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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)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Nina Ching Y. Wang, PhD
National Center for Environmental Assessment, Cincinnati, OH

CONTRIBUTORS

Michael Griffith, PhD
National Center for Environmental Assessment, Cincinnati, OH

Jon Reid, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

ICF International
9300 Lee Highway
Fairfax, VA 22031

Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300)

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COMMONLY USED ABBREVIATIONS

BMC	Benchmark Concentration
BMD	Benchmark Dose
BMCL	Benchmark Concentration Lower bound 95% confidence interval
BMDL	Benchmark Dose Lower bound 95% confidence interval
HEC	Human Equivalent Concentration
HED	Human Equivalent Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure (oral)
RfC	reference concentration (inhalation)
RfD	reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor
WOE	weight of evidence

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), THALLIUM (I) OXIDE (1314-12-1), THALLIUM (III) OXIDE (1314-32-5), THALLIUM (I) SELENITE (12039-52-0), AND THALLIUM (I) SULFATE (7446-18-6)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program.

This PPRTV assessment was developed using only information provided in the Toxicological Review of Thallium and Compounds (CAS No. 7440-28-0) (U.S. EPA, 2009). All of the information provided in this document was available to peer reviewers according to the standard IRIS peer review process.

No toxicity values were posted on the IRIS database (U.S. EPA, 2009) for thallium because of limitations in the database of toxicological information. However, the Toxicological Review presents information which could be used for development of an RfD. In this document, an appendix with a "screening subchronic and chronic p-RfD" is provided, recognizing the quality decrements, which may be of value under certain circumstances, described later in this document.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

DISCLAIMERS

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

An IRIS Toxicological Review of Thallium and Compounds was previously developed and posted (http://www.epa.gov/iris/toxreviews/1012tr.pdf). However, due to study and data quality limitations as stated in the IRIS Toxicological Review, an RfD was not derived. Although these limitations precluded the derivation of an RfD, there are dose-response data that may be used in the derivation of screening subchronic and chronic p-RfDs (see Appendix A). This PPRTV for Thallium and Compounds is based mostly on the IRIS Toxicological Review; all relevant text and tables were either reproduced or adapted from the IRIS Toxicological Review.

Metallic thallium (Tl) is insoluble in water; however, the majority of the thallium salts are soluble in water with the exception of thallium (III) oxide. Thallium compounds and their chemical and physical properties are listed in Table 1. Thallium occurs naturally in the earth's crust. It is used in industry, but is also released due to combustion of fossil fuels, refinement of oil fractions, smelting of ores, and by some other industrial processes such as cement production and brickworks (Kazantzis, 2007; IPCS, 1996). A summary of past uses and possible health effects of thallium (I) sulfate as cited in the IRIS Toxicological Review is provided as follows:

Due to its ability to remove hair, thallium (I) sulfate was used in the past as a depilatory agent. Thallium (I) sulfate was once used in medicine to treat infections, such as venereal diseases, ringworm of the scalp, typhus, tuberculosis, and malaria. It was also used in the past as a pesticide for various rodents and insects but has been banned for this use in the U.S. since 1972. Currently, thallium is used in the semiconductor industry and the manufacture of optic lenses. When thallium is alloyed with mercury, it is used on switches and closures, which can operate at subzero temperatures. Thallium compounds are also used to manufacture low-melting glass, low-temperature thermometers, alloys, electronic devices, mercury lamps, fireworks, and imitation gems. Thallium radioisotopes are used in medicine for scintigraphy of certain tissues and the diagnosis of melanoma (Ibrahim et al., 2006; National Library of Medicine [NLM], 1998; IPCS, 1996; Agency for Toxic Substance and Disease Registry [ATSDR], 1992; U.S. EPA, 1991).

Table 1. Chemical and Physical Properties of Thallium and Selected Thallium Compounds[a]

Name	CASRN	Chemical Formula	Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Solubility in Water (g/L)
Metallic thallium	7440-28-0	Tl	204.38	303.5	1457	Insoluble
Thallium (I) acetate	563-68-8	$TlC_2H_3O_2$	263.43	131	No data	Very soluble
Thallium (I) carbonate	6533-73-9	Tl_2CO_3	468.78	273	No data	40.3 (15.5°C)
Thallium (I) chloride	7791-12-0	TlCl	239.84	430	720	Very soluble (20°C)
Thallium (I) nitrate	10102-45-1	$TlNO_3$	266.39	206	430	95.5 (20°C)
Thallium (I) oxide	1314-12-1	Tl_2O	424.77	596	No data	Soluble (as TlOH)
Thallium (III) oxide	1314-32-5	Tl_2O_3	456.76	717	875	Insoluble
Thallium (I) selenite	12039-52-0	Tl_2SeO_3	535.72	No data	No data	No data
Thallium (I) sulfate	7446-18-6	Tl_2SO_4	504.82	632	Decomposes	48.7 (20°C)

[a]Sources: IPCS (1996); Downs (1993); ATSDR (1992). Table was obtained directly from Table 2-1 in U.S. EPA (2009).

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides a summary of studies of thallium toxicity in humans. Table 3 provides a summary of oral toxicity studies of thallium (and compounds) in animals. No inhalation studies in animals or human were identified. A literature search through May 2009 was conducted in support of the IRIS Toxicological Review of Thallium and Compounds (U.S. EPA, 2009); an updated literature search was not conducted in developing the PPRTV for Thallium and Compounds. All pertinent data on thallium and related compounds have been reviewed by IRIS, and a Toxicological Review is available (U.S. EPA, 2009). Tables 2 and 3 are adapted from the Toxicological Review with minor clarifications (U.S. EPA (2009), Tables 4-1 and 4-5, respectively).

