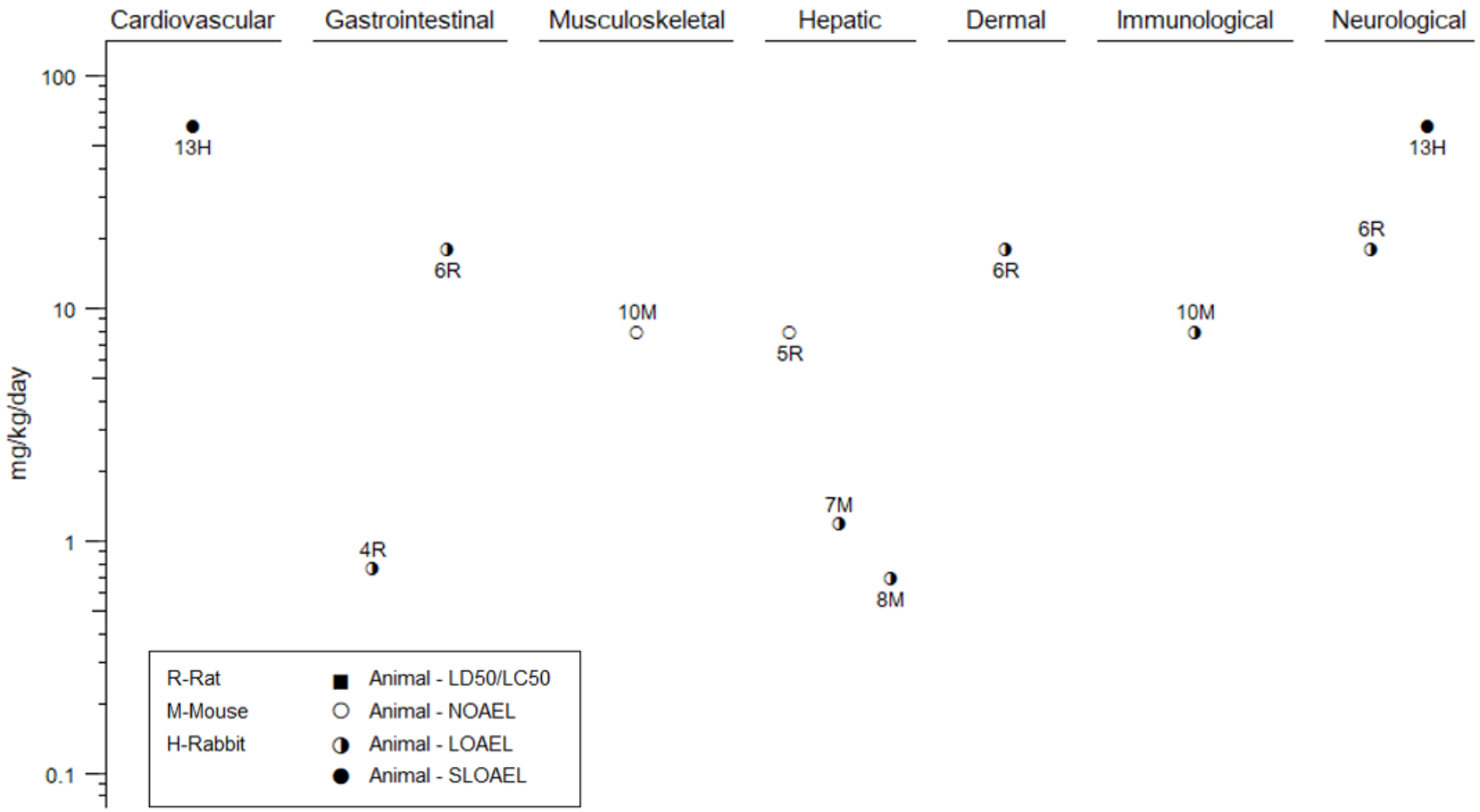


Figure 2-2. Levels of Significant Exposure to Thallium – Oral
Intermediate (15–364 days)

