NTP
National Toxicology Program

Thallium Compounds

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Nomination of Thallium Compounds

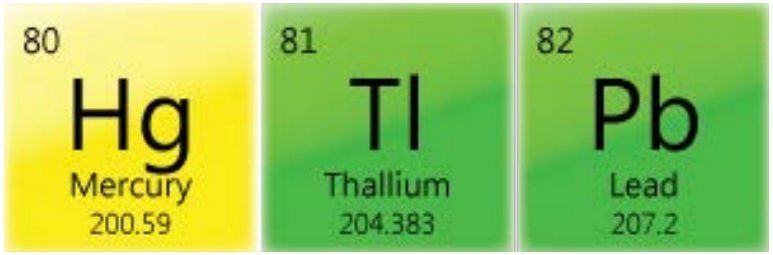
- Nominated by U.S. EPA Office of Land and Emergency Management
  - Subchronic toxicity studies to generate data to establish an oral reference dose (RfD)
- Potential for widespread human exposure
  - Primarily drinking water and dietary (hazardous waste and industrial sites)
- Wide spectrum of potential adverse health effects in humans
  - Alopecia
  - Neurological, cardiovascular, and reproductive toxicity
  - Lethal doses for humans reported at 0.9 – 9.4 mg Tl/kg body weight

EPA's Key Questions and Data Gaps

- No adequate subchronic or chronic toxicity studies in mammals
- Request for data to support hazard identification and dose-response assessment
  - 90-day subchronic study with neurological, reproductive, and developmental endpoints
- EPA indicated they would use information to derive toxicity values whenever available

Thallium and Thallium Compounds

- Metallic thallium (Tl)
  - Heavy metal, insoluble in water
  - Soft and malleable, bluish-white or grey
  - Utilized in the semiconductor industry, often as an alloy of mercury
- Thallium compounds
  - Two oxidation states: monovalent (+1) and trivalent (+3)
  - Monovalent form is more stable, trivalent form is strongly oxidizing
  - Industrial uses include electronics, fireworks, imitation gems



Human Exposure

- Human exposure to thallium compounds can occur from both anthropogenic and naturally occurring sources
  - ~ 1.67 million pounds of thallium and thallium compounds released from industrial sources in 2014 (EPA Toxics Release Inventory)
  - Coal-fired power plants, mining operations
  - Thallium occurs naturally in the Earth's crust at 0.7 – 1.0 ppm
  - Soil thallium concentrations range from 0.1 – 1.0 ppm

Drinking Water Contamination

- Major concern for human exposure to thallium compounds is through contaminated drinking water
- Maximum Contaminant Level for thallium in drinking water = **2.0 ppb**
- Thallium detected in treated tap water in 34 states since 2004
- Ten highest concentrations ranged from 2.0 – 3.15 ppb
  - Environmental Working Group National Drinking Water Database (2009)

*ppb = parts per billion

Absorption, Distribution, Metabolism, Excretion

- Limited data indicates water-soluble thallium compounds are readily absorbed from the skin, gastrointestinal tract, and respiratory tract
- Thallium ions rapidly distributed throughout the body in humans and experimental animals
- No available studies on the metabolism of thallium compounds
  - Unknown if thallium compounds transform valence state *in vivo*
- Eliminated primarily in urine and feces
  - Reported half-life in rats: 3.3 - 4 days
- No available information on the toxicokinetics of metallic thallium
  - Not metabolized in its elemental form

Toxicity of Thallium Compounds

- Indications in the literature that thallium may be a neurotoxicant
  - Targets peripheral and central nervous systems following oral exposure
  - Case studies in humans indicate significant neurotoxic effects
- May induce developmental and reproductive toxicity
  - High maternal urinary thallium levels (≥ 0.78 µg/g creatinine) directly associated with increased incidences of low birth weight
  - Studies in rodents indicate the possibility of testicular effects and effects on sperm parameters in rats and mice following oral exposure

