

U.S. Army Center for Health Promotion
and Preventive Medicine

**Wildlife Toxicity Assessment for
Thallium**

**FINAL REPORT
DECEMBER 2007**

**Prepared by
Health Effects Research Program
Environmental Health Risk Assessment Program**

**USACHPPM Document No: 37-EJ1138-01O
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Wildlife Toxicity Assessment for Thallium and Compounds

CAS No. 7440-28-0

December 2007

1. INTRODUCTION

Thallium is a metallic element that occurs in the earth's crust at a concentration of 0.3–0.6 ppm. The element is frequently found in sulfur-containing ores and potassium minerals and often forms salts with bromine, chlorine, fluorine, and iodine (HSDB 2001). When refined, thallium is a soft bluish-white heavy metal that oxidizes rapidly in air to form a coating of thallium oxide. Elemental thallium is highly reactive and exists in two states of oxidation, thallium (I) and thallic (III) and can also form alloys and amalgams with mercury. The CAS number, 7440-28-0, refers to the elemental form of thallium although this Wildlife Toxicity Assessment also considers the potential toxicity of the thallium compounds that are most often encountered in the environment. Thallium was primarily used as a rodenticide and insecticide until 1972 when it was banned because of its potential harm to humans (ATSDR 1992). Currently, thallium compounds are used in photoelectric cells, highly reflective and low melting glasses, electrical switches and closures that will work at subzero temperatures, low range thermometers, fireworks, in the manufacture of synthetic gems, and as catalysts in chemical syntheses (Windholtz 1983, ATSDR 1992). Thallium cannot be broken down further, and as such, is highly persistent. It is often released from coal-burning plants and smelting of zinc, copper, and lead ores; therefore, thallium exposure to wildlife receptors occurs via wet and/or dry deposition from these sources (ATSDR 1992).

This Wildlife Toxicity Assessment summarizes the toxicity of thallium with emphasis on identifying adverse effects and developing toxicity reference values (TRVs). The TRVs are intended to serve as benchmarks for screening-level ecological risk assessments. The protocol for the development of TRVs is documented in the U.S. Army Center for Health Promotion and Preventive Medicine Technical Guide 254, *Standard Practice for Wildlife Toxicity Reference Values* (USACHPPM 2000).

2. TOXICITY PROFILE

2.1 Literature Review

Relevant biomedical, toxicological, and ecological databases were searched electronically July 19, 2001, using Dialog[®] to identify primary reports of studies and reviews on the toxicology of thallium and compounds. Separate searches were carried out linking the compounds to laboratory mammals, birds, reptiles and amphibians (combined), or wild mammals. In general, a two-tiered approach was used in which all citations were first evaluated as titles and “key words in context.” All available abstracts of

those articles selected in the first tier as potentially relevant to TRV development were retained and re-evaluated for relevancy in the second tier. For thallium and compounds, 34 articles were marked for retrieval from 377 initial hits. Details of the search strategies and the results of each are documented in Appendix A. Secondary references and sources of information on thallium and compounds included an Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile (ATSDR 1990), the National Library of Medicine's Hazardous Substances Databank (HSDB 2001), and the U.S. EPA's Integrated Risk Information System (IRIS; USEPA 2001).

2.2 Environmental Fate and Transport

Although natural sources of thallium exist, man-made sources predominate in areas of industrial activities. Thallium is released into the atmosphere mainly from the combustion of coal, cement production, and smelting operations (USEPA 1988). Various mining and refining operations, iron and steel production, and ore processing releases a significant amount of thallium into water (USEPA 1980, WHO 2002). Soil contamination occurs mainly from solid wastes from coal combustion and smelting (Ewers 1988). Table 1 presents the physico-chemical properties of elemental thallium. Once deposited on land or water, thallium compounds are unlikely to volatilize, although wind dispersion from soil surfaces in dry conditions is possible. Although elemental thallium is insoluble in water, thallium compounds possess a high solubility in water, where thallium exists mostly as a monovalent cation in freshwater and a trivalent ion in oxidized freshwater and marine water (Peter and Viraraghavan 2005). As such, thallium is almost always determined as total metal rather than specific thallium compounds; "the determination of specific compounds that contain thallium are relatively unimportant because of the uncomplicated chemistry of this element" (ATSDR 1992). Thallium can leach to groundwater, and/or be taken up by plants from the soil. The degree of leaching is dependent on the composition and pH of soil, with an increase in leaching corresponding to an increase in acidity. HSDB (2001) identifies a number of field experiments that have quantified the thallium content of various food crops. In addition, some data are available that indicate that thallium can bioaccumulate in aquatic and terrestrial food chains (Zitko and Carson 1975, Zitko et al. 1975, Sharma et al. 1986, Ewers 1988).

There is little information on the environmental degradation of thallium although moisture increases the oxidation of thallium. Thallium adsorbs to soils containing clays, organic matter, and iron oxides (Callahan et al. 1979, Frantz & Carlson 1987, WHO 2002) and is not transformed or biodegraded (Callahan et al. 1979). No scientific studies have been found regarding the abiotic or biotic transformation of thallium compounds in water. Thallium has been found to oxidize slowly in the atmosphere, and although it is not degraded by photochemical reactions, thallos chloride has been shown to be photosensitive (Cotton and Wilkinson 1980, ATSDR 1992).