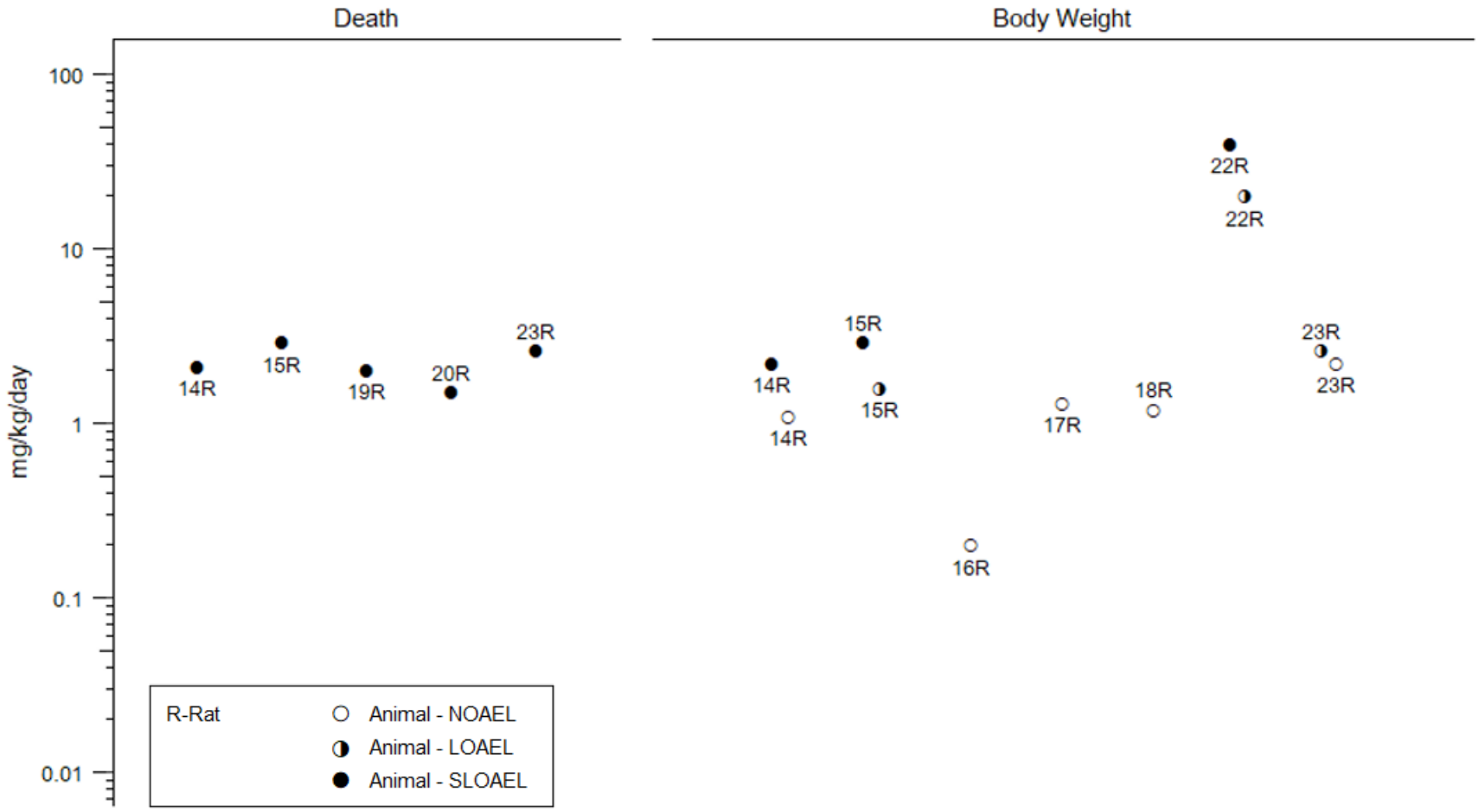


Figure 2-2. Levels of Significant Exposure to Thallium – Oral