Low Confidence in Available Toxicity Data

- EPA Integrated Risk Information System assessment (2009) concluded there was a lack of adequate toxicity studies to derive an oral reference dose (RfD) or inhalation reference concentration (RfC)
- 90-day subchronic study in rats exposed to thallium sulfate (Tl_2SO_4) by oral gavage
  - EPA and California drinking water guidelines derived from study results
  - External peer review (2006) indicated low confidence in reported data and conclusions

Research Program

- Evaluate the potential for water-soluble thallium compounds to induce neurological, reproductive, and developmental toxicity following oral exposure in rodents
- Propose utilization of a +1 thallium compound
  - Both +1 and +3 states are water-soluble, however the +1 state is more stable
- Oral exposure route is most relevant due to concerns regarding exposure through contaminated drinking water

Test Compound Selection

- Select a representative thallium compound and evaluate stability in drinking water formulations

  1. Investigate chemistry of several +1 thallium compounds to aid in selection of a compound for subchronic toxicity studies

  2. Evaluate solubility, pH, stability, and speciation in water

Thallium Compound Selection

- Proposing utilization of Tl_2SO_4 as the representative thallium compound for *in vivo* oral exposure studies
  - High water-solubility
  - Available information in the literature
  - Previous use as a pesticide
  - May be a current contaminant of groundwater near industrial sites

Toxicity Studies

- Evaluate the subchronic toxicity of a **representative** +1 thallium compound in rodents following perinatal exposure via drinking water

  1. Exposures during gestation and lactation to assess developmental neurotoxicity

  2. Inclusion of endpoints to broadly assess developmental and potential reproductive toxicity

  3. Plasma and/or tissue concentrations will be assessed to determine internal exposures to thallium

  – Based on the data from these studies, other studies may be considered to evaluate additional endpoints

Assessment of Biological Activity

- Utilize *in vitro* approaches and lower animal models to assess the comparative biological activity of multiple thallium compounds
  - Reduce uncertainty as to whether there are any substantial differences in toxicity between thallium salts of the same or different valence state
- Evaluate stability and speciation of multiple thallium compounds in artificial gastric and intestinal fluids to mimic *in vivo* conditions
- Will also consider *in vitro* assays to evaluate cytotoxicity and genotoxicity
- Zebrafish models may be utilized for evaluation of different biological targets

Significance and Expected Outcomes

- Oral exposure to thallium compounds via drinking water and dietary sources may represent a significant human health concern
- The U.S. EPA Office of Land and Emergency Management identified subchronic toxicity studies of thallium compounds as a key research need
- The information provided by these studies will serve to reduce uncertainty in the available toxicological data, characterize dose response, and more fully assess the potential hazards of thallium compounds

Review Questions

1. Comment on the merit of the proposed project relative to the mission and goals of the NTP. *The NTP's stated goals are to: Provide information on potentially hazardous substances to all stakeholders; Develop and validate improved testing methods; Strengthen the science base in toxicology; Coordinate toxicology testing programs across DHHS (http://ntp.niehs.nih.gov/go/about).*

2. Comment on the clarity and validity of the rationale for the proposed project. Has the scope of the problem been adequately defined? Are the relevant knowledge gaps identified and clearly articulated? Please identify any additional scientific issues or challenges that are missing and should be considered.

3. Comment on the strategy and approach proposed to meet the stated objectives of the project. Are specific aims reasonable and clearly articulated? Is the scope of proposed work appropriate relative to the public health importance of the issue(s) under consideration? If not, what modifications would you recommend? Where steps to further refine the strategy and/or approach are proposed, are they appropriate?

4. Rate the overall significance and public health impact of this project as low, moderate, or high. Identify any elements of the proposed project that you feel are more important than others, and/or that have a higher likelihood of success at meeting pre-defined specific aims.

5. Provide any other comments you feel NTP staff should consider in developing this project.