Table 1. Summary of Physical-chemical Properties of Thallium

CAS No.	7440-28-0
Atomic weight	204.38
Color	Bluish-white
Physical state	Soft heavy metal
Melting point	304°C
Boiling point	1473°C
Odor	None
Solubility in water	Insoluble; slightly soluble in nitric acid
Partition coefficients:	NA
Log K _{ow}	NA
Log K _{oc}	NA
Vapor pressure at 25 °C	1.412×10^{-23} mm Hg
Henry's Law constant at 25 °C	NA
Conversion factors	1 ppm = 8.36 mg/m ³ 1 mg/m ³ = 0.12 ppm

Sources: HSDB (2001), ATSDR (1990)

2.3 Summary of Mammalian Toxicity

2.3.1 Mammalian Oral Toxicity

2.3.1.1 Mammalian Oral Toxicity - Acute

Acute thallium toxicity in mammals is characterized by the following: anorexia, vomiting, diarrhea, skin changes including hair loss (alopecia), dyspnea and nervous disorders, and respiratory failure leading to death (WHO 2002). A number of LD₅₀ values for thallium compounds have been documented in the secondary toxicological/pharmacological literature, including 41.2 mg/kg for thallium acetate in rats and 16 mg/kg for thallium sulfate in brown rats (HSDB 2001). The National Toxicology Program (NTP 2001) lists LD₅₀s in rats, mice, and dogs for a number of monovalent salts of thallium, all within the 20-40 mg/kg range.

Downs et al. (1960) studied the effects of thallium acetate (TA) and thallic oxide (TO) in Wistar-strain albino rats, albino rabbits, guinea pigs, and beagle dogs. The study evaluated the effects of acute TA and TO exposure in four types of mammals and subchronic exposures in rats. The acute exposure analysis consisted of a single oral dose of TA or TO to each of the four mammalian species. Details were not provided as to how TA and TO were orally administered, and treatments generally consisted of one individual animal/per dose. As another assessment of acute toxicity, single doses of TA and TO were

administered to rabbits, guinea pigs, and rats via intravenous and/or intraperitoneal injections. Thallium acetate was administered as an aqueous solution with a concentration of 1%, 2%, or 5%. Five percent TO was suspended in a solution containing distilled water and 0.8% carboxy methylcellulose. Results indicated that the lowest lethal dose for a mammal (guinea pig) was 5 mg TO/kg and 12 mg TA/kg via single-dose oral administration. Downs et al. (1960) had also calculated a 7-day LD₅₀ value for female rats for intraperitoneal and oral routes of exposures. The LD₅₀s were 23 mg TA/kg and 72 mg TO/kg for intraperitoneal exposures and 32 mg TA/kg and 39 mg TO/kg for oral exposures.

Using SWS mice, Achenbach et al. (1980) determined the oral LD₅₀ of thallium (as thallium sulfate) as a function of time, and obtained values ranging from 150 mg TI/kg (36-hours) to approximately 2000 mg TI/kg (1-hour).

Aoyama et al. (1988) evaluated the possible association of thallium toxicity to peroxidation processes in male golden hamsters. Lipid peroxidation damages lipids in cellular membranes and generates endogenous toxicants (free radicals and electrophiles). Free radicals and electrophiles may react with nearby molecules such as membrane proteins, or disperse and react with molecules such as DNA. Glutathione (GSH) protects lipids against peroxidation via electron transfer from glutathione to the peroxidase free radical. Glutathione peroxidase (GSH Px) is the enzyme used in the oxidation reaction of glutathione (Casarett & Doull 2001). The amount of GSH decreases when thallium binds to sulfhydryl groups (Aoyama et al. 1988), thereby increasing lipid peroxidation and preventing protection against free radicals. One dose of thallium malonate was administered orally via gavage to male golden hamsters at 10 mg/kg and 50 mg/kg doses. The study found that there was an increase in lipid peroxidation in the kidney one day after the 10 mg/kg dose. A significant decrease in the non-protein sulfhydryls (NPSH) and GSH Px was observed in the kidney at 10 mg/kg. NPSH and GSH Px concentrations had also significantly decreased in the liver and kidney at 50 mg/kg. Indicators of renal and liver damage were also noted.

2.3.1.2 Mammalian Oral Toxicity – Subacute

No studies on the subacute oral toxicity of thallium were found.

2.3.1.3 Mammalian Oral Toxicity – Subchronic

Downs et al. (1960) conducted a range-finding study and a subchronic study to investigate the subchronic oral toxicity of thallium acetate (TA) and thallic oxide (TO). Initially, a total of seven groups of 5 Wistar rats/group were exposed to dietary concentrations of 0%, 0.0002%, 0.001%, 0.005%, 0.01%, 0.05%, and 0.50% TA for one month. Dietary levels of 0.005% or greater resulted in death rates from 60-100% within ten days. No effects were seen at the 0.001% and 0.0002% levels.