Table 2. Thallium Toxicity In Humans Following Oral Exposure

Reference	Sex	Age	Dose	Symptoms[a]	Final Outcome
Males-Adult					
Gefel et al. (1970)	Male	41 years	Unknown but chronic; urine thallium 0.15 mg/100 mL	High blood pressure; lower back pain; vomiting; severe pain in the feet; weakness of the calf muscle; alopecia; slurred speech; atrophic lower limbs; limited vision	Death
Cavanagh et al. (1974)	Male	60 years	0.93 g thallium (I) acetate in 2 divided doses	Diarrhea; vomiting; dizziness; back pain; paresthesia of the feet and lower legs; high blood pressure; facial weakness; dysphagia; difficulty breathing	Death within a week of symptoms
Cavanagh et al. (1974)	Male	56 years	0.93 g thallium (I) acetate in 3 divided doses	Abdominal pain; diarrhea; vomiting; paresthesia; photophobia, nystagmus, visual impairment; facial weakness; bilateral ptosis	Death within 3 weeks of symptoms
Cavanagh et al. (1974)	Male	26 years	0.31 g thallium (I) acetate	Paresthesia in both feet; chest pain; tenderness over the sternum; vomiting, weakness, pain in the knees and ankles that inhibited walking; alopecia	Recovery
Davis et al. (1981)	Male	19 years	5–10 g thallium (I) nitrate	Nausea; vomiting; slurred speech; paresthesia of hands and feet; respiratory weakness	Death
Limos et al. (1982)	Male	56 years	Unknown	Visual disturbances; alopecia; elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT); high blood glucose and creatine kinase; decreased myelinated fibers; denervated Schwann cell clusters	Bedridden; could not speak
Limos et al. (1982)	Male	26 years	Unknown	Visual disturbances; alopecia; elevated AST and ALT; high blood glucose and creatine kinase; decreased myelinated fibers; denervated Schwann cell clusters	Residual tremors of the extremities and muscle weakness of the lower limbs
Roby et al. (1984)	Male	45 years	Unknown; urine thallium: 2000 µg/L	Burning pain in feet; inability to walk; alopecia; acute fibrillation	Continued neurological dysfunction
Heyl and Barlow (1989)	Male	"Five young men"	Unknown	Follicular plugging of the skin (nose, cheeks, and nasolabial folds) by keratinous material; crusted eczematous lesions and acneiform eruptions on the face; dry scaling on palms and soles; and alopecia (scalp, eyelashes, lateral eyebrows, arms, and legs). Skin biopsies (scalp and cheek): disintegrating hair shafts, gross follicular plugging, and eosinophilic keratohyalin granules in the epidermis; necrotic sebaceous glands; pustular lesions on the face: folliculitis and necrosis of the follicles; (feet) marked hyperkeratosis and hypergranulosis	4/5 recovered; 1/5 experienced permanent neurological damage

Table 2. Thallium Toxicity In Humans Following Oral Exposure

Reference	Sex	Age	Dose	Symptoms[a]	Final Outcome
Yokoyama et al. (1990)	Male	31 years	Unknown; urine thallium: 3.5 mg/L	Nausea, vomiting; leg pain; alopecia; abnormal behavior; decreased conduction velocity of fast nerve fibers	Recovery
Hantson et al. (1997)	Male	48 years	200 mg thallium (I) sulfate	No overt symptoms within 24 hours; increase in binucleated cells with micronuclei 15 days after exposure	Recovery
Hirata et al. (1998)	Male	29 years	Unknown; hair thallium: 20 ng/g (32 months after possible exposure)	Alopecia; abdominal pain; diarrhea; tingling in extremities; neuropathy	Recovery
Atsmon et al. (2000)	Male	40 years	Unknown; urine thallium: 7 mg	Weakness of the limbs; vomiting; severe neurological symptoms; alopecia; high blood pressure; increased ALT and AST; Mees lines; decreased visual acuity; bilateral foot drop	Recovery
Sharma et al. (2004)	Male	48 years	Unknown; serum thallium: 870 µg/100 mL urine thallium: 5000 µg/mL	Painful peripheral neuropathy; decreased consciousness	Death
Females-Adult					
Roby et al. (1984)	Female	51 years	Unknown; serum thallium: 50 µg/100 mL; urine thallium: 5000 µg/L	Numbness and weakness of the legs and hands; alopecia; fluctuating pulse and blood pressure; bradycardia; hypotension	Persistent ventricular ectopy and neurological dysfunction, necessitating placement at a nursing home
Roby et al. (1984)	Female	61 years	Unknown; serum thallium: 740 µg/100 mL	Burning chest pain; paresthesia; difficulty speaking and swallowing; inability to walk; hypotension; acute respiratory distress syndrome[b] (ARDS)	Death
Roby et al. (1984)	Female	80 years	Unknown; serum thallium: 422 µg/100 mL; urine thallium: 21,600 µg/L	ARDS	Death
Hoffman (2000)	Female	Pregnant; ages not specified	150–1350 mg thallium (I) sulfate	Paresthesia; abdominal pain; muscle weakness; lethargy; alopecia; Mees lines [lines of discoloration across the nails of the fingers and toes]	None specified

