NTP Research Concept: Thallium Compounds

Project Leader

Kelly A. Shipkowski, Ph.D.
NIEHS/DNTP/Toxicology Branch

Nomination Background and Rationale

Thallium, Tl, is a heavy metal that is soft, malleable, and insoluble in water in its metallic state. Thallium salts exist in a monovalent (+1) or trivalent (+3) state. Thallium and thallium salts are currently used in the semiconductor and electronic industries, as additives in fireworks, and in the manufacturing of imitation gems, optic lenses, thermometers, and machinery parts operating at sub-zero temperatures. Thallium and thallium salts were nominated by the U.S. Environmental Protection Agency's Office of Land and Emergency Management (EPA's OLEM) for subchronic toxicity studies to generate data to establish an oral reference dose (RfD) for protecting human health. The EPA Integrated Risk Information System (IRIS) *Toxicological Review of Thallium and Compounds* (2009) evaluated the literature available for metallic thallium and eight thallium compounds:

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

There is potential for widespread human exposure to thallium due to its presence as a contaminant in drinking water in the vicinity of hazardous waste and industrial sites, via inhalation from fireworks emissions, and from instances of accidental or deliberate poisoning. Thallium has the potential to induce a broad spectrum of adverse health effects in humans, including alopecia, neurological, cardiovascular, reproductive, and developmental toxicity, and mortality at high doses. Case studies of human exposure indicate that thallium salts may be neurotoxicants, and results from animal studies suggest that thallium salts may induce reproductive and developmental effects including decreased sperm motility and count, low birth weight, and alterations in bone development. There are no available human or animal data on the potential carcinogenic activity of thallium compounds following oral exposure.

Thallium does not have a known biological function in humans, but it has been established that Tl^+ can replace K^+ in vital biological pathways. Tl^+ is similar to K^+ in

ionic radius and electric charge and Tl^+ has a ten-fold higher affinity for Na^+/K^+ ATPase than K^+. The putative mechanism of thallium toxicity is thought to involve inhibition of the Na^+/K^+ ATPase pump and depolarization of membranes.

Human Exposure

Human exposure to thallium and thallium salts can occur from anthropogenic and naturally occurring sources. The EPA Toxics Release Inventory (TRI) estimated that approximately 1.67 million pounds of thallium and thallium compounds were released from industrial sources in 2014. Thallium also occurs naturally in the Earth's crust at an abundance of 0.7 – 1.0 parts per million (ppm), and soil thallium concentrations naturally range from 0.1 – 1.0 ppm.

A major concern for human exposure to thallium and thallium salts is through drinking water contamination following the release of thallium into the environment. Thallium is released into the atmosphere from a variety of industrial sources, including coal-fired power plants, mining operations, metal smelters, and cement plants. Limited data are available for thallium concentrations in ambient air, though the U.S. EPA (1988) estimated thallium concentrations near a coal-fired power plant to be approximately 0.08 parts per billion (ppb).

The EPA's Maximum Contaminant Level (MCL) for drinking water and Human Health Water Quality Criteria (HHWQC) for thallium are currently set at 2.0 and 0.24 ppb, respectively. In California, the MCL and Public Health Goal (PHG) for thallium in drinking water are currently set at 2.0 and 0.1 ppb, respectively. All of these levels were derived based on a 90-day subchronic toxicity study performed by Midwest Research Institute (MRIGlobal, Kansas City, MO) for the EPA. In this study, male and female Sprague-Dawley rats were exposed to Tl_2SO_4 via oral gavage and the incidences of alopecia were considered as the critical endpoint.

Information from the Environmental Working Group's (EWG's) 2009 National Drinking Water Database showed that thallium had been detected in treated tap water in 34 states since 2004, exposing an estimated 8 million people. Of those reported instances, 31 were above EPA's HHWQC (0.24 ppb) and California's PHG (0.1 ppb), and 15 were above EPA's and California's MCL (2.0 ppb). The highest level of thallium reported was 3.15 ppb.