In another part of the study, an additional ten weanling Wistar rats (5 rats/sex/group) received 0%, 0.0005%, 0.0015%, 0.003%, or 0.005% TA, or 0%, 0.002%, 0.0035%, 0.005%, 0.01%, or 0.05% TO in the diet for 15 weeks. Growth, survival, and organ weights were assessed. A decrease in growth was observed in males and increased mortality was noted in males and females exposed to 0.003% TA. Eighty percent of males and 60% of females died between four and eight weeks of the study. After two weeks, alopecia was found in rats fed 0.0015% (LOAEL) and 0.003% TA. At the end of the fifteen-week study, surviving rats from all dose groups were sacrificed for histopathological analysis. No significant histological changes were found in the lungs, liver, kidneys, heart, spleen, brain, stomach, and skin. The NOAEL was determined to be 0.0005%, and the LOAEL was at 0.0015%..

A considerable decrease (up to 180g) in body weight was observed in males and females at 0.005% TO, 0.01% TO, and 0.05% TO and a moderate reduction at 0.0035% TO and 0.002% TO in males. Increased mortality occurred in rats of both sexes at \geq 0.005% TO. At the end of the fifteen-week study, one male rat and three female rats from the 0.0035% TO group and all males and three females from 0.002% TO group had survived. It was noted by the researchers that the deaths observed in the females at the 0.0035% TO level may not have been due to thallium exposure since the same number of deaths were observed in the females fed 0.002% TO. Alopecia was observed in rats at 0.002% TO and 0.0035% TO. At the end of the fifteen-week study, surviving rats from all dose groups were sacrificed for histopathological analysis of the organs. Significant histological changes were noted in the kidneys but not in the lungs, liver, and brain. Effects were noted at 0.002% TO (1.51 mg/kg-day), which is the lowest-observed-adverse-effect-level (LOAEL) and also the lowest dose used in this study. Appendix B illustrates how 0.002% TO was converted to a dose of 1.51 mg/kg-day.

Stoltz et al. (1986) exposed rats by gavage for 90-days to levels of 0, 0.01, 0.05, and 0.25 mg/kg-d thallium (as thallium sulfate). No deaths were reported. Alopecia and observations of lacrimation and rough coat were found in all thallium treatments with increasing incidence. No significant treatment – related changes were reported in hematology parameters, though blood sugar content was reduced with moderate increases in SGOT, LDH, and sodium levels in rats from all treatment groups. No changes in body weight, feed consumption, or organ weights attributable to treatment were found.

Formigli et al. (1986) studied the toxicological effects to the male reproductive system by exposing 10 male Wistar rats to 10 ppm thallium (as thallium sulfate) in drinking water for 60 days, a dose equivalent to about 0.3 mg thallium/kg-day (see Appendix B for derivation of dose). The control group consisted of 10 male Wistar rats. The researchers evaluated sperm motility and conducted histopathological examinations of the testis and epididymis using electron microscopy. A histopathological examination found that there were changes to the tubular epithelium and structural changes in the Sertoli cells. The study found a significant increase in the number of immature sperm in the epididymis and a significant decrease in sperm motility. In an evaluation of various reproductive endpoints, Chapin et al. (1997)

found that fertility had decreased when sperm motility in Swiss mice was 37% or less. Based on the findings in Formigli et al. (1986) and Chapin et al. (1997), it can be concluded that the LOAEL for likely fertility decreases in male rats was 0.3 mg/kg-day thallium. Since the rats were not given thallium doses lower than 0.3 mg/kg-day, a NOAEL is not possible.

2.3.1.4 Mammalian Oral Toxicity – Chronic

Manzo et al. (1983) was the only chronic oral toxicity test located, reporting structural and functional changes in the peripheral nerves of rats. Eighty female Sprague-Dawley rats (180-200g) were exposed to thallium as thallium sulfate in drinking water at 10 mg thallium/L (25 µm) and followed for 36 weeks. Overt symptoms included alopecia (hair loss), periorbital redness, and irritability. Alopecia occurred in about 20% of the treated animals. Overall mortality rate was 15% and 21% after 40 and 240-280 days of treatment, respectively.

In the same study, a 44% decrease in motor action potential amplitude, a 30% decrease in sensory action potential amplitude, and a 25% increase in motor action potential latency were observed at 240 days. Axonal destruction and myelin sheath alterations also were observed.

2.3.1.5 Mammalian Oral Toxicity – Other

According to the World Health Organization (WHO 2002), seed-eating animals, farm animals, and predators exposed to thallium via the use of rodenticides exhibit adverse effects to their central nervous system and gastrointestinal tract. Additional adverse effects in mammals also include salivation from the mouth and nose in cattle and reduced growth in sheep (WHO 2002).