Table 2. Thallium Toxicity In Humans Following Oral Exposure

Reference	Sex	Age	Dose	Symptoms[a]	Final Outcome
Saha et al. (2004)	Female	26 years	Unknown; serum thallium: 12 µg/100 mL	Headache; lethargy; abdominal pain; muscle cramps; joint pain; backache; numbness of fingers; alopecia; erosion of nails	Not specified
Both Sexes-Adult					
Brockhaus et al. (1981)	Both	Not reported	Unknown	Sleep disorders; tiredness; weakness; nervousness; headache; other psychic alterations; neurological and muscular symptoms	Not reported
Schoer (1984); Gosselin et al. (1984)	Both	Adult	10–15 mg/kg thallium	None specified	Death (average lethal dose)
Rusyniak et al. (2002)	Both	Various	Unknown; various levels were detected in urine	Myalgia; arthralgia; paresthesia; dysesthesia; joint stiffness; insomnia; alopecia; abdominal pain	Recovery in seven adults; five had ongoing psychiatric problems
Tsai et al. (2006)	Both	48-year old female; 52-year old male	1.5–2.4 g	Confusion; disorientation; hallucination; anxiety; depression; memory impairment; peripheral neuropathy; erythematous skin rashes; diarrhea; tachycardia; alopecia	Impairment of memory and verbal fluency remained at six months; neuropsychological impairment persisted at nine months
Lu et al. (2007); Kuo et al. (2005)	Both	48 and 52 years	1.5 and 2.3 g/person (estimated); serum thallium: 950−2056 µg/L; Urine thallium: 11,325−14,520 µg/L	Nausea, vomiting; general aching muscle pain; numbness of tongue and mouth within a few hours; severe paresthesia and dysesthesia in hands and feet (one day post exposure); erythematous rash; diarrhea; urine retention; hyporeflexia; muscle weakness; hypoesthesia; acneiform eruptions; alopecia (1–3 weeks); Mees lines (2–3 months). Skin biopsy: parakeratosis; dilated hair follicles filled with keratin and necrotic sebaceous materials; mild epidermal atrophy; vacuolar degeneration of the basal layer. Cutaneous nerve biopsy: axonal degeneration; loss of epidermal nerves indicating involvement of the small sensory nerves (2 months).	At 1-year follow-up, persistent paresthesia, dysesthesia, and impairment of small sensory nerve fibers in skin

Table 2. Thallium Toxicity In Humans Following Oral Exposure

Reference	Sex	Age	Dose	Symptoms[a]	Final Outcome
Children					
Reed et al. (1963)	Both	1–11 years	Unknown	Alopecia; lethargy; ataxia; abdominal pain; vomiting; abnormal reflexes; neuropathy; muscle weakness; coma; convulsion	Neurological abnormalities; retardation; psychosis; death
Feldman and Levisohn (1993)	Male	10 years	Unknown; serum thallium: 296 µg/L; urine thallium: 322 µg/24 hours	Alopecia; leg paresthesia; abdominal pain; seizures	Recovery
Hoffman (2000)	Both	Trans-placental	Unknown	Premature birth; low birth weight; alopecia	None specified
Ammendola et al. (2007)	Male	16 years	1.3 g thallium sulfate; urine thallium: 3400 µg/L	Acute stage: gastrointestinal disturbances; alopecia; clinical and electrodiagnostic signs of severe polyneuropathy	3 years postpoisoning: neurological symptoms making progress; electrophysiological signs of peripheral neuropathy mainly confined to lower limbs. 6 years postpoisoning: persistent weakness and sensory disturbances of distal lower extremities; neurological and electrodiagnostic abnormalities affecting mainly the feet.

[a]ALT = alanine aminotransferase; AST = aspartate aminotransferase
[b]ARDS = acute respiratory distress syndrome

Table 3. Thallium Toxicity in Animals Following Oral Exposure[a]

Reference	Species	Age	Sex	Route	Dose and Duration	NOAEL	LOAEL	Effect
Acute studies								
Leloux et al. (1987)	Rat 3/sex	Adult	Both	Oral (gavage)	20 mg/kg thallium (I) nitrate; single dose	NI[b]	15 mg/kg Tl	Difficulty breathing; rough coat; increased absolute kidney, adrenal weights; death
Leloux et al. (1987)	Rat 10/sex/ group	Adult	Both	Oral (gavage)	0, 1 mg/kg thallium (I) nitrate; once daily for 4 days	NI	0.77 mg/kg Tl	Alopecia; diarrhea; increased absolute kidney, eye weights; death
Mourelle et al. (1988)	Rat 10/group	NS[c]	Male	Oral (gavage)	0, 10 mg/kg thallium (I) sulfate; single dose. Sacrificed at 24 hours to 2 days after dosing	NI	8.1 mg/kg Tl	Liver changes: increased triglycerides and lipid peroxidation; decreased glutathione and glycogen; increased alkaline phosphatase in serum and liver cell membranes
Subchronic studies								
Downs et al. (1960)	Rat/ 5/sex/ group	NS	Both	Oral (feed)	0, 5, 15, or 50 ppm thallium (I) acetate (corresponding to 0, 0.4, 1.2, or 3.9 mg/kg-day Tl); 15 weeks 0 or 30 ppm (corresponding to 0 or 2.4 mg/kg-day Tl); 9 weeks	0.4 mg/kg-day Tl*	1.2 mg/kg-day Tl*	Alopecia; increased kidney weight; mortality in treated and control groups. *The NOAEL and LOAEL are for alopecia. Because of reported mortality in the control and treated groups, a study NOAEL and LOAEL cannot be reliably determined.
Downs et al. (1960)	Rat 5/sex/ group	Weanling	Both	Oral (feed)	0, 20, 35, 50, 100, and 500 ppm thallium (III) oxide (corresponding to 0, 1.8, 3.1, 4.5, 9.0, and 44.8 mg/kg-day Tl); 15 weeks	NI	1.8 mg/kg-day Tl (20 ppm)	Reduced body weight; alopecia; increased mortality; increased absolute and relative kidney weights
El-Garawany et al. (1990)	Rat *n* = 10	NS	Male	Oral[d]	0.8 mg/kg thallium (I) sulfate; 90 days	NI	0.65 mg/kg-day Tl	Increased blood urea; serum creatinine; serum bilirubin; serum ALT
Manzo et al. (1983)	Rat *n* = 80	NS	Female	Oral (DW[e])	10 mg/L Tl as thallium (I) sulfate; 36 weeks	NI	1.4 mg/kg-day Tl	Nerve histopathology; alopecia; mortality

