CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Thallium is a naturally occurring element in the earth's crust. In the environment, it combines with other elements (primarily oxygen, sulfur, and the halogens) to form inorganic compounds. Thallium is quite stable in the environment since it is neither transformed nor biodegraded.

Thallium compounds are generally soluble in water; thallium is primarily found as the monovalent ion (Tl^+). It tends to be sorbed to soils and sediments (Frantz and Carlson 1987; Karlsson 2006; Mathis and Kevern 1975; Wallwork-Barber et al. 1985; Wick et al. 2020) and to bioconcentrate in aquatic plants, invertebrates, and fish (Barrows et al. 1978; Lin et al. 2001; Zitko and Carson 1975). Terrestrial plants can also absorb thallium from soil (Ewers 1988; Rader et al. 2019; Sharma et al. 1986).

The primary sources of thallium releases to the environment are from processes such as coal-burning and smelting and the production of cement, in which thallium is a trace contaminant of the raw materials, rather than from facilities producing or using thallium compounds (Karbowska 2016). Humans may be exposed to thallium by ingestion, inhalation, or dermal absorption (EPA 1980, 1988; Ewers 1988). The general population is primarily exposed via ingestion of thallium-containing foods, particularly fruits and green vegetables. Inhalation exposure to thallium may also occur near emission sources or in the workplace.

1.2 SUMMARY OF HEALTH EFFECTS

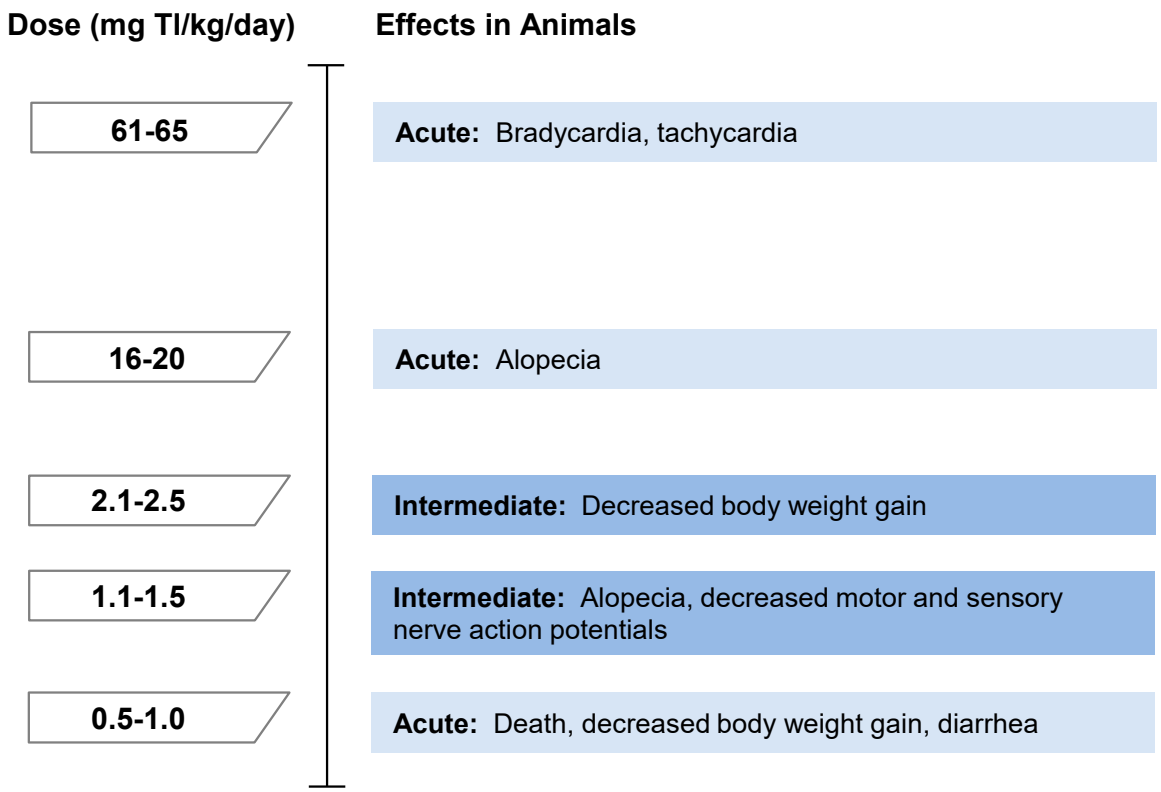
Information on the toxicity of thallium primarily comes from case studies and case series reports in humans orally exposed to thallium, epidemiological studies of the general population presumably orally exposed to thallium, and oral exposure studies in laboratory animals. Collectively, the epidemiological and toxicological studies have evaluated a wide range of potential endpoints following acute, intermediate, or chronic-duration exposure.

As illustrated in Figure 1-1, the most sensitive effects in animals appear to be alopecia, decreased body weight, decreased motor and sensory nerve action potentials, and diarrhea following oral exposure; Figure 1-1 only contains endpoints that have been corroborated in at least two animal studies or in human studies. Of these endpoints, only dermal effects (specifically alopecia) underwent a systematic review.

Systematic reviews of the other endpoints were not conducted because animal studies have not adequately evaluated the endpoint (e.g., only examined in one study or studies did not evaluate function). The systematic review of the alopecia endpoint resulted in the following hazard identification conclusion:

- Alopecia is a presumed health effect for humans.

