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FINAL

DRINKING WATER CRITERIA DOCUMENT

FOR

THALLIUM

Health and Ecological Criteria Division
Office of Science and Technology
Office of Water
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FOREWORD

Section 1412 (b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish Maximum Contaminant Level Goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology, and mechanisms of toxicity were evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document was comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to April 1987; however, more recent data have been added during the review process and in response to public comments.

When adequate health effects data exist, Health Advisory values for less-than-lifetime exposures (One-day, Ten-day, and Longer-term, approximately 10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

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I. SUMMARY

Thallium (Tl) occurs in the environment in sulfides and selenides containing various proportions of copper, silver, arsenic, and lead. The main valence states of thallium are +1 and +3. Trivalent thallium (e.g., $Tl(OH)_2^+$) will be the predominant species of ionic thallium in natural waters in equilibrium with atmospheric oxygen. The common salts of Tl^{+1} are slightly to moderately soluble in water. In 1984, no thallium was produced in the United States; all consumers of thallium were supplied by imports. Thallium is currently used in the manufacture of lenses and jewelry, in electrical and electronic equipment, in mineralogy, and in medicine as ^{201}Tl for radioactive myocardial imaging. Laboratory modeling of thallium transport indicates that thallium will exchange among water, vegetation, and fish, but not with sand. Levels of thallium in the range of 3.7 ng/L to 88.3 μg/L have been reported in natural waters.

It is estimated that the absorption of thallous nitrate from the gastrointestinal (GI) tract of rats is 100% of the dose; absorption in dogs and humans is at least 62 and 61%, respectively. Cutaneous absorption of thallium has been documented but not quantified. Following absorption, thallium is rapidly and unevenly distributed throughout the body in mammals.

The tissue distribution of thallium in rats has been found to be largely independent of the valence state of the orally administered salt. Furthermore, the intracellular distribution of thallium was found to be largely the same regardless of whether Tl^{+1}, Tl^{+3}, or organometallic thallium was administered orally to rats. After rats were administered a single oral dose of thallium nitrate, the highest levels of thallium were found in the kidney, followed by the salivary glands, testes, muscle, bone, GI tract, spleen, heart, liver, hair, skin, and brain. Following dietary administration of thallium salts to rats, the highest levels of thallium were also found in the kidneys, and the lowest levels were found in the brain. A slightly different distribution was found after a single oral dose of $^{204}TlNO_3$ was administered to a female human cancer patient. The highest levels of thallium

were found in scalp hair, followed by the kidney, heart, and spleen; lower levels were found in the nervous tissue.

Several studies indicate that the transplacental transfer of thallium in mammals is rapid. Thallium has been found in fetal tissues within 30 minutes after oral dosing of pregnant mice and rats. In these studies, fetal levels rarely exceed 10% of those observed in maternal tissues, but fetal levels amounting to 50% of maternal levels have been reported.

Studies have also been performed on the distribution of thallium after intraperitoneal administration of thallium to mice and rats and intravenous administration of thallium to humans. In mice, thallium was found to be present in the epididymis and deferent ducts 24 hours after intraperitoneal dosing. In rats dosed intraperitoneally with ^{201}Tl-labeled thallous sulfate, the tissue distribution of thallium was largely independent of dose in the range of 0.00021 to 10,256 μg Tl/kg. In humans, after intravenous dosing, the volume of distribution of Tl was consistent with its migration into the intracellular space.

No information was found on the form or speciation of valence states of thallium in mammals. Based on similar intracellular and tissue distribution of thallium in rats orally dosed with Tl^{1+} and Tl^{3+} salts, it is suggested that biochemical conversion of Tl^{1+} and Tl^{3+} into a single species occurs in vivo.

In rats, thallium is excreted primarily via the feces. The ratio of fecal to urinary excretion of thallium has been found to vary from 2 to 5. Thallium is excreted directly into the lumen of the intestinal tract, with limited excretion occurring via the bile. In contrast to rats, the ratio of fecal to urinary excretion of thallium was greater than 30 in a human patient dosed orally with thallous sulfate. The biological half-life of thallium in rats has been reported to be 7.3 days in one study and 3.3 days in another study. A mean whole-body half-life of 9.8 days has been reported in humans.

The acute oral LD_{50} of various thallium compounds in mice and rats ranges from 16 to 46 mg Tl/kg.

Degenerative changes in mitochondria of the kidneys, liver, brain, intestines, and liver have been observed subsequent to subcutaneous or intraperitoneal injections of thallium salts. Similarly, subacute toxicity studies in rats revealed histopathological changes in the brain, kidney, liver, and intestines. No studies of lifetime exposure to thallium compounds were available.