Table 3. Thallium Toxicity in Animals Following Oral Exposure[a]

Reference	Species	Age	Sex	Route	Dose and Duration	NOAEL	LOAEL	Effect
MRI (1988)	Rat 20/sex/ group	45 days	Both	Oral (gavage)	0, 0.01, 0.05, or 0.25 mg thallium (I) sulfate/kg (corresponding to 0, 0.008, 0.04, or 0.20 mg/kg-day Tl); 90 days	NI	0.008 mg/kg-day Tl[f]	Increased incidence of alopecia and other observations related to coat (rough coat, piloerection, shedding); lacrimation, exophthalmos, and miosis; and various behavioral observations; statistically significant increases in AST, LDH, and sodium levels; decreased blood sugar levels. The study authors identified 0.2 mg/kg-day Tl as the NOAEL.
Reproductive and developmental toxicity								
Formigli et al. (1986); Gregotti et al. (1985)	Rat 10/group	Adult	Male	Oral (DW)	0, 10 ppm thallium (I) sulfate; 30 or 60 days	NI	0.7 mg/kg-day Tl	Testicular effects: tubular epithelium disarrangement; cytoplasmic vacuolation; reduced sperm motility; distention of smooth endoplasmic reticulum of Sertoli cells; reduced β-glucuronidase activity
Wei (1987)	Mouse	NS	Male	Oral (DW)	0, 0.001, 0.01, 0.1, 1.0, and 10 mg/L thallium (I) carbonate (corresponding to 0, 0.0003, 0.003, 0.03, 0.3, and 3 mg/kg-day Tl); 6 months	NI	0.0003 mg/kg-day Tl	Decreased sperm motility and counts; increase in deformed sperm; decrease in live fetuses. Dose estimated from an assumed average body weight of 20 g and drinking water ingestion rate of 6 mL/day.
Rossi et al. (1988)	Rat	Perinatal	Both	[Oral (Mother's, then pup's DW)]	0, 1 mg/dL of thallium (I) sulfate Day 1 of gestation to weaning then thru 60 days	NI	NI	Prenatal and postnatal exposure caused a delay in the development of the pilus apparatus [the formation of hair] by 50 days; reduction of the α- and β-adrenergic and muscarinic vasomotor reactivity noted.

[a]U.S. EPA (2009) Table 4-5.
[b]NI = not identified.
[c]NS = not specified.
[d]Presumably via gavage.
[e]DW = drinking water.
[f]See discussion of the NOAEL and LOAEL determination in Section 5.1.1 of U.S. EPA (2009).

HUMAN AND ANIMAL STUDIES

Refer to the IRIS Toxicological Review (U.S. EPA, 2009) for summaries of human and animal studies. The principal study selected for derivation of screening subchronic and chronic p-RfDs (Midwest Research Institute, 1988) is summarized in Appendix A.

Carcinogenicity Studies

No studies of the carcinogenicity of thallium or thallium compounds were identified in the IRIS Toxicological Review (U.S. EPA, 2009).

Inhalation Exposures

No studies were identified in the IRIS Toxicological Review (U.S. EPA, 2009) regarding the effects of subchronic or chronic inhalation exposure of animals to thallium or thallium compounds.

DERIVATION OF PROVISIONAL VALUES

DERIVATION OF PROVISIONAL ORAL REFERENCE DOSES

Although there are substantial data available on human exposure to thallium, the majority are case reports of poisonings, suicide attempts, or accidental ingestion of rodenticides. There are two population surveys with oral thallium exposure through contaminated homegrown foods (Dolgner et al., 1983; Brockhaus et al., 1981). However, these studies are limited by the lack of objective tests for toxicity, reliance on the incidence of symptoms obtained from questionnaires, and characterization of chronic thallium exposure by measuring the levels in urine and hair at a single point in time (U.S. EPA, 2009). In addition, three occupational exposure studies (Ludolph et al., 1986; Marcus, 1985; Schaller et al., 1980) provide no conclusive associations between thallium exposure and any specific health effects, possibly due to the small study populations and study design limitations. Therefore, the available human studies are not suitable for derivation of a p-RfD.

There are numerous animal studies on the effects of thallium; however only four repeat-dose oral toxicity studies with more than one dose level were identified (Midwest Research Institute, 1988; Wei, 1987; Zasukhina et al., 1983; Downs et al., 1960). Wei (1987), Zasukhina et al. (1983), and Downs et al. (1960) were not considered adequate for RfD derivation (see U.S. EPA (2009) for details). The MRI (1988) 90-day study in rats was evaluated in the IRIS Toxicological Review as a candidate principal study as the most comprehensive of the available thallium studies. Histopathological changes in the skin (hair follicle atrophy in high-dose female rats with alopecia) and clinical observations, including those related to animal coat (rough coat, piloerection, shedding, and alopecia), eyes (including lacrimation, exophthalmos, and miosis), and behavior were considered as possible endpoints for POD derivation.