Intermediate (15–364 days)

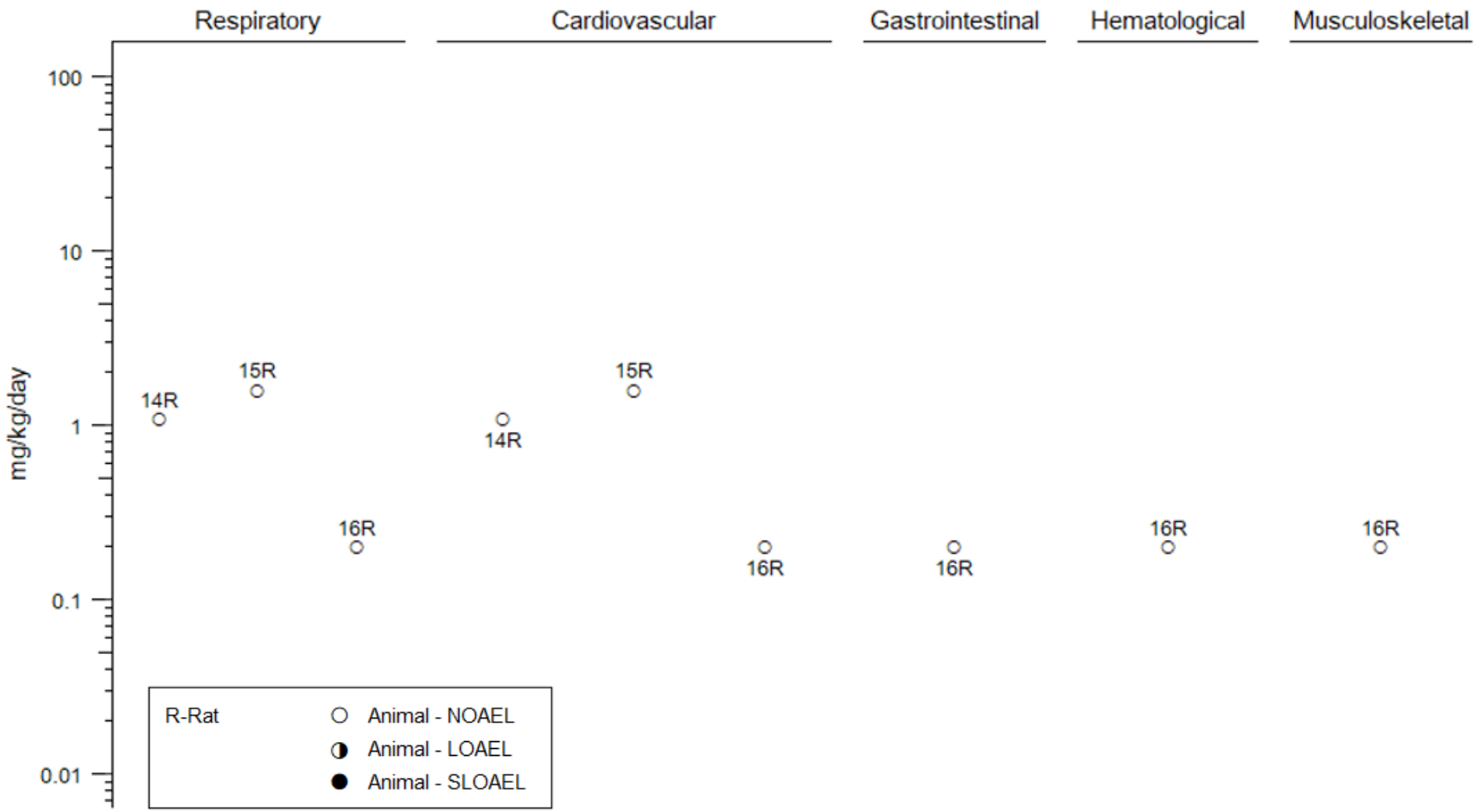


Figure 2-2. Levels of Significant Exposure to Thallium – Oral