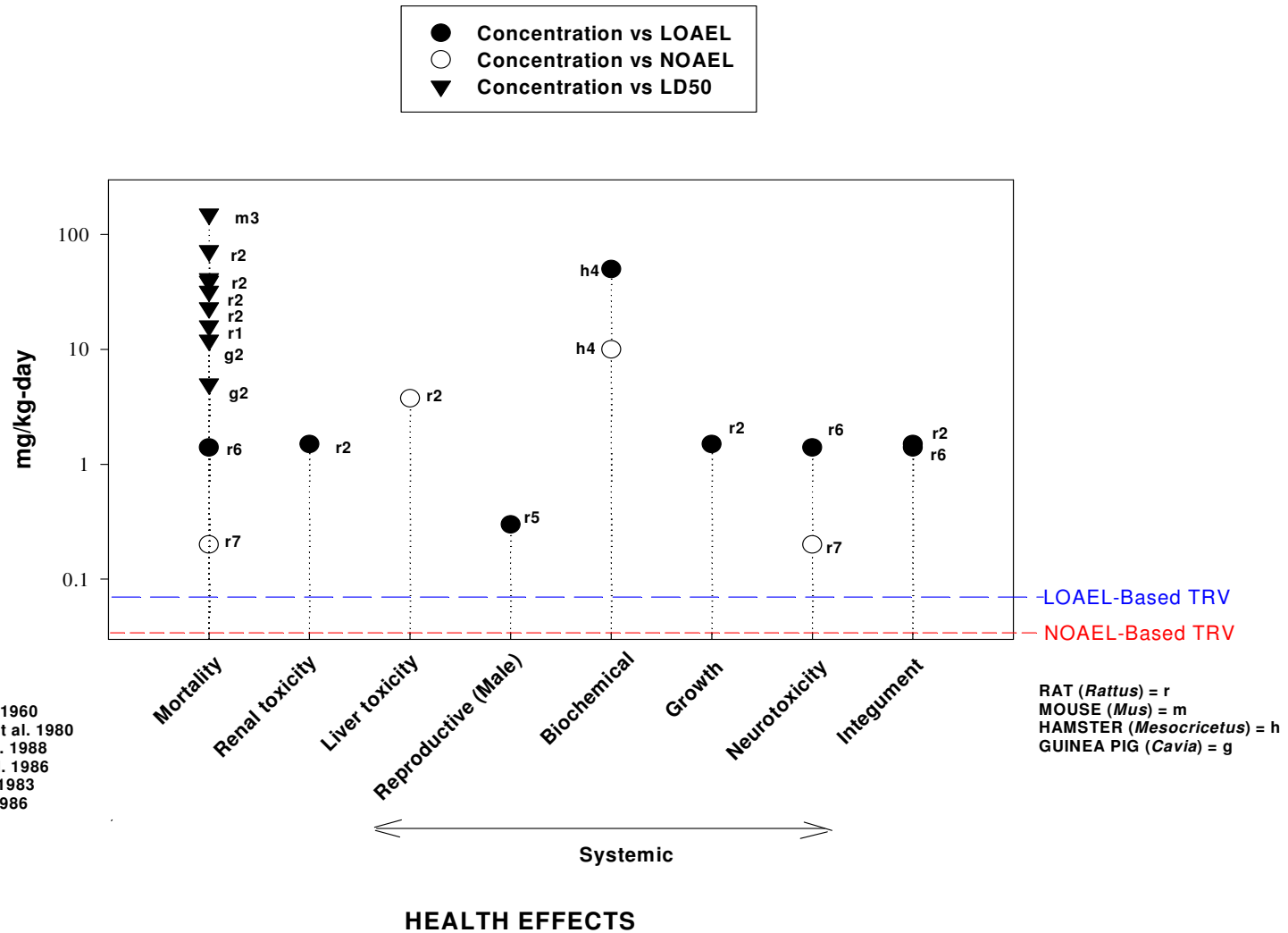
Table 2. Summary of Relevant Mammalian Data for TRV Derivation

Study	Test Organism	Test Duration	Test Results		
			NOAEL (mg/kg/d)	LOAEL (mg/kg/d)	Effects Observed at the LOAEL
Stoltz et al. 1986	Rats	15-w	ND	0.01	Mild alopecia, lacrimation, trends in increased sodium, LDH, SGOT levels; decreased glucose.
Manzo et al. 1983	Rats	240-d	ND	1.4	Change in neuroconduction, lesions on myelin sheaths, 15 – 21% mortality after 40-d, alopecia
Formigli et al. 1986	Rats(Wistar)	60-d	ND	0.3	Reproductive effects (decreased sperm motility)

NA = not applicable; ND = not determined

Figure 1

THALLIUM: HEALTH EFFECTS TO MAMMALS



- 1 = HSDB 2001
- 2 = Downs et al. 1960
- 3 = Achenbach et al. 1980
- 4 = Aoyama et al. 1988
- 5 = Formigli et al. 1986
- 6 = Manzo et al. 1983
- 7 = Stoltz et al. 1986

2.3.1.6 Studies Relevant to Mammalian TRV Development: Thallium Ingestion Exposures

There are relatively few studies on the toxicity of thallium, most focusing on acute toxicity. Acute and subchronic thallium toxicity is characterized by anorexia, vomiting, diarrhea, skin changes including hair loss, dyspnea and nervous disorders, and respiratory failure.

Formigli et al. (1986) and Downs et al. (1960) evaluated the subchronic toxicity of thallium in rats. Downs et al. (1960) showed that thallium affected growth and survival of rats, however, no statistical analyses were conducted and the data presented were insufficient for further independent analysis. Although this study had shown apparent biologically significant effects of thallium at 0.002% thallium oxide (1.51 mg/kg-day), the lack of statistical analyses precludes the use of this study for TRV development. Consistent with those results are the findings of Manzo et al. (1983), where alopecia, irritability, and periorbital redness were observed, as well as low chronic mortality rates (15-20% after 40 weeks).