Rats dosed by gavage with thallous sulfate at 0, 8.1, 40.5, or 202.4 μg Tl/kg/day for 90 days exhibited moderate but significant elevations in serum enzymatic (SGOT and LDH) activities and elevations in serum sodium and calcium; however, no histopathological effects were reported. In the absence of histopathology, this study provides a No-Observed-Adverse-Effect Level (NOAEL) of 0.2 mg Tl/kg/day. No Lowest-Observed-Adverse-Effect Level (LOAEL) is defined by this study.

Administration of thallous acetate to rats in the diet for up to 15 weeks provided a LOAEL of 1.2 mg Tl/kg/day and a NOAEL of 0.4 mg Tl/kg/day, based on the appearance of alopecia in the rats after 2 weeks on the diet. No histopathological changes were found at the time of sacrifice. Administration of thallium sulfate at levels of approximately 1.4 mg Tl/kg body weight (bw)/day in the drinking water for up to 36 weeks produced abnormal electro-physiological parameters and histopathological findings in nervous tissue.

Subcutaneous administration of thallous acetate (at an initial dose of 7.8 to 15.5 mg Tl/kg, followed by weekly doses of 3.9 mg Tl/kg) for up to 24 weeks produced histological changes in the kidney, brain, and liver of rats.

In a 60-day reproduction study, rats exposed to thallium sulfate in the drinking water at 740 μg Tl/ kg/day exhibited adverse effects in sperm cell maturation and motility, and alterations in Sertoli cells and in the epithelium of the seminiferous tubules.

Several studies indicate that thallium salts are teratogenic in mammals. However, teratogenic doses are close to doses causing maternal toxicity. A teratology study in mice dosed, by gavage, with thallous chloride at levels of 2.6 and 5.1 mg Tl/kg/day on days 6 through 15 of gestation provided a NOAEL for developmental toxicity of 2.6 mg Tl/kg/day and a LOAEL of 5.1 mg Tl/kg, based on postimplantation losses. In a parallel group of mice dosed with thallous acetate at levels of 2.3 and 4.7 mg Tl/kg/day, teratogenic effects were observed at both dose levels.

In pregnant rats orally administered thallous acetate or chloride at levels of 3, 4.5, or 6 mg thallium salt/kg/day (2.6, 3.8, and 5.1 mg Tl/kg/day) on days 6 to 15 of gestation, all of the dams died at the two higher doses. Significant incidences of wavy ribs and dumbbell-shaped sternebrae were noted for both salts at the lower dose. Teratogenic effects were observed at both dose levels in pregnant rats intraperitoneally administered thallous sulfate at 2.0 or 8.1 mg Tl/kg/day on days 12 through 14 of gestation.

Intraperitoneal administration of thallous sulfate to 6- and 9-day-old rat pups at doses of 16 and 32 mg Tl/kg/day produced adverse effects on calcification and hypoplastic cartilage. An unspecified thallium salt at levels of 3 to 100 μg/mL produced dose-related growth retardation in 10.5-day-old rat embryos in culture.

Some thallium salts have been found to be clastogenic in both rat somatic and germinal cells, to damage bacterial and rodent DNA, and to enhance in vitro viral transformation of hamster cells. Thallium compounds have not been evaluated in gene mutation assays suitable for the detection of metal mutagens.

No studies on the carcinogenic potential of thallium were found.

Numerous reports were found on the effects of thallium ingestion in humans. Neurologic symptoms may range from mild peripheral neuropathy to irreversible coma and death. It is suggested that cardiac and pulmonary distress may dominate the acute phase of toxicity. The minimal lethal dose of thallium has been estimated to be 0.2 to 1.0 g (2.9 to 14.2 mg/kg for a 70-kg adult) in humans.

The mechanism of thallium toxicity has not been elucidated. In vitro studies indicate that the thallous ion may replace K^+ in activation of the (Na^+-K^+)-dependent ATPase of rabbit kidney and rat erythrocytes. Likewise, uptake of thallium into rat erythrocytes is inhibited by K^+, and thallous ion may stimulate Na^+ efflux and inhibit K^+ influx into human erythrocytes.

Similarly, interactions between K^+ and Tl^+ have been reported in vivo and in organ culture. It was observed in rats that the LD_{50} for thallous nitrate increased with an increase of K^+ levels in the diet. In rats and dogs, the urinary excretion of thallium increased with an increase in K^+ intake. Furthermore, infusion of K^+ increased the renal clearance and mobilization of thallium from tissues. In in vitro studies of mammalian limb development, it was observed that thallium-induced teratogenesis was affected by the ratio of Tl^+/K^+ in the medium.

In vitro studies with mitochondria indicate that thallium may interfere with potassium movement across the mitochondrial membrane and may also uncouple oxidative phosphorylation, thus interfering with energy metabolism in the mitochondria. Furthermore, thallium may bind to mitochondrial proteins and is known to produce degenerative changes in mitochondria and other organelles.

Several in vivo and in vitro studies indicate that thallium may produce disturbances at the presynaptic level of nerve impulse transmission and ultra-structural damage of neurons. Cytotoxic effects of thallium include the production of decreased cloning efficiency of Chinese hamster ovary (CHO)

cells in culture, and a decrease in the mitotic rate of hair follicle cells after subcutaneous dosing in rats.