The conclusion reached in the IRIS Toxicological Review of Thallium and Compounds (U.S. EPA, 2009) was that the available toxicity database for thallium contains studies that are generally of poor quality. The MRI (1988) study that was selected as a candidate principal study for RfD derivation suffers from certain critical limitations (e.g., high background incidence of alopecia, lack of histopathological examination of skin tissue in low- and mid-dose groups, and

inadequate examination of objective measures of neurotoxicity), and there are particular difficulties in the selection of appropriate endpoints. Therefore, a RfD for soluble thallium salts was not derived.

However, Appendix A of this document contains Screening Values (screening subchronic and chronic p-RfD) that may be useful in certain instances. See the attached Appendix A.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

As reviewed in the Toxicological Review of Thallium and Compounds (U.S. EPA, 2009) no subchronic or chronic p-RfC values can be derived because there are no suitable studies of inhalation exposures.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

The Cancer WOE descriptor for thallium is provided in the Toxicological Review of Thallium and Compounds (U.S. EPA, 2009) as "*Inadequate Information to Assess Carcinogenic Potential (both oral and inhalation)*."

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The lack of data on the carcinogenicity of any thallium compound as indicated in the IRIS Toxicological Review (U.S. EPA, 2009) precludes the derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure.

APPENDIX A. PROVISIONAL SCREENING VALUES

For the reasons noted in the main document, it is inappropriate to derive a subchronic or chronic p-RfD for thallium. However, information is available which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an appendix and develops a screening value. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of a supplemental screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Heath Risk Technical Support Center.

DERIVATION OF SCREENING PROVISIONAL ORAL REFERENCES DOSES

The 90-day study by MRI (1988) is selected as the principal study for derivation of the screening subchronic and chronic p-RfD. This study was summarized in the Toxicological Review (U.S. EPA, 2009) as follows:

> *In a study performed by Midwest Research Institute (Midwest Research Institute, 1988) for EPA's Office of Solid Waste, male and female Sprague-Dawley rats (45 days old, 20/sex/group) were administered 0 (untreated and vehicle controls), 0.01, 0.05, or 0.25 mg/kg-day of an aqueous solution of thallium (I) sulfate (approximately 0, 0.008, 0.04, or 0.20 mg/kg-day Tl) by gavage for 90 days. The study was conducted in compliance with EPA good laboratory practice (GLP) mandates. The MRI (1988) study is an unpublished study; accordingly, an external peer review was initiated by EPA in November 2006. Body weight, food consumption, hematologic and clinical chemistry parameters, ophthalmologic examinations, gross pathological observations, and organ weights (liver, kidneys, brain, gonads, spleen, heart, and adrenals) were recorded for all animals. Neurotoxicological examinations (three times/week) were performed on six rats/sex/group; these examinations were apparently observational (further details were not provided in the study report). Tissues from three rats/sex/group were prepared for neuropathologic examination. Complete histopathologic examinations (including neuropathologic examinations) were conducted for the vehicle control and 0.2 mg/kg-day Tl groups only; for the other three groups, only the livers, lungs, kidneys and gross lesions were examined histopathologically. Neuropathologic examinations included the following: dorsal and ventral root fibers of the spinal nerves, dorsal root ganglia, spinal cord at C3–C6 and L1–L4, and six sections of the brain.*
>
> *There were no statistically significant differences in body weight, food consumption, or absolute and relative organ weights among control groups and groups receiving thallium (I) sulfate* (Midwest Research Institute, 1988). *The study authors concluded that the histopathologic examination did not reveal any treatment-related effects.*

Lacrimation (secretion of tears), exophthalmos (abnormal protrusion of the eyeball), and miosis (contraction of the pupil) were observed at higher incidences in the treated male and female rats compared with both untreated and vehicle controls (see Table B.1;Midwest Research Institute, 1988). *Ophthalmologic examination and gross and histopathologic examination of the eyes, however, revealed no treatment-related abnormalities. The incidence of clinical observations related to the coats (including rough coat, piloerection, shedding, and alopecia) and behavior (including aggression, tension/agitation, hyperactivity, vocalization, and self-mutilation) were also elevated in male and female rats at the higher doses* (see Table B.1; Midwest Research Institute, 1988).

As noted above, the incidence of alopecia was increased, particularly in female rats (see Table B.2; Midwest Research Institute, 1988). Examination of individual animal clinical observation data for female rats from the MRI (1988) study showed that alopecia was first observed in control and treated groups anywhere from study day 44 to 60. Based on a statistical analysis performed by the U.S. EPA, the incidence of alopecia (total number of cases in each dose group) was statistically significantly elevated relative to controls in mid-dose males and mid- and high-dose females. Most instances of alopecia in females were attributed to barbering behavior (where fur was present but cropped short). Of the 12 high-dose females with alopecia, 5 instances were not totally attributed to barbering behavior. Histopathologic examination revealed atrophy of the hair follicles in two high-dose female rats. Because the skin was examined for histopathologic changes only in the vehicle control and high-dose groups, no information on dermal histopathology was available for the low- and mid-dose groups. The two high-dose females with atrophy of the hair follicles also had alopecia; whether the hair follicle atrophy and alopecia occurred at the same location on the rats could not be determined from the study report. The study authors concluded that the alopecia was attributable to the cyclic pattern of hair growth in rodents. Consequently, the authors did not consider these findings to be toxicologically significant.