Intermediate (15–364 days)

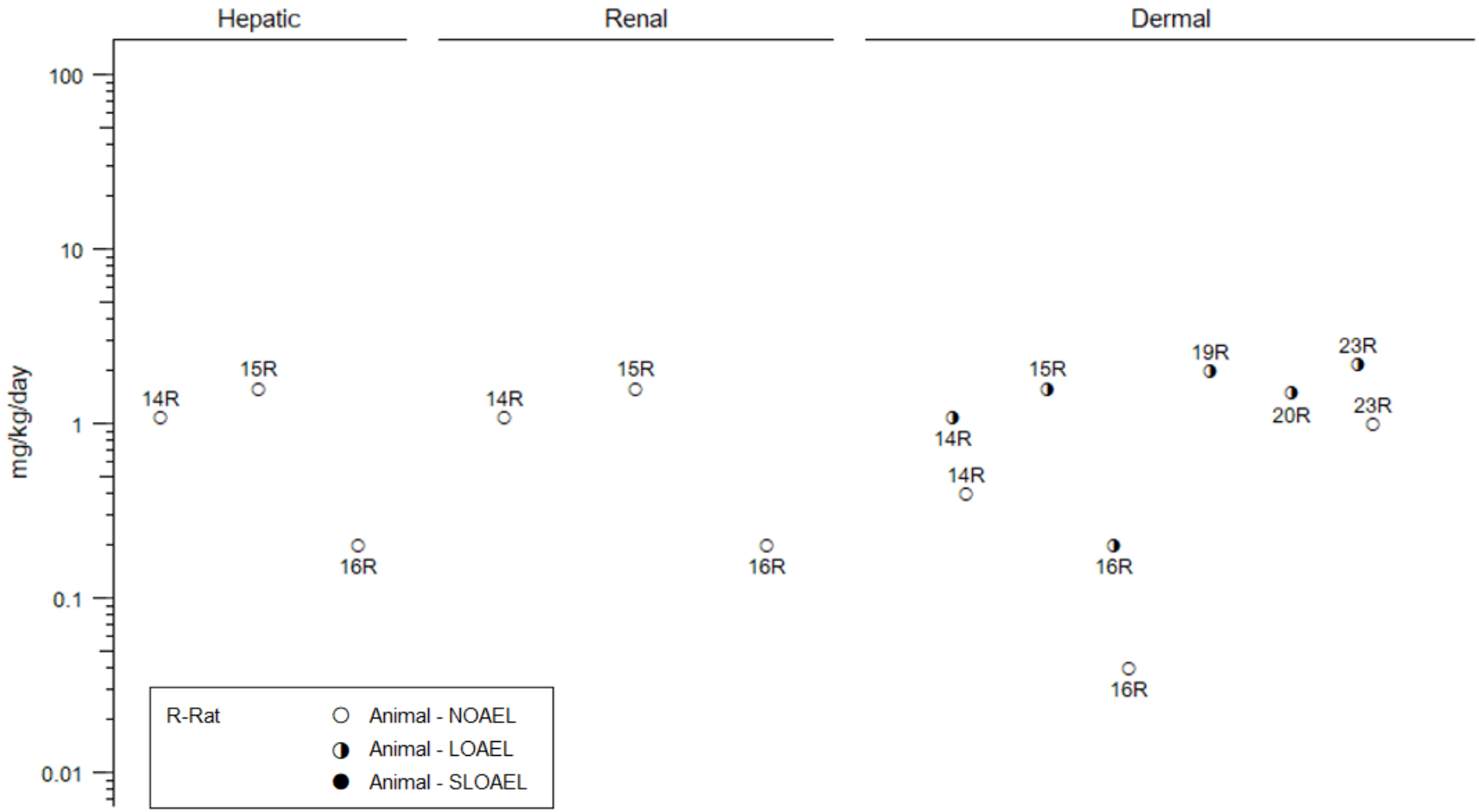
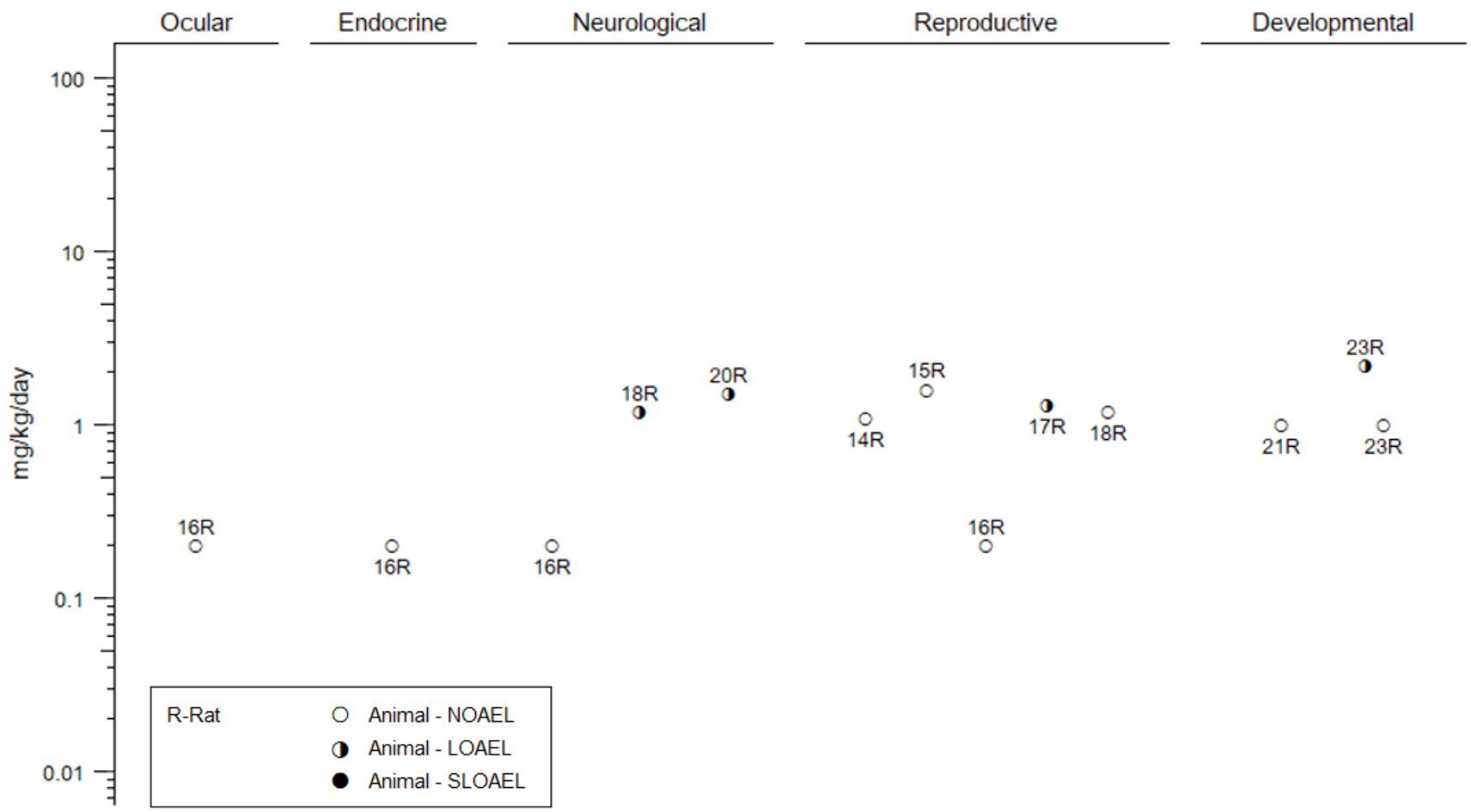


Figure 2-2. Levels of Significant Exposure to Thallium – Oral
Intermediate (15–364 days)



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).