No suitable data are available for calculating the One-day or Ten-day Health Advisory (HA) values. Using a NOAEL of 0.2 mg Tl/kg/day based on the absence of histopathological effects in rats dosed orally in a 90-day study, Longer-term HAs of 7.0 and 20.0 μg Tl/L were calculated for a 10-kg child and a 70-kg adult, respectively. It is recommended that the Longer-term HA for a 10-kg child be used as a conservative estimate of the One-day and Ten-day HAs for a 10-kg child. Using a NOAEL of 0.2 mg Tl/kg/day based on the absence of histopathological effects in rats dosed orally in a 90-day study, a Reference Dose (RfD) of 0.07 μg Tl/kg/day and a Drinking Water Equivalent Level (DWEL) of 2.0 μg Tl/L were calculated. No estimations of excess cancer risk were performed.

Thallium salts are designated as a hazardous substance under Section 311(b)(2)(A) of the Federal Water Pollution Control Act and further regulated by the Clean Water Act Amendments of 1977 and 1978. These regulations apply to discharges of these substances.

The reportable quantity of thallium salts, when discharged into or upon the navigable waters and adjoining shorelines of the United States, is 1,000 pounds (454 kg).

II. PHYSICAL AND CHEMICAL PROPERTIES

A. GENERAL PROPERTIES

Thallium, a bluish-white heavy metal with an atomic number of 81 and atomic weight of 204.383, is very soft, inelastic, and easily fusible (Windholz, 1983; Clayton and Clayton, 1981). It forms alloys with other metals and readily amalgamates with mercury. Thallium metal is insoluble in water and is soluble in HNO_3 and H_2SO_4 (Windholz, 1983). The main valence states of thallium are +1 and +3. A valence state of +2 is known but is rare and very unstable (Cotton and Wilkinson, 1980). Trivalent thallium (e.g., $Tl(OH)_2^+$) will be the predominant ionic species of thallium in both seawater and freshwater in equilibrium with atmospheric oxygen (Batley and Florence, 1975). Thallium metal is very reactive, but is slower in bulk reactions because of the formation of coatings of Tl_2O over the surface. When heated to decomposition, toxic fumes of thallium are emitted. Table II-1 summarizes the physical and chemical properties of thallium and some Tl compounds.

B. SOURCE, PRODUCTION, AND USE

It is estimated that thallium constitutes 0.003% (0.7 ppm) of the Earth's crust. Thallium is found to occur mainly in the rare minerals crookesite ($(TlCuAg)_2Se$), orabite ($TlAs_2SbS_5$), lorandite ($TlAsS_3$), and hutchinsonite ($(TlAgCu)_2S\cdot As_2S_3 + PbS\cdot As_2S_3$). It is also found in pyrites and is recovered from the roasting ore in sulfuric acid production (Weast, 1986; Clayton and Clayton, 1981). Lorandite found in gold ore is approximately 60% thallium. On the ocean floor, magnesium nodules contain some elemental thallium. Although thallium is widely distributed, it is not plentiful. Even deposits of main thallium minerals are so small that, at present, they have no commercial significance (Clayton and Clayton, 1981). The main emissions from commercial sources are flue dusts from pyrites (FeS_2), lead and zinc smelters, or refineries as a result of cadmium production (Clayton and Clayton, 1981).

Table II-1. Physical and Chemical Properties of Thallium and Some Thallium Compounds

Chemical	Synonym	Molecular weight	Melting point (°C)	Boiling point (°C)	Solubility
Thallium	Ramor	204.383	303.5	1457±10	Insoluble in hot or cold water; soluble in HNO_3 and H_2SO_4; slightly soluble in HCl.
Thallium acetate	Thallous acetate	263.42	131	--	Very soluble in water at 20°C; insoluble in acetone.
Thallium azide	--	246.39	330(vac)	--	Insoluble in alcohol and ether; very soluble in hot water; slightly soluble in cold water.
Thallium bromide	Thallous bromide	284.28	approx. 460	815	Soluble in water 0.5 g/L (25°C) and 2.5 g/L (68°C); soluble in alcohol; insoluble in HBr and acetone.
Thallium carbonate	Thallous carbonate	468.75	273	--	Soluble in water 40.3 g/L (15°C) and 272.0 g/L (100°C); insoluble in alcohol, ether, and acetone.
Thallium chloride	Thallium mono-chloride	239.82	430	720	Soluble in water 2.9 g/L (15.6°C) and 24.1 g/L (99.35°C); insoluble in alcohol and acetone; (alpha) decomposes in acid.
Thallium nitrate	Thallous nitrate (alpha)	266.40	206	430	Soluble in water 9.6 g/L (20°C) and 4.1 g/L (100°C); insoluble in alcohol; soluble in acetone.
Thallic oxide	Thallium sesquioxide	456.78	717	--	Insoluble in water. Decomposed by HCl and H_2SO_4.
Thallium sulfate	Eccothal, thallous sulfate	504.85	632	Decomposes	Soluble in water 48.0 g/L (20°C) and 191.4 g/L (100°C); insoluble in alcohol, ether, and acetone.
Dimethyl thallium bromide	--	314.34	--	--	--

SOURCE: Adapted from Sax (1984); Clayton and Clayton (1981); Weast (1986); Windholz (1983).