Subtle but statistically significant changes were observed in several blood chemistry parameters that the investigators considered probably treatment related (Midwest Research Institute, 1988). *Specifically, dose-related increases in AST, lactate dehydrogenase (LDH), and sodium levels and decreases in blood sugar levels were detected in male and female rats after 30 and 90 days of exposure. Reported values for the selected blood chemistry parameters are summarized in* Table B.3. *Other changes in blood chemistry parameters were less consistent across species, dose groups, and exposure durations.*

At 90 days, the differences in AST, LDH, sodium, and blood sugar levels in dosed male and female rats were no greater than +31, +38, +4, and -21%, respectively, of the vehicle control group values (Midwest Research Institute, 1988). *The investigators observed that the increases in AST and LDH levels could indicate a possible effect of treatment on cardiac function, that increases in LDH coupled with subtle changes in electrolytes could indicate an effect on renal function, and that, in rare instances, a decrease in blood sugar coupled with an increase in sodium occurs as a defense mechanism for maintaining cellular*

integrity. The investigators concluded that none of the changes observed in the blood chemistries of male or female rats during the study were of sufficient magnitude to significantly affect the health status of the animals. Further, histopathologic evaluation did not confirm any cellular damage suggested by the clinical chemistry findings.

The authors concluded that the minor dose-related changes in this study did not affect the health status of the treated animals and therefore were not toxicologically significant and identified the highest dose, 0.25 mg/kg-day thallium (I) sulfate (0.20 mg/kg-day Tl [2 moles of soluble thallium (I) in one mole of the soluble thallium salt, Tl_2SO_4]), as a no-observed-effect level (NOEL). However, after review, EPA (2009) came to different conclusions as indicated below:

Several candidates for critical effects were considered, but ultimately EPA (2009) considered that only two endpoints were appropriate for RfD development: (1) hair follicle atrophy in female rats that also had alopecia and (2) clinical observations; those related to animal coat (rough coat, piloerection, shedding, and alopecia), eyes (including lacrimation, exophthalmos, and miosis) and behavior. Endpoint (2) was not selected as the critical effect in this PPRTV because there is a high background occurrence of alopecia in control animals and the potential for misclassification. As a result, there is some uncertainty about the incidence of treatment-related alopecia in the treated animals. In addition, the underlying basis for other clinical observations is unknown. Endpoint (1) was selected as the critical effect because atrophy of hair follicles is consistent with the atrophic changes observed in the cases of human thallium poisoning (e.g., follicular plugging of the skin including alopecia) and may be the best indicator for human response to thallium exposure. For this PPRTV, hair follicle atrophy is selected as the critical effect because it may serve as a better indicator of alopecia resulting from thallium exposure.

The high dose (0.25 mg/kg-day thallium [I] sulfate or 0.2 mg/kg-day soluble Tl) was characterized as a LOAEL. Because skin tissue from rats in the low- and mid-dose groups was not examined for histopathologic changes, the NOAEL for this endpoint cannot be determined with certainty. Given the low incidence of hair follicle atrophy in females in the high dose group and absence of cases of hair follicle atrophy in male rats, the mid-dose can reasonably be assumed to approximate a NOAEL for skin histopathology. Thus, an estimated NOAEL of 0.05 mg/kg-day thallium (I) sulfate (Tl_2SO_4) or 0.04 mg/kg-day Tl (soluble form) was used as the POD for hair follicle atrophy from the MRI (1988) study.

The screening subchronic p-RfD was derived using a composite UF of 1000 as follows:

Screening Subchronic p-RfD = NOAEL ÷ UF_C
(Thallium [I] Sulfate) = 0.05 mg/kg-day Tl_2SO_4 ÷ 1000
= **5×10^{-5} mg/kg-day Thallium (I) Sulfate**

Screening Subchronic p-RfD = NOAEL ÷ UF_C
(Soluble Thallium) = 0.04 mg/kg-day Tl ÷ 1000
= **4×10^{-5} mg/kg-day Tl**

The calculation of the NOAEL for soluble Tl being:

$$0.04 \text{ mg/kg-day} = 0.05 \text{ mg/kg-day} \times \frac{2 \text{ moles } Tl^{+}}{1 \text{ mole } Tl_2SO_4} \times \frac{204.38 \text{ g (MW } Tl^{+})}{504.82 \text{ g (MW } Tl_2SO_4)}$$

An interspecies UF_A of 10 is applied for extrapolation from laboratory animals to humans since no information is available to characterize the toxicokinetic or toxicodynamic differences between experimental animals and humans.

An intraspecies UF_H of 10 is applied to account for variation in human susceptibility in the absence of information on the variability of response to thallium in the human population.

A database UF_D of 10 is applied to account for a lack of adequate developmental toxicity studies and a two-generation reproductive study, and additional uncertainty associated with the limited data available on neurotoxicity.

An UF_S of 1 applied for extrapolation from subchronic studies since the principal study is considered a subchronic study.

An UF_L of 1 is applied to account for extrapolation from LOAEL to NOAEL, because a NOAEL was utilized.

The screening chronic RfD was derived using a composite UF of 3000 as follows:

Screening Chronic p-RfD = NOAEL ÷ UF_C
(Thallium [I] Sulfate) = 0.05 mg/kg-day Tl_2SO_4 ÷ 3000
= **2×10^{-5} mg/kg-day Thallium (I) Sulfate**

Screening Chronic p-RfD = NOAEL ÷ UF_C
(Soluble Thallium) = 0.04 mg/kg-day Tl ÷ 3000
= **1×10^{-5} mg/kg-day Tl**

An interspecies UF_A of 10 is applied for extrapolation from laboratory animals to humans since no information is available to characterize the toxicokinetic or toxicodynamic differences between experimental animals and humans.