Thallium has been measured in the urine of the U.S. population as part of the National Health and Nutrition Examination Survey (NHANES). A slight decreasing trend was evident from 1999-2010, and, for the 2009-2010 reporting cycle, the geometric mean and 95^{th} percentile concentrations for all participants were 0.144 µg/g creatinine and 0.410 µg/g creatinine, respectively. The urinary concentrations for ages 6-11 were slightly higher than those of the group as a whole.

Knowledge Gaps

The EPA IRIS assessment (2009) concluded that there was a lack of adequate data to derive an RfD or reference concentration (RfC) for human health following thallium exposure. In general, there are relatively few toxicity studies and those that are available are of poor quality, however specific knowledge gaps noted in the IRIS assessment included neurotoxicity, developmental and reproductive toxicity, genotoxicity, and carcinogenicity. The database limitations as well as the low confidence in the available studies hinder informed decisions on dose selection and route of exposure. A 90-day subchronic study of Tl_2SO_4 in rats (MRI, 1988) is considered to be the most informative study on toxicity following oral thallium exposure, and has been utilized by the EPA and OEHHA to derive drinking water guidelines for thallium contamination. However, the 2009 IRIS assessment indicated low confidence in the reported data and conclusions from the subchronic study. Limitations noted included dose selection was likely too low and that there were inconsistencies with the interpretation and reporting of data regarding instances of alopecia.

Dose selection for the subchronic study was deemed inappropriate for evaluation of alopecia, a trademark sign of thallium exposure and the most sensitive endpoint of toxicity in the study. A 14-day range-finding study (MRI, 1986) performed prior to the 90-day study indicated hair follicle alterations alongside minimal decreases in body weight gain at a dose of 2.5 mg/kg/day Tl_2SO_4, however a dose of 0.25 mg/kg/day Tl_2SO_4, ten-fold lower, was utilized as the high dose in the subchronic study. In addition, alopecia was the only reported treatment-related finding, however further review of the results indicated that there were difficulties distinguishing between normal hair cycling, self-barbering, and incidences of alopecia.

Proposed Approach

The goal of this research program is to evaluate the potential for water-soluble thallium salts to induce neurological, reproductive, and developmental toxicity following subchronic exposure in rodents. A systematic approach will be taken to select an appropriate and representative test compound, as there is low confidence in the thallium toxicity data currently in the literature. Numerous thallium salts are utilized in industrial applications and there is little information on the specific toxicity and/or use of individual compounds. Likewise, little information is available on the speciation of thallium in the environment, making compound selection based on occurrence and potential for human exposure difficult.

Thallium salts are found in two different oxidation states: a stable, water-soluble +1 state and a less stable, oxidizing +3 state. Due to the stability and water solubility of the +1 state, we propose utilizing a +1 thallium salt for evaluating subchronic toxicity following oral exposure. There is little basis to indicate that different +1 thallium salts will exert different toxicities *in vivo*. While human exposure to +3 thallium salts is also relevant, the potential instability of +3 thallium salts due to their oxidizing properties may not be ideal for oral exposure studies.

Human exposure to thallium can occur through multiple routes including oral (drinking water, dietary), inhalation, and dermal. After considering the possible routes of exposure it was determined that oral exposure, either through drinking water or gavage, is the most relevant route of exposure for this program due to concerns regarding exposure through contaminated drinking water. Inhalation exposure is also relevant, as thallium is released from industrial and fireworks emissions, but is less of a concern. Due to their previous use as depilatory agents, thallium compounds are believed to be absorbed by the skin, but dermal exposure is not considered to be a major route of exposure for these compounds currently. While oral exposure will be the focus, steps may also be taken to extrapolate from oral exposure to other routes.

While the literature on thallium and thallium salts is limited, the majority of the available information is related to Tl_2SO_4, which is highly water-soluble, similar to other available thallium compounds. Tl_2SO_4 was previously used as a pesticide, but was banned in the U.S. in 1972 due to high, non-selective toxicity. Specific information regarding the current use of Tl_2SO_4 is limited, but Tl_2SO_4 could be a contaminant of groundwater near coal-fired power plants due to the presence of sulfates in the water near these operations.

Specific Aims

1) Select a representative test compound and evaluate stability in drinking water formulations.