Use of thallium as a sulfate in rodent poison has been banned in the
United States since 1972. U.S. production was curtailed to a very small
amount in 1974. Although thallium production was banned, extractable U.S.
reserves in lead, iron, and zinc ores totaled 266 tons in 1974. U.S. imports
account for 1,500 pounds of thallium compounds (Clayton and Clayton, 1981).
In 1984, the United Stated reported no thallium production; all consumer
demand for thallium was supplied by imports (HSDB, 1987).

Thallium rodenticide poisonings have been reported in other countries,
such as Spain, Denmark, Great Britain, and India. During World War II, the
properties of the bromoiodide crystals in thallium, which transmit radiation
of very long wavelengths, were found to be of value in detection and signaling
equipment where visible radiation must be absent (Clayton and Clayton, 1981).
In addition, because of its high refractive index, thallium is incorporated
into the production of optical lenses and imitation precious jewelry.
Thallium can also be alloyed with mercury in switches and closures that
operate at subzero temperatures (Windholz, 1983; Arena, 1979). Other
scientific and technological applications of thallium are seen in ionizing
radiation counters; semiconductors (photoresistors, photocells, vidicons); and
gas discharge and luminiscent tubes. Thallium formyl malonate (Clerici fluid)
is used in mineralogical analyses and in geological and mineralogical research
with rocks and ores (Shabalina and Spiridonova, 1979). Thallium-201 is
currently finding widespread medical application in myocardial imaging,
although thallium ointments are no longer used in medicine because of their
extreme toxicity (Clayton and Clayton, 1981). Currently, thallium is finding
application in experimental high-temperature superconductors (Waldrop, 1988).

C.   ENVIRONMENTAL FATE AND STABILITY

Wallwork-Barber et al. (1985) studied the transport of thallium in a
laboratory ecosystem consisting of water, sand, vegetation, and fish. A 7-
liter glass aquarium was filled with 1 inch of sterilized and washed sea sand
and 6 liters of distilled water. Goldfish and the submergent aquatic
angiosperms Valliapenia and Ceratophyllum were then added. Tracer levels of

[204]Tl plus thallous nitrate were added to a concentration of 100 ng Tl/mL. Transport of thallium among the four components of the ecosystem was measured for 220 hours. Exchange of thallium was observed among water, vegetation, and fish. Transport between sand and the other community components was not observed. The concentration of thallium in water decreased from the initial value of 100 ng Tl/mL to a final value of approximately 60 ng Tl/mL. Final concentrations of thallium in sand, fish, and vegetation were on the order of 50, 1,750, and 1,450 ng Tl/g, respectively. Deficiencies of this study included the short duration, which did not allow for development of algae, plankton, and excretion buildup in the sand that would have permitted more thallium accumulation.

Several authors have studied thallium levels in natural waters. Batley and Florence (1975) reported mean thallium levels of 13.0 ng/L for Pacific Ocean surface waters off the coast of Australia and 3.7 ng/L for freshwater samples from Woronora Weir (Australia). These authors concluded that trivalent thallium is the predominant valence species of thallium in both seawater and freshwater in equilibrium with atmospheric oxygen. Matthews and Riley (1969) reported mean thallium levels of 10.1 and 18.7 ng/L for water samples from the Bay of Biscay (Spain) and the Irish Sea, respectively. Zitko (1975) reported thallium levels in the range of 2.5 to 88.3 μg/L in water samples from three rivers draining a base-metal mining area in New Brunswick, Canada.

D. SUMMARY

Thallium occurs in the environment in sulfides or selenides containing various proportions of copper, silver, arsenic, and lead. The main valence states of thallium are +1 and +3. A valence state of +2 is known but is less stable and rare. Trivalent thallium (e.g., $Tl(OH)_2^+$) will be the predominant valence state of ionic thallium in natural waters in equilibrium with atmospheric oxygen. Solubility of some thallous salts in water ranges from 0.5 g/L to 48 g/L at temperatures of 15 to 25°C. In 1984, there was no reported U.S. production of thallium; all consumers were supplied by imports.

Thallium is currently used in the manufacture of lenses and jewelry, in electrical and electronic equipment, in mineralogy, and in medicine for myocardial imaging as its radioactive ^{201}Tl isotope. Use of thallium as a rodenticide in the United States was discontinued in 1972. A study in a model ecosystem consisting of water, sand, vegetation, and fish indicated that thallium exchanged among water, vegetation, and fish but not between sand and other community components. Levels of thallium in the range of 3.7 ng/L to 88.3 μg/L have been reported in natural waters.