Formigli et al. (1986) found that reproduction was deleteriously affected by thallium when male Wistar rats were exposed to 0.3 mg thallium/kg-day (as thallium sulfate) in drinking water for 60 days. The LOAEL for sperm motility of thallium-exposed rats was 0.3 mg thallium/kg-day compared to a $40 \pm 8.11\%$ motile for treated male rats versus $66.5 \pm 4.47\%$ of controls. Chapin et al. (1997) evaluated various reproductive endpoints in Swiss mice and determined a threshold for biological significance for each reproductive endpoint, including altered sperm motility. The study found that fertility was decreased significantly when sperm motility was 37% or less. Thus, it can be concluded that the thallium-induced decrease in sperm motility found in Formigli et al. (1986) would likely cause a reduction in reproductive success, potentially affecting species at the population level. Moreover, the levels at which these effects occur seem to be protective of other reported adverse effects.

2.3.2 Mammalian Inhalation Toxicity

No studies on the inhalation toxicity of thallium were located.

2.3.3 Mammalian Dermal Toxicity

No studies on the dermal toxicity of thallium were located.

2.4 Summary of Avian Toxicology

2.4.1 Avian Oral Toxicity

2.4.1.1 Avian Oral Toxicity – Acute

Bean and Hudson (1976) conducted an acute toxicity experiment on thallium in three golden eagles (*Aquila chrysaetos*). Single oral doses of thallium administered as thallium sulfate in a gelatin capsule

were given to each bird. One bird received a dose of 60 mg/kg and the remaining two birds received a dose of 120 mg/kg. Since the bird given the dose of 60 mg/kg survived and the remaining two birds died, the researchers concluded that the LD₅₀ was between 60 and 120 mg/kg. Although the methods are not adequately described, Schafer (1972) has reported an LD₅₀ for starlings to be 35 mg/kg.

2.4.1.2 Avian Oral Toxicity - Other

A number of studies exist on the toxicity of thallium compounds to chicken embryos. Teratogenic effects (Ford et al. 1968), growth inhibition (Hall 1976) and disturbances in the development of bones (Karnofsky et al. 1950) were found to occur in chicken embryos after injection of thallium into the egg.

Karnofsky et al. (1950) were among the first to describe the onset of achondroplasia when thallium sulfate was injected into the yolk or onto the chondrioallantoic membrane. Achondroplasia is the occurrence of short-limbed dwarfism marked by severe shortening of the long bones of the wing and leg, bending of the tibia and overgrowth of the upper jaw (parrot beak) (Hall 1976). Karnofsky et al. (1950) determined that LD₅₀s for thallium were between 1.3 and 2.0 mg/egg, depending on the timing of injection relative to developmental stage. The site of injection (yolk sac or chondroallantoic membrane) also appeared to be important (Ridgway & Karnofsky 1952) in the manifestation of toxicity.

Ford et al. (1968) conducted a range-finding experiment to establish optimum conditions for inducing chondrodystrophy in developing chicken embryos. The researchers injected 0.2–1.6 mg of thallium sulfate into the yolk of white leghorn eggs and examined the developing embryos at different time intervals. An injection of 1.2 mg of thallium sulfate resulted in pronounced skeletal deformities that were characterized by alterations in cartilage formation, skeletal deformity, and defective maturation of the chondrocytes at embryonic day (ED) 11. In one of a series of research reports on this topic, Hall (1972) injected 0.6 mg thallium sulfate on ED7 and studied the ensuing development at 2-day intervals up to ED18. In observing reduced growth of the long bones and the formation of necrotic cartilage, Hall (1972) speculated that these consequences might be related to a thallium-induced depletion of acid mucopolysaccharide. Hall (1976) conducted experiments to define the critical period of embryonic development as it relates to the point where tibias first deviate from normal after thallium injection. After thallium sulfate was injected into white leghorn eggs at ED5, it was determined that the critical period ranged from ED5 to 9.

2.4.1.3. Studies Relevant to Avian TRV Development: Thallium Ingestion Exposures

Although there are several studies on the toxicity of thallium to avian species, none of the data generated are appropriate for deriving an avian TRV. The egg injection studies will not be used to derive an avian TRV since the studies do not accurately represent real-life thallium exposures to birds nor could the exposure regime be calculated back to an oral dose. Additionally, the study by Bean and Hudson

(1976) will not be used since the study lacked statistical analysis, did not narrow the range in determining a more accurate LD₅₀, and presented some design deficiencies.

2.5 Summary of Amphibian Toxicology

No data are available.

2.6 Summary of Reptilian Toxicology

No data are available.

3. RECOMMENDED TOXICITY REFERENCE VALUES

3.1 Toxicity Reference Value for Mammals

3.1.1 TRVs for Ingestion Exposures for the Class Mammalia

Formigili et al. (1986) showed that male Wistar rats exposed to thallium sulfate in their drinking water for 60 days had a significant decrease in sperm motility compared to controls. Sperm motility was 40.5 +/- 8.11% in rats at 0.3 mg Tl/kg-day, compared to 66.5 +/- 4.47% in the control group. According to Chapin et al. (1997), fertility in mice is reduced if sperm motility is 37% or less; therefore, the sperm effects seen in Formigili et al. (1986) would likely cause a decrease in reproductive success, and a concomitant reduction in fitness.