An intraspecies UF_H of 10 is applied to account for variation in human susceptibility in the absence of information on the variability of response to thallium in the human population.

A database UF_D of 10 is applied to account for a lack of adequate developmental toxicity studies and a two-generation reproductive study, and additional uncertainty associated with the limited data available on neurotoxicity.

An UF_S of 3 is applied to account for extrapolation from subchronic to chronic exposure duration. As explained in the IRIS Toxicological Review, "Oral toxicity data for thallium suggest that an UF of 10 would overestimate the difference in response following subchronic and chronic oral exposures. Effects on the coat/skin as well as other clinical observations occur

within weeks of exposure to thallium (i.e., these sensitive effects do not require chronic exposure in order to manifest)."

An UF_L of 1 is applied to account for extrapolation from LOAEL to NOAEL, because a NOAEL was utilized.

Based on molecular weight (MW) adjustments and stoichiometric calculations, a summary of screening subchronic and chronic p-RfDs for other soluble thallium salts is presented in Table A.1.

Table A.1. Screening Subchronic and Chronic p-RfDs for Other Thallium Salts

Thallium Salt (Formula; MW)	Screening Subchronic p-RfD (mg/kg-day)	Screening Chronic p-RfD (mg/kg-day)
Thallium (I) acetate ($TlC_2H_3O_2$; 263.43)	5×10^{-5}[a]	1×10^{-5}[b]
Thallium (I) carbonate (Tl_2CO_3; 468.78)	5×10^{-5}[c]	2×10^{-5}[d]
Thallium (I) chloride (TlCl; 239.84)	5×10^{-5}[a]	1×10^{-5}[b]
Thallium (I) nitrate ($TlNO_3$; 266.39)	5×10^{-5}[a]	1×10^{-5}[b]

[a]Based on the screening subchronic p-RfD for soluble thallium and the molecular weight conversion as follows: screening subchronic p-RfD of (1:1) thallium salt = screening subchronic p-RfD of soluble thallium × (Molecular weight of (1:1) thallium salt ÷ Molecular weight of thallium), rounded to one significant figure. For example, for the screening subchronic p-RfD of thallium (I) acetate = 4×10^{-5} mg/kg-day Tl × MW($TlC_2H_3O_2$) ÷ MW(Tl) = 4×10^{-5} mg/kg-day × (263.43 ÷ 204.38) = 5×10^{-5} mg/kg-day.

[b]Based on the screening chronic p-RfD for soluble thallium and the molecular weight conversion as follows: screening chronic p-RfD of (1:1) thallium salt = screening chronic p-RfD of soluble thallium × (Molecular weight of (1:1) thallium salt ÷ Molecular weight of thallium), rounded to one significant figure. For example, for the screening chronic p-RfD of thallium (I) acetate = 1×10^{-5} mg/kg-day Tl × MW($TlC_2H_3O_2$) ÷ MW(Tl) = 1×10^{-5} mg/kg-day × (263.43 ÷ 204.38) = 1×10^{-5} mg/kg-day.

[c]Based on the subchronic screening p-RfD for thallium (I) sulfate and the molecular weight conversion as follows: screening subchronic p-RfD of (2:1) thallium salt = screening subchronic p-RfD of thallium (I) sulfate × (Molecular weight of (2:1) thallium salt ÷ Molecular weight of thallium [I] sulfate), rounded to one significant figure. For the screening subchronic p-RfD of thallium (I) carbonate = 5×10^{-5} mg/kg-day Tl_2SO_4 × MW(Tl_2CO_3) ÷ MW(Tl_2SO_4) = 5×10^{-5} mg/kg-day × (468.78 ÷ 504.82) = 5×10^{-5} mg/kg-day.

[d]Based on the chronic screening p-RfD for thallium (I) sulfate and the molecular weight conversion as follows: screening chronic p-RfD of (2:1) thallium salt = screening chronic p-RfD of thallium (I) sulfate × (Molecular weight of (2:1) thallium salt ÷ Molecular weight of thallium [I] sulfate), rounded to one significant figure. For the screening chronic p-RfD of thallium (I) carbonate = 2×10^{-5} mg/kg-day Tl_2SO_4 × MW(Tl_2CO_3) ÷ MW(Tl_2SO_4) = 2×10^{-5} mg/kg-day × (468.78 ÷ 504.82) = 2×10^{-5} mg/kg-day.

APPENDIX B. DATA TABLES

Table B.1. Selected Clinical Observations in Sprague-Dawley Rats Treated with Thallium Sulfate for 90 Days[a]

Observation[b]	Untreated Control	Vehicle Control	0.008 mg/kg-day	0.04 mg/kg-day	0.2 mg/kg-day
Male					
Coat/skin					
Rough coat	1/20	3/20	11/20	16/20	19/20
Piloerection	0/20	0/20	1/20	4/20	13/20
Shedding	0/20	0/20	4/20	10/20	8/20
Alopecia	2/20	1/20	4/20	9/20	4/20
Eyes					
Lacrimation	1/20	6/20	19/20	20/20	20/20
Exophthalmos	1/20	5/20	12/20	20/20	20/20
Miosis	0/20	1/20	5/20	7/20	15/20
Behavior[c]	3/20	0/20	7/20	6/20	7/20
Female					
Coat/skin					
Rough coat	1/20	0/20	1/20	5/20	11/20
Piloerection	0/20	0/20	0/20	3/20	8/20
Shedding	0/20	0/20	2/20	3/20	13/20
Alopecia	4/20	1/20	4/20	9/20	12/20
Eyes					
Lacrimation	7/20	6/20	20/20	20/20	20/20
Exophthalmos	5/20	6/20	19/20	20/20	20/20
Miosis	2/20	3/20	1/20	11/20	8/20
Behavior[c]	2/20	2/20	0/20	1/20	7/20

[a]MRI (1988). Table was obtained directly from Table 4-2 in U.S. EPA (2009).
[b]Listed as number of animals with the sign observed at least once during the 90-day study.
[c]Animals exhibiting one or more behavioral observations at least once during the 90-day study, including the following: aggression, tension/agitation, hyperactivity, vocalization, self-mutilation.