III. TOXICOKINETICS

A. ABSORPTION

Thallium is readily absorbed following oral and dermal administration of soluble thallium salts. Ziskoven et al. (1983) detected thallium in maternal kidney and brain and in fetuses of pregnant Wistar rats and Kissleg mice by 10 minutes after the animals were administered thallous sulfate orally at a dose level of 8 mg Tl/kg.

Lie et al. (1960) administered ^{204}Tl, as thallous nitrate, to male Wistar-derived rats by six routes: oral (767 μg Tl/kg), intravenous (38 μg Tl/kg), intramuscular (96 μg Tl/kg), subcutaneous (96 μg Tl/kg), intratracheal (123 μg Tl/kg), and intraperitoneal (146 μg Tl/kg). The body burden of ^{204}Tl, as percent of dose, was similar for all routes of exposure and was found to decay with a single exponential function, which extrapolated to 100% at zero time, regardless of route of administration. On this basis, the author concluded that thallium is completely absorbed from the gastrointestinal (GI) tract.

Shaw (1933) administered a single oral dose of thallium sulfate (25 mg Tl/kg) to one dog. At least 61.6% of the dose was absorbed from the GI tract, as measured by recovery of thallium in urine after 36 days.

Thallium can be absorbed through the skin as evidenced by the toxicity of topically applied thallium ointments. Munch (1933) reviewed 51 case histories of women treated for thallium poisoning following external application of an ointment containing thallous acetate at a concentration of 3 to 8%. In 29 cases, between 2 and 24 ounces of the ointment (approximately 53 to 636 mg Tl/kg for a 5.5% ointment and a 50-kg woman) had been applied an unspecified number of times. By several weeks after application, neurological and gastrointestinal symptoms and alopecia were observed.

Hallopeau (1898, as cited in Heyroth, 1947) reported that guinea pigs died without any loss of hair within 48 hours after a cutaneous application of an ointment containing 50% of an unspecified thallium salt.

B. DISTRIBUTION

Lie et al. (1960) studied the tissue distribution of thallium in male Wistar rats. Some animals were dosed with ^{204}Tl, as thallium nitrate, by the oral route (767 μg Tl/kg) and by five other routes as indicated above. In orally dosed animals, over the first 7 days, the highest levels of thallium per gram of tissue were found in kidney (4.71% of the body burden per gram of tissue), followed in decreasing order by salivary glands (1.08%), testes (0.88%), muscle (0.79%), bone (0.74%), GI tract (0.62%), spleen (0.56%), heart (0.54%), liver (0.52%), respiratory system (0.49%), hair (0.37%), skin (0.37%), and brain (0.27%). For all routes of administration, the half-life for thallium was 3.3 days. Except for hair, which accounted for 60% of the body burden after 21 days, the relative concentrations of thallium in tissues were largely independent of time.

Downs et al. (1960) studied the tissue distribution of thallium in Wistar rats of unspecified sex. The animals were fed a diet containing thallous acetate at a concentration of 0.003% (approximately 1.4 mg Tl/kg body weight/day, assuming 15 g of diet/day and a body weight of 250 g). After 63 days on the diet, the highest levels of thallium were found in kidney (24 μg Tl/g wet tissue), followed by liver, bone, spleen, lung, and brain. Levels in these other tissues decreased from 16 μg Tl/g wet tissue in liver to 5 μg Tl/g wet tissue in brain.

Sabbioni et al. (1980) studied the intracellular and tissue distribution of different thallium compounds in rats. Male Sprague-Dawley rats were dosed orally with 3.15 mg Tl/rat (approximately 16.2 mg Tl/kg) as ^{201}Tl-labeled dimethylthallium bromide, thallous sulfate, or an unspecified salt of trivalent thallium. Tissues were removed 16 hours after dosing and assayed for radioactivity. As summarized in Table III-1, monovalent and trivalent thallium have similar intracellular and tissue distributions. Highest values

Table III-1. Intracellular and Tissue Distribution of Different Thallium
Species in Rats[a]

Organ or cell fraction	Tl[1+]	Tl[3+]	Dimethyl-Tl
Organ	Average thallium content in tissues (as percent of dose)		
Kidneys	6.80	6.10	0.56
Liver	3.80	2.90	0.12
Testes	3.70	3.90	0.07
Salivary glands	1.21	1.32	0.02
Heart	0.65	0.51	0.06
Brain	0.57	0.75	0.02
Subcellular fraction from kidney	Average thallium content in subcellular fractions from kidney (as percent of total kidney homogenate)		
Nuclei	26.1	26.5	23.2
Mitochondria	9.7	10.8	10.6
Lysosomes	14.6	18.5	15.6
Microsomes	9.0	8.1	8.4
Cytosol	40.6	36.1	42.2

[a]Rats were sacrificed 16 hours after oral administration of 3.15 mg Tl/rat
(approximately 16.2 mg Tl/kg) as ^{201}Tl-labeled inorganic Tl[1+] or Tl[3+] ions, or
dimethylthallium bromide.