Figure 1-1. Health Effects Found in Animals Following Oral Exposure to Thallium



There is also strong evidence that cardiovascular, gastrointestinal, and neurological systems are sensitive targets of thallium toxicity based on the consistency of these findings in individuals acutely poisoned with thallium, as reported in case studies and case-series reports.

Cardiovascular Effects. Tachycardia, hypertension, and alterations in electrocardiogram (EKG) have been reported in humans acutely exposed to oral thallium (Cavanagh et al. 1974; Davis et al. 1981; Meggs et al. 1994; Rayisyan et al. 2021; Riyaz et al. 2013; Roby et al. 1984; Sojáková et al. 2015; Tromme et al. 1998; Vrij et al. 1995; Zhao et al. 2008). In general, epidemiological studies either have not found associations or have found inverse associations between urinary thallium levels and cardiovascular disease (Fan et al. 2023; Guo et al. 2022; Li et al. 2023b; Nuvolone et al. 2021; Wang et al. 2022a). Bradycardia, tachycardia, and other EKG alterations were observed in rabbits administered a single lethal

dose of thallium (Grunfeld et al. 1963). Animal studies have not found histological alterations in the heart following intermediate-duration oral exposure (Downs et al. 1960; EPA 1986).

Gastrointestinal Effects. Gastrointestinal effects such as abdominal pain, nausea/vomiting, and/or diarrhea or constipation are often reported in individuals acutely exposed to oral thallium (Al Hammouri et al. 2011; Almassri and Sekkarie 2018; Cavanagh et al. 1974; Dai-xing and Ding-nan 1985; Davis et al. 1981; Meggs et al. 1994; Rayisyan et al. 2021; Wang et al. 2007, 2021; Zhang et al. 2014; Zhao et al. 2008). The effects often occur within the first 3 days of exposure. Diarrhea has also been reported in rats exposed to a high oral dose (Rusyniak et al. 2003).

Dermal Effects. Alopecia (hair loss) is a classic symptom of acute thallium poisoning (Al Hammouri et al. 2011; Almassri and Sekkarie 2018; Desenclos et al. 1992; Gastel 1978; Grunfeld and Hinostroza 1964; Lu et al. 2007; Meggs et al. 1994; Rayisyan et al. 2021; Sojáková et al. 2015; Sun et al. 2012; Villanueva et al. 1990; Wang et al. 2007, 2021; Zavaliy et al. 2021; Zhang et al. 2014; Zhao et al. 2008). It is typically observed several weeks after exposure, and in most cases, the hair loss is temporary. Alopecia is also frequently observed in animals following exposure to a high single dose of thallium (Rusyniak et al. 2003) or following intermediate-duration oral exposure to low thallium doses (Downs et al. 1960; EPA 1986; Gross et al. 1948; Manzo et al. 1983; Shipkowski et al. 2023). It has also been observed in the offspring of rats exposed to thallium during gestation and lactation (Shipkowski et al. 2023).

Neurological Effects. Peripheral nervous system effects are commonly reported after acute-duration oral exposure to high levels of thallium in humans. The observed effects include paresthesia (tingling and numbness) and hyperalgesia (abnormally increased sensitivity to pain) in the hands and feet (Al Hammouri et al. 2011; Almassri and Sekkarie 2018; Cavanagh et al. 1974; Davis et al. 181; Desenclos et al. 1992; Gastel 1978; Li et al. 2014; Meggs et al. 1994; Rayisyan et al. 2021; Roby et al. 1984; Sun et al. 2012; Wang et al. 2007, 2021; Zhao et al. 2008). The neurological effects are commonly reported within a week of exposure. Animal studies have not adequately evaluated the potential neurotoxicity of thallium. Some studies have reported overt signs of neurotoxicity such as convulsions (Grunfeld et al. 1963) and decreased spontaneous activity (Rusyniak et al. 2003). Decreases in the amplitude of motor and sensory action potentials were observed in rats (Manzo et al. 1983).

Cancer. There is limited information on the carcinogenicity of thallium. A study of workers did not find an increase in benign neoplasms, as compared to unexposed workers (Marcus 1985). Mixed results have been reported in epidemiological studies, with two studies finding inverse associations (Fan et al. 2023;

Nuvolone et al. 2021) and one study finding an association with prostate cancer (Cao et al. 2023). No animal studies have evaluated the carcinogenicity of thallium.

The U.S. Environmental Protection Agency (EPA) concluded that the database for thallium provides inadequate information to assess carcinogenic potential (IRIS 2009). The Department of Health and Human Services (HHS) and the International Agency for Research on Cancer (IARC) have not evaluated the carcinogenicity of thallium.

1.3 MINIMAL RISK LEVELS (MRLs)

MRLs for thallium have not been derived. No reliable inhalation studies were identified. Body weight decreases, dermal effects, nervous system effects, gastrointestinal effects, and death were the most sensitive targets following oral exposure to thallium; the lowest LOAELs for these endpoints are presented in Figure 1-2. The database for thallium was not considered adequate for derivation of inhalation or oral MRLs for thallium for any exposure duration (Table 1-1).

Figure 1-2. Summary of Sensitive Targets of Thallium – Oral

Available data indicate that body weight decreases, alopecia, nervous system effects, gastrointestinal effects, and death are the most sensitive targets of thallium oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

Table 1-1. Minimal Risk Levels (MRLs) for Thallium[a]

No MRLs were derived for any exposure route or duration for thallium.

[a]See Appendix A for additional information.