Table B.2. Incidence of Alopecia in Rats[a]

Dose (mg/kg-day Tl)	Males		Females	
	Alopecia[b,c]	Hair follicle atrophy[c]	Alopecia[b,c]	Hair follicle atrophy[d]
0 (untreated control)	2/20	--[e]	4/20	--[e]
0 (vehicle control)	1/20	0/20	1/20	0/20
0.008	4/20	--[e]	4/20	--[e]
0.04	9/20[f]	--[e]	9/20[g]	--[e]
0.2	4/20	0/20	12/20[f]	2/20

[a]MRI (1988). Table was obtained directly from Table 4-3 in U.S. EPA (2009).
[b]Number of animals with alopecia at least once during the 90-day study based on clinical observations.
[c]Of the animals with alopecia, the following are the numbers of cases in each dose group that the study authors stated are not totally attributed to "barbering behavior":
Males: untreated control, 1; vehicle control, 0; 0.008 mg/kg-day, 2; 0.04 mg/kg-day, 4; 0.2 mg/kg-day, 1.
Females: untreated control, 0; vehicle control, 0; 0.008 mg/kg-day, 1; 0.04 mg/kg-day, 3; 0.2 mg/kg-day, 5.
[d]Based on histopathologic observation.
[e]Skin was not examined for histopathologic lesions.
[f]Incidence of alopecia (total number of cases) was statistically significantly elevated ($p < 0.05$) relative to incidence in vehicle control, incidence in untreated control, and pooled incidence of vehicle and untreated control, based on Fisher's exact test performed by EPA.
[g]Incidence of alopecia (total number of cases) was statistically significantly elevated ($p < 0.05$) relative to incidence in vehicle control and pooled incidence of vehicle and untreated control, based on Fisher's exact test performed by EPA.

Table B.3. Selected Blood Chemistry Values[a]

Endpoint	Study Day	Untreated Control	Vehicle Control	0.008 mg/kg-day	0.04 mg/kg-day	0.2 mg/kg-day
Males[b]						
AST (I.U.)	30 90	91 ± 26.5 77 ± 19.7	108 ± 18.6 87 ± 17.8	128 ± 24.5[c] 99 ± 20.4	134 ± 29.0[c,d] 113 ± 27.0[c,d]	152 ± 20.1[c,d] 114 ± 31.1[c,d]
LDH (I.U.)	30 90	795 ± 322 587 ± 305	1206 ± 424[c] 856 ± 385	1333 ± 340[c] 1003 ± 363[c]	1396 ± 407[c] 1071 ± 507[c]	1802 ± 341[c,d] 1119 ± 477[c]
Na (meq/L)	30 90	148 ± 1.3 144 ± 1.6	149 ± 2.4 147 ± 2.0[c]	152 ± 4.0[c] 147 ± 1.9[c]	154 ± 2.5[c,d] 149 ± 2.0[c,d]	153 ± 2.1[c,d] 151 ± 2.2[c,d]
Blood sugar (mg/l00 mL)	30 90	100 ± 22.1 158 ± 15.6	97 ± 18.1 138 ± 16.8[c]	93 ± 10.0 131 ± 17.6[c]	90 ± 18.3 121 ± 15.7[c]	62 ± 14.8[c,d] 113 ± 22.4[c,d]
Females[b]						
AST (I.U.)	30 90	95 ± 22.8 77 ± 19.2	115 ± 30.3 90 ± 19.1	127 ± 27.8[c] 93 ± 33.1	149 ± 26.8[c,d] 111 ± 30.7[c]	154 ± 18.2[c,d] 112 ± 31.0[c]
LDH (I.U.)	30 90	1047 ± 335 745 ± 320	1277 ± 495 881 ± 273	1402 ± 501 823 ± 354	1763 ± 370[c,d] 1044 ± 436	1764 ± 361[c,d] 1219 ± 338[b]
Na (meq/L)	30 90	148 ± 1.7 146 ± 1.8	150 ± 1.9 146 ± 1.0	153 ± 4.1[c,d] 148 ± 1.8[c,d]	154 ± 2.8[c,d] 150 ± 2.0[c,d]	155 ± 2.5[c,d] 152 ± 1.0[c,d]
Blood sugar (mg/l00mL)	30 90	103 ± 23.9 110 ± 28.7	80 ± 13.3[c] 89 ± 15.9	80 ± 9.0[c] 103 ± 19.9	67 ± 20.0[c] 88 ± 20.4	50 ± 11.8[c,d] 70 ± 18.0[c]

[a]MRI (1988). Table was obtained directly from Table 4-4 in U.S. EPA (2009).
[b]Mean ± standard deviation of 7–10 rats.
[c]Significantly different (p <0.05) from the untreated control group.
[d]Significantly different (p < 0.05) from the vehicle control group.

APPENDIX C. REFERENCES

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