SOURCE: Adapted from Sabbioni et al. (1980).

were found in kidney for all forms of thallium. As shown in Table III-1, levels of thallium in tissues from the organometallic compound dimethyl thallium bromide were much lower than those observed for the inorganic salts. The intracellular distribution of thallium was similar for all three thallium species.

Sabbioni et al. (1982) reported transplacental transfer of thallium in pregnant rats dosed orally and intraperitoneally with thallium salts. In one series of experiments, COBS rats were injected intraperitoneally with thallous sulfate (2 μg Tl/rat) plus 50 μCi of ^{204}Tl (specific activity not specified), as the sulfate salt (approximate dose, 10 μg Tl/kg for a body weight of 200 g) on day 13 of pregnancy. By 4 hours postdosing, ^{204}Tl was detected in the placenta (0.23% of the dose/g of tissue) and in the fetal liver and brain (0.07 and 0.04% of the dose/g of tissue, respectively). Maternal levels of thallium in the liver and brain amounted to 0.37 and 0.05% of the dose/g of tissue, respectively. In a parallel series of experiments, pregnant rats were administered, on day 17 of gestation, thallium sulfate, by gavage, at a dose level of 10 mg Tl/kg. As summarized in Table III-2, by 72 hours postdosing fetal levels of thallium in liver and brain were approximately half those observed in the corresponding maternal organs.

Ziskoven et al. (1983) observed rapid distribution of thallium into maternal brain and kidney and fetal portions of the uterus in rats and mice. Pregnant Kisslegg mice and Wistar rats were administered an oral dose of thallous sulfate (8 mg Tl/kg) on days 10 and 9 of gestation, respectively. Thallium levels in tissues were assayed starting at 10 minutes after dosing in rats, and at 30 minutes after dosing in mice. Thallium content of tissues was not explicitly specified. Instead, tissue levels were given in relative units. Rapid absorption and distribution of thallium were indicated by its presence in maternal brain and kidney and in fetal tissue at the start of sampling in both species. Maximum levels of thallium were found in fetal tissue at 1 hour in rats and at 4 hours in mice. These values were approximately tenfold lower than levels found in maternal kidney. Thallium

Table III-2. Thallium Concentrations in Tissues of Pregnant Rats and Fetuses at 72 Hours After Oral Dosing[a,b]

Tissue	Average thallium concentrations (μg Tl/g of tissue)
Pregnant rats	
Kidney	60.2
Liver	18.5
Salivary glands	10.6
Brain	18.4
Small intestine[b]	57.8
Blood	2.0
Fetuses	
Live	8.9
Brain	10.1
Whole fetus	29.0
Amniotic fluid	0.9
Placenta	18.2

[a]Pregnant rats were administered thallous sulfate (10 mg Tl/kg) by gavage.
[b]Intestinal wall plus contents.

SOURCE: Adapted from Sabbioni et al. (1982).

levels in maternal brain and kidney of rats were not different from those in the respective organs in mice.

Barclay et al. (1953) studied the tissue distribution of ^{204}Tl in a female cancer patient weighing 45.4 kg and orally administered 1.8 μg of ^{204}Tl NO$_3$ (approximately 4 ng Tl/kg). Starting at an unspecified time after the radioactive dose was administered, the patient received an oral dose of 45 mg thallium sulfate (approximately 36 mg Tl/kg) every 3 days for a total of five doses. Peak levels of thallium observed in blood 2 hours after radioactive dosing amounted to approximately 3% of the administered dose. At 48 hours postdosing, blood radioactivity amounted to approximately 1.5% of the dose. Following the death of the patient 24 days after the initial ^{204}Tl dose, analysis of tissue radioactivity indicated that thallium was widely and unevenly distributed throughout the organs. It was estimated that radioactivity in tissues amounted to 45% of the dose. Levels of thallium in tissues were represented on a relative scale, as percent per gram of the average body distribution per gram (i.e., the total body radioactivity at death/weight of patient in grams). Highest tissue levels were found in scalp hair (420% per gram), followed by renal papilla (354%), renal cortex (268%), heart (236%), and spleen (200%). Intermediate levels were found in adrenal medulla (157%), pancreas (129%), liver (125%), rib marrow (124%), and adrenal cortex (109%). Lower values were found in nervous tissue (70 to 13%), ovary and capsule (54%), and abdominal subcutaneous fat (6.7%).