While some information is available in the literature regarding the use of Tl_2SO_4, we propose to investigate the chemistry of several +1 and +3 thallium salts to aid in compound selection for the toxicology studies proposed below. This investigation will evaluate the solubility, pH, and the stability and speciation of various +1 and +3 thallium salts in water. Evaluations will also include stability and speciation in artificial gastric and intestinal fluids to mimic *in vivo* conditions.

2) Evaluate the subchronic toxicity of a representative thallium salt in rodents via exposure in drinking water, with the inclusion of endpoints to assess neurotoxicity and reproductive toxicity. Additional exposures during gestation and lactation will be included to broadly assess developmental toxicity.

We propose selecting a representative thallium salt for subchronic toxicity studies based on bulk availability, physicochemical properties (i.e. water-solubility, pH), and information on both current and past human exposures. Case studies of human exposure indicate that thallium is a neurotoxicant, and therefore the potential for neurotoxicity will be assessed. Based on the available background literature, endpoints for reproductive toxicity will be assessed and perinatal exposures will be included to evaluate developmental toxicity. Internal exposure to thallium will be assessed by measuring plasma and/or selected tissue concentrations, and the need for additional ADME and toxicokinetic studies will be determined. As thallium is a soluble metal, further evaluations of chronic toxicity and carcinogenicity may be warranted. Based on

the results of the subchronic studies, discussions will be initiated with agency partners to receive feedback on the value of specific additional work.

3) Use *in vitro* approaches and lower animal models to assess the biological activity of thallium salts.

The primary mechanism of toxicity of thallium is thought to be inhibition of the Na^+/K^+ ATPase pump and depolarization of membranes. We propose utilizing *in vitro* models to: a) better assess this mechanism of toxicity, and b) reduce uncertainty as to whether there are any substantial differences in toxicity between thallium compounds of the same valence state. *In vitro* assays to evaluate cytotoxicity, genotoxicity, and other potential biological targets, such as neurotoxicity, will be considered. Zebrafish screening may also be utilized for evaluation of different biological targets including developmental toxicity.

Significance and Expected Outcome

Human exposure to thallium compounds via contaminated drinking water, particularly from industrial sources such as coal-fired power plants, may represent a significant human health concern. The U.S. EPA OLEM identified subchronic toxicity studies of thallium as a key research need, as the existing data in the literature are inadequate for establishing a RfD for human health risks following oral exposure to thallium or thallium salts. The information provided by these studies will serve to reduce uncertainty, characterize dose response, and more fully characterize potential hazards of thallium compounds, which may ultimately impact federal and state drinking water regulations.

Supporting Documents

ATSDR (Agency for Toxic Substances and Disease Registry). (1992) Toxicological Profile for Thallium.

CalEPA (California Environmental Protection Agency). (1999) Public Health Goal for Thallium in Drinking Water.

CDC (Centers for Disease Control and Prevention). (2015) Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, February 2015.

EWG (Environmental Working Group). (2009) National Drinking Water Database, Chemical Contaminants: Thallium (Total).

IPCS (International Programme on Chemical Safety). (1996) Environmental Health Criteria No. 182: Thallium.

IPCS. (1990) Poisons Information Monograph 525: Thallium.

MRI (Midwest Research Institute). (1986) Toxicity of thallium (I) sulfate (CAS NO. 7446-18-6) in Sprague-Dawley rats. Volume 1: Range-finding (14-day) study [final report]. Docket ID: EPA-HQ-ORD-2008-0057-0005.

MRI (Midwest Research Institute). (1988) Toxicity of thallium (I) sulfate (CAS NO. 7446-18-6) in Sprague-Dawley rats. Volume 2: Subchronic (90-day) study [revised final report]. Docket ID: EPA-HQ-ORD-2008-0057-0002 and EPA-HQ-ORD-2008-0057-0003.

U.S. EPA (Environmental Protection Agency). (2009) Toxicological Review of Thallium and Compounds.

U.S. EPA. (2016) TRI Explorer (2014 Dataset (released March 2016)), Thallium and Thallium Compounds.

USGS (U.S. Geological Survey). (2016) Mineral Commodity Summaries: Thallium.