The 0.3 mg Tl/kg-day dose of the male rat in this study was derived from a cohort of male rats exposed to 10 ppm of thallium sulfate in their drinking water for 60 days (see Appendix B for derivation of dose). The body weights in the study ranged from 0.350 kg to 0.380 kg. The average body weight, 0.365 kg, was used to calculate the average daily intake. According to the Toxicological Benchmarks for Wildlife (1996), average body weights of the laboratory animals in the study should be used when calculating NOAELs and LOAELs (Sample et al. 1996). Since data from the chronic toxicity test were not adequate enough to use the NOAEL/LOAEL approach, the approximation approach was used to derive the mammalian TRV (USACHPPM 2000). An uncertainty factor of 20 was used to calculate the NOAEL-based TRV from the subchronic LOAEL (0.3 mg Tl/kg-day) and an uncertainty factor of 4 was used to calculate the LOAEL-based TRV from the study LOAEL (0.3 mg Tl/kg-day) (USACHPPM 2000). Table 3 presents the calculated mammalian TRVs. These TRVs were given low confidence rating. While study design was adequate, the lack of adequate chronic toxicity tests and the lack of data on other mammalian classes precludes a medium confidence rating for these TRVs.

Table 3. Selected Ingestion TRVs for the Class Mammalia

TRV	Dose	Confidence
NOAEL-based	0.015 mg/kg-d	Low
LOAEL-based	0.075 mg/kg-d	Low

3.2 Toxicity Reference Value for Birds

Not available at this time.

3.3 Toxicity Reference Values for Amphibians

Not available at this time.

3.4 Toxicity Reference Values for Reptiles

Not available at this time.

4. IMPORTANT RESEARCH NEEDS

The limited availability of data on the toxicity of thallium to wildlife species precludes the development of a high-confidence TRV. Moreover, for many of the studies on thallium toxicity to wildlife, the experimental design did not incorporate realistic exposures and hence these studies were not useful for deriving TRVs. In general, more research on the toxicity of thallium to wildlife species is needed. Particularly warranted are long-term, chronic toxicity studies on mammals. There are no useful studies of thallium on birds, reptiles or amphibians and therefore, it is impossible to obtain TRVs for these important wildlife receptors.

5. REFERENCES

- Achenbach, C., O. Hauswirth, C. Heindrichs et al. 1980. Quantitative measurement of time-dependent thallium distribution in organs of mice by field desorption mass spectrometry. *J. Toxicol. Environ. Health* 6: 519-528.
- Agency for Toxic Substances and Disease Registry (ATSDR). 1992. Toxicological Profile for Thallium. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.
- Aoyama, H., M. Yoshida, and Y. Yamamura. 1988. Induction of lipid peroxidation in tissues of thallous malonate-treated hamster. *Toxicology* 53: 11-18.
- Bean, J.R., and R.H. Hudson. 1976. Acute oral toxicity and tissue residues of thallium sulfate in Golden eagles, *Aquila chrysaetos*. *Bull. Environ. Contam. Toxicol.* 15: 118-121.
- Casarett and Doull. 2001. Toxicology: The Basic Science of Poisons, 6th Edition. Ed. C.D. Klaassen. NY: McGraw-Hill.
- Callahan, M.A., M.W. Slimak, and N.W. Gabel. 1979. Water-related environmental fate of 129 priority pollutants. Vol I. Introduction and technical background, metals and inorganics, pesticides and PCBs. Report to U.S. Environmental Protection Agency, Office of Water Planning and Standards, Washington, DC, by Versar Incorporated, Springfield, VA. EPA-440/4-79-029a. NTIS No. PB80-204373.
- Chapin, Robert E., R. Sloane, and J.K. Haseman. 1997. The Relationships Among Reproductive Endpoints in Swiss Mice, Using the Reproductive Assessment by Continuous Breeding Database. *Fundamental and Applied Toxicology*. 38: 129-142.
- Cotton, F.A. and G. Wilkinson. 1980. Advanced inorganic chemistry: A comprehensive text. 4th revised ed. New York, NY: John Wiley and Sons 349.
- Downs, W.L., J.K. Scott, L.T. Steadman, and E.A. Maynard. 1960. Acute and sub-acute toxicity studies of thallium compounds. *Am. Ind. Hyg. Assoc.* 21: 399-406.
- Ewers, U. 1988. Environmental exposure to thallium. *Sci. Total Environ.* 71: 285-292.
- Ford, J.K., E.J. Eyring, and C.E. Anderson. 1968. Thallium chondrodystrophy in chick embryos: An historical and biochemical investigation. *J. Bone Joint Surg.* 50A: 687-700.
- Formigli, L., R. Scelsi, P. Poggi et al. 1986. Thallium-induced testicular toxicity in the rat. *Environ. Res.* 40: 531-539.
- Frantz G, and R.M. Carlson. 1987. Division S-2-soil chemistry: Effects of rubidium, cesium, and thallium on interlayer potassium release from Transvaal vermiculite. *Soil Sci Soc Am J.* 51:305-308.
- Hall, B.K. 1972. Thallium-induced achondroplasia in the embryonic chick. *Dev. Biol.* 28: 47-60.
- Hall, B.K. 1976. Thallium-induced achondroplasia in chicken embryos and the concept of critical periods during development. *Teratology* 15: 1-16.
- Hazardous Substances Databank (HSDB). 2001. On-line Database, <http://toxnet.nlm.nih.gov>. National Library of Medicine, Bethesda, MD.