A series of intraperitoneal and intravenous studies indicate extensive tissue distribution and transplacental transfer of thallium. Andre et al. (1960) studied the distribution of thallium in 10 adult white mice dosed intraperitoneally with ^{204}Tl, as thallous sulfate, at a level of 5 mg/kg (4 mg Tl/kg). Autoradiographic examination of thallium distribution was performed at various times, up to 28 days after dosing. At 1 hour after dosing, there was a heavy accumulation of radioactivity in bone tissue. High concentrations were also noted in the kidney (particularly in the medulla), in the pancreas, and in the large intestine. In animals sacrificed more than 24 hours after injection, the epididymal and deferent ducts showed a high accumulation of

radioactivity. At this time, radioactivity was also found in the gastric and intestinal mucosa, and in the pancreas and salivary glands. Signs of thallium excretion were seen in the mucosa of the stomach and small intestine. In animals sacrificed 10 days or more after dosing, concentrations of thallium in the renal medulla and epididymis were still high, and concentrations in bone had decreased. Concentrations of thallium in the central nervous system (CNS) were somewhat higher than in the liver, and a high concentration of thallium could be seen in hair. At 28 days after dosing, thallium was still detectable in the renal medulla. Blood levels of thallium were low at the outset and undetectable after several days.

Sabbioni et al. (1980) examined the effect of dose level on the distribution of thallium in rat tissues. Sprague-Dawley male rats were dosed intraperitoneally with ^{201}Tl-labeled thallous sulfate at levels of 0.00004, 2, 20, or 2,000 μg Tl/rat (approximately 0.00021, 10.3, 102.6, or 10,256 μg Tl/kg, respectively). As shown in Table III-3, negligible differences in the distribution pattern of ^{201}Tl were found in the tissue distribution of thallium by 16 hours after dosing, regardless of the wide range of doses employed.

Olsen and Jonsen (1982) administered ^{204}Tl as thallium sulfate (50 μCi, of unstated specific activity) to NMRI/BOM albino mice via the intraperitoneal route on day 15 of pregnancy. Using autoradiographic techniques, thallium could be seen within the fetuses by 15 minutes after dosing. Maximum fetal levels of thallium were seen at 2 to 4 hours after injection and decreased thereafter. In parallel, unspecified experiments at the same dose level, transplacental transfer was detected in mice injected on days 5 to 16 of pregnancy.

Rade et al. (1982) administered to pregnant rats an intraperitoneal dose of thallous sulfate (2 μg/rat) plus 50 uCi of carrier-free $^{201+202}$Tl, salt unspecified, on day 13 of pregnancy. Peak thallium levels were reached at 4 hours after dosing in most maternal tissues (except for brain and muscle), in placenta, and in whole fetuses. At this time, mean thallium levels in fetal liver and brain amounted to 0.07 and 0.04% of the dose/g of wet tissue,

Table III-3. Tissue Distribution of Thallium in Rats Following
Intraperitoneal Doses of Thallous Sulfate[a]

Tissue	Average thallium content in tissues (as percent of dose, μg Tl/kg)			
	0.00021	10.3	102.6	10,256
Kidneys	4.65	5.65	5.10	4.90
Liver	1.70	2.16	2.60	2.80
Testes	1.10	1.22	1.70	1:30
Lung	0.20	0.20	0.26	0.40
Heart	0.20	0.28	0.20	0.47
Muscle[b]	28.35	27.54	33.21	40.98
Brain	0.23	0.23	0.31	0.27
Blood[c]	0.34	0.34	0.34	0.51

[a]Male Sprague-Dawley rats were dosed intraperitoneally with ^{201}Tl-labeled
thallous sulfate at levels of 0.00004, 2, 20, or 2,000 μg Tl/rat
(approximately 0.00021, 10.3, 102.6, or 10,256 μg Tl/kg, for body weights in
the range 190 to 200 g). Animals were sacrificed at 16 hours after dosing.
[b]Body mass was estimated to be 30% weight.
[c]Calculated for blood volume of 63 mL/kg.

SOURCE: Adapted from Sabbioni et al. (1980).

respectively. Maximum levels of thallium in maternal brain were observed at 24 hours after dosing and amounted to 0.090% of the dose. Total body burden of thallium was found to decay with an average half-life of 64.2 hours (2.7 days). An unspecified half-life, but of the same magnitude as above, was reported for thallium in the placenta and in the whole fetus.

Gibson and Becker (1970) studied levels of thallium in maternal and fetal blood of pregnant rats. Pregnant Sprague-Dawley rats were infused continuously on day 20 of gestation with ^{204}Tl, as thallous sulfate, at doses of 0.2, 0.4, 0.8, 1.6, 3.2, and 6.4 mg/min/kg. These infusion rates correspond to 0.16, 0.32, 0.64, 1.3, 2.6, and 5.2 mg Tl/min/kg. Thirty-two minutes after the initiation of infusion, maternal blood levels of thallium were approximately 15 times higher than fetal blood levels, on a weight basis, at the lowest dose, and approximately 30 times higher at the highest dose (e.g., approximately 450 nmol/mL and 15 to 16 nmol/g in maternal and fetal blood, respectively).

Talas et al. (1983) studied the pharmacokinetics of thallium in humans. Each of five female and five male patients was administered intravenously a tracer dose of ^{201}Tl, as thallium chloride (less than or equal to 106 and 130 ng/kg for male and female patients, respectively). Levels of radioactivity were serially assayed in plasma for up to 1 day after dosing, and the data were analyzed in terms of a two-compartment model. For the central compartment, the distribution volume was found to be 0.26 L/kg, which is similar to the adult's extracellular volume of about 0.2 L/kg. Distribution into the peripheral compartment was very fast ($t_{1/2}$ = 3.9 min). The total volume of distribution was found to be 4.23 L/kg, which is much larger than the average total body water volume in humans (0.6 L/kg). This large observed total volume of distribution is consistent with a migration of thallium into the intracellular space. The average terminal half-life of thallium was determined to be 2.15 days.

The distribution of thallium administered via drinking water has been studied in two subchronic studies. Manzo et al. (1983) studied the effects

of thallium sulfate in the drinking water at 10 mg Tl/L for 36 weeks (approximately 1.4 mg Tl/kg bw/day, assuming a weight of 200 g). Compared to untreated controls, thallium was found to accumulate most in the kidney, followed by the heart, brain, bone, skin, and blood (see Table III-4).

Formigli et al. (1986) studied the effects of thallium on the testes. Male Wistar rats were administered 10 ppm thallous sulfate in drinking water (approximately 740 μg Tl/kg bw/day, based on a reported consumption of 270 μg Tl/rat weighing in the range of 0.35 to 0.38 kg). After 60 days' treatment, 6.3 μg Tl/g tissue was found in the testes of treated rats compared with less than 0.08 μg Tl/g tissue in untreated controls.

D. METABOLISM

No information was found on the form and speciation of valence states of thallium in mammals. Based on the observation that oral dosing with Tl^{1+} and Tl^{3+} salts (Table III-1) produces a similar intracellular and tissue distribution of thallium in rats, Sabbioni et al. (1980) suggested a biochemical conversion of Tl^{1+} and Tl^{3+} into a single chemical species.

D. EXCRETION

Lehmann and Favari (1985) studied the excretion of thallium in female Wistar rats. The animals were administered thallous sulfate by gavage at a dose of 12.35 mg/kg (approximately 10 mg Tl/kg). By day 8 postdosing, 32% of the dose was eliminated in feces and 21% in urine. Based on excretion data, the authors estimated that residual thallium in the test animals decreased with a half-life of 7.3 days.

Lie et al. (1960) reported that in Wistar rats dosed orally with ^{204}Tl as thallous nitrate (767 μg Tl/kg), the ratio of fecal to urinary excretion of thallium increased from about 2 to 5 between days 2 and 16 after dosing, and decreased thereafter to about 3 by day 20. The ratios of fecal to urinary excretion were similar, regardless of whether dosing was oral, intravenous,

Table III-4. Tissue Distribution of Thallium in Rats Administered Thallium in Drinking Water Compared to Untreated Controls

Tissue	Tl-treated rats (μg Tl/g tissue)	Untreated rats (μg Tl/g tissue)	Ratio
Kidney	17.15 ± 1.23	0.038 ± 0.011	451
Heart	6.89 ± 0.60	0.070 ± 0.010	98
Skin	2.57 ± 0.22	0.040 ± 0.013	63
Bone	7.71 ± 0.88	0.119 ± 0.023	65
Brain	6.11 ± 1.03	0.088 ± 0.011	69
Blood	0.67 ± 0.08	0.045 ± 0.006	15

intraperitoneal, intravenous, or intramuscular. The biological half-life of thallium was determined to be 3.3 days. By 21 days, residual radioactivity in tissues amounted to 1% of the dose.

Shaw (1933) administered a single oral dose of thallous sulfate (25 mg Tl/kg) to one dog. Excretion of thallium in urine amounted to 32 and 61.6% of the dose at 3 and 36 days after dosing, respectively. No data for excretion in feces were given.

Barclay et al. (1953) studied the excretion of thallium in a female patient with osteogenic sarcoma. The patient was dosed orally as described above (see Distribution). In 5.5 days, the patient had excreted 15.3% of the radioactive dose in urine, and in 3 days only 0.4% in the feces. It was found that 3.2% of the amount of thallium in the body was excreted per day. Based on the daily excretion of thallium, it was calculated that at the time of death, 24 days after dosing, radioactivity in tissues amounted to 45% of the administered dose.

Other studies using the intravenous, intraperitoneal, or subcutaneous routes indicate that the thallium is excreted into the intestinal tract of rats, with little excretion via the bile. Lund (1956) studied the excretion of rats administered ^{204}Tl intraperitoneally, as thallous sulfate, at a dose of 10 mg/kg (approximately 8.1 mg Tl/