- Karnofsky, D., L.P. Ridgway, and P.A. Patterson. 1950. Production of achondroplasia in the chick embryo with thallium. *Proc. Soc. Exp. Biol. Med.* 78: 255-259.
- Manzo, L., R. Scelsi, and A. Moglia, et al. 1983. Long-term toxicity of thallium in the rat. Pp. 401-405 *in: Chemical Toxicology and Clinical Chemistry of Metals*, Academic Press, London, England.
- Peter, A.L. and T. Viraraghavan. 2005. Thallium: a review of public health and environmental concerns. *Environ. Int.*, 31:493-501.
- Ridgway, L.P., and D.A. Karnofsky. 1952. The effects of metals on the chick embryo: Toxicity and production of abnormalities in development. *Ann. N.Y. Acad. Sci.* 55: 203-215.
- Sample, B.E., D.M. Opresko, and G.W. Suter II. 1996. Toxicological Benchmarks for Wildlife: 1996 Revision. Oak Ridge National Laboratory, Oak Ridge, TN.
- Sharma, J., R.L. Sharma, and H.B. Singh. 1996. Hazards and analysis of thallium—a review. *Toxicol Environ. Chem.* 11: 93-116.
- Stoltz, M.L., M.A. Stedham, L.K. Brown, et al. 1986. Subchronic (90-day) toxicity of thallium (I) sulfate in Sprague-Dawley rats. Project No. 8702-L. Report to the U.S. Environmental Protection Agency, Office of Solid Waste, Washington D.C., by Dynamac Corp., Rockville, MD.
- U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM). 2000. *Standard Practice for Wildlife Toxicity Reference Values*, Technical Guide 254. U.S. Army Center for Health Promotion and Preventive Medicine, Aberdeen Proving Ground, MD.
- U.S. Environmental Protection Agency (USEPA). 1980. Ambient water quality criteria for thallium. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA-440/5-80-074. NTIS No. PB81-117848.
- U.S. Environmental Protection Agency (USEPA). 1988. Health and environmental effects document for thallium and compounds. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, ECAO-CIN-G031.
- U.S. Environmental Protection Agency (USEPA). 1993. *Wildlife Exposure Factors Handbook*. Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington D.C. <http://www.epa.gov/ncea/ecolmeth.htm>
- U.S. Environmental Protection Agency (USEPA). 1999. Hazardous Waste Combustion: Screening Level Ecological Risk Assessment Protocol for Hazardous Waste Combustion Facilities, Volume 3, Appendix E: Toxicity Reference Values. Office of Solid Waste, U.S. Environmental Protection Agency, Region 6, South Central. <http://www.epa.gov/epaoswer/hazwaste/combust/ecorisk.htm>
- U.S. Environmental Protection Agency (USEPA). 2001. Integrated Risk Information System. Online. Office of Health and Environmental Assessment, National Center for Environmental Assessment, Cincinnati, OH.
- World Health Organization (WHO). 2002. World Health Organization. Environmental Health Criteria, 182. Thallium. WHO: Geneva, Switzerland.

Windholz, M., ed. 1983. The Merck index: An encyclopedia of chemicals, drugs, and biologicals. 10th ed. Rahway, NJ: Merck and Company, Inc., 1324-1325.

Zitko, V. and W.V. Carson. 1975. Accumulation of thallium in clams and mussels. *Bull. Environ. Contam. Toxicol.* 14: 530-533.

Zitko, V., W.V. Carson, and W.G. Carson. 1975. Thallium: Occurrence in the environment and toxicity to fish. *Bull. Environ. Contam. Toxicol.* 13: 23-30.

APPENDIX A

LITERATURE REVIEW

The following files were searched in DIALOG:

File 155 MEDLINE; File 156, TOXLINE, File 5 BIOSIS, File 35 Dissertation Abstracts, File 76 Life Sciences Collection, and File 185 Zoological Record.

The search strategy for **Amphibians & Reptiles**:

- ◆ Names and CAS Nos. for the following compounds: thallium, thallium oxide, thallium chloride, thallium acetate, thallium carbonate, thallium sulfate, thallium selenite and thallium nitrate.
- ◆ AND (amphibi? or frog or frogs or salamander? or newt or newts or toad? or reptil? or crocodil? or alligator? or caiman? snake? or lizard? or turtle? or tortoise? or terrapin?)
- ◆ AND (reproduc? or dietary or systemic or development or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ RD (reduce duplicates)

The search strategy for **Birds**:

- ◆ Names and CAS Nos. for the following compounds: thallium, thallium oxide, thallium chloride, thallium acetate, thallium carbonate, thallium sulfate, thallium selenite and thallium nitrate.
- ◆ And chicken? or duck or duckling? or ducks or mallard? or quail? or (japanese()quail?) or coturnix or (gallus()domesticus) or platyrhyn? or anas or aves or avian or bird? or (song()bird?) or bobwhite? or (water()bird) or (water()fowl)
- ◆ AND (reproduc? or dietary or systemic or development or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ RD (reduce duplicates)

The search strategy for **Wild Mammals**:

- ◆ Names and CAS Nos. for the following compounds: thallium, thallium oxide, thallium chloride, thallium acetate, thallium carbonate, thallium sulfate, thallium selenite and thallium nitrate.
- ◆ AND (didelphidae or opossum? or soricidae or shrew? Or talpidae or armadillo? or dasypodidae or ochotonidae or leporidae)or canidae or ursidae or procyonidae or mustelidae or felidae or cat or cats or dog or dogs or bear or bears or weasel? or skunk? or marten or martens or badger? or ferret? or mink? Or aplodontidae or beaver? or sciuridae or geomyidae or heteromyidae or castoridae or equidae or suidae or dicotylidae or cervidae or antilocapridae or bovidae arvicolinae or mycocastoridae or dipodidae or erethizontidae or sigmodon? or (harvest()mice) or (harvest()mouse) or microtus or peromyscus or reithrodontomys or onychomys or vole or voles or lemming?
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))

- ◆ NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumor? or inhalation or carcin? or cancer?)/ti,de
- ◆ NOT (patient? or cohort? or worker? or child? or infant? or women or men or occupational)
- ◆ RD (reduce duplicates)

The search strategy for **Laboratory Mammals:**

- ◆ Names and CAS Nos. for the following compounds: thallium, thallium oxide, thallium chloride, thallium acetate, thallium carbonate, thallium sulfate, thallium selenite and thallium nitrate.
- ◆ AND (rat or rats or mice or mouse or hamster? or (guinea()pig?) or rabbit? or monkey?)
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumor? or inhalation or carcin? or cancer?)/ti,de
- ◆ NOT (patient? or cohort? or worker? or child? or infant? or women or men or occupational)
- ◆ RD (reduce duplicates)
- ◆ NOT (radioisotope)
- ◆ NOT (diagnostic)

The strategy outlined above yielded 12 articles for thallium and compounds with reptiles/amphibians, 39 articles with birds, 112 articles with wild mammals and 214 articles with laboratory mammals.

All abstracts from the DIALOG search were reviewed and encoded in ProCite. When the search retrieved an appreciable number of hits, *keywords in context* were reviewed to minimize costs before any abstracts were downloaded (Tier 1). However, when only a limited number of studies were identified by the search, the abstracts were downloaded at the time of the search (Tier 2).

As noted above and in Section 2.1, 377 hits on thallium and compounds were obtained in the initial search, of which 34 were selected (Tier 2) as being relevant to this survey of the impacts of thallium and compounds on wildlife.

APPENDIX B

MAMMALIAN DOSE CALCULATIONS

A dose, in mg/kg-day, is required to derive a TRV. Formilgi et al. (1986) was used to derive the mammalian TRVs, however, this study did not provide a dose yet provided sufficient information to derive dose. The following equation was used to calculate dose:

$$(\text{Amount given (mg)/rat-day}) * (1/\text{average rat body weight (kg)}) = \text{dose (mg/kg-day)} \quad (1-1)$$

The average daily intake for each rat per day stated in the study was 0.270 mg thallium sulfate. The body weight of rats ranged from 0.350 kg to 0.380 kg. The mean value, 0.365 kg, was chosen to represent the body weight. The dose of thallium received by male rats in the Formilgi et al. study (1986) was derived as follows:

$$\frac{0.270 \text{ mg Tl}_2\text{SO}_4}{\text{Rat-day}} \times \frac{1 \text{ rat}}{0.365 \text{ kg}} \times \frac{204.3833 \text{ g Tl}}{504.831 \text{ g Tl}_2\text{SO}_4} = \boxed{\frac{0.3 \text{ mg Tl}}{\text{kg-day}}}$$

Downs et al. (1960) did not provide oral dose estimates, yet provided information to calculate a dose. The purpose in calculating a dose was to compare this value with the dose from Formigli et al. (1986). The study found that thallic oxide (TO) was more toxic than thallium acetate (TA); thus, the data on TO will be used to derive a dose since it is more protective for the species. The study stated that 0.002% of TO in males had a toxic effect on growth, kidney weight, and resulted in alopecia thereby making this value the LOAEL. The NOAEL is 0 mg TO/kg-day (0% TO). To convert 0.002% TO to a dose, the following equation was used (USEPA 1999):

$$D = \frac{C * IR}{BW} \quad (1-2)$$

where D = Dose (mg/kg-day),

C = Concentration of chemical or substance in diet (mg/kg),

IR = Food ingestion rate (kg/day), and

BW = Test organism body weight (kg)

Since the food ingestion rate was not provided in the study, a food ingestion rate was calculated by the following equation (US EPA 1993):

$$\text{Food ingestion rate} = 0.621 * BW^{0.564} \quad (1-3)$$

where BW = body weight (g)

Body weight data were obtained from the study. Doses were calculated for each week the rats were on the thallium diet (Table 4). The average dose was calculated to be 1.51 mg TO/kg-day, the LOAEL. The purpose in calculating an average dose was to account for variation of exposure through time.

Table 4. Calculated Thallium Doses in Male Wistar Rats over Fifteen Weeks.

Duration on Diet (week)	Male Dose (mg TO/kg-day)
0	2.237
0.5	2.054
1	1.682
2	1.513
4	1.323
8	1.101
12	1.081
15	1.073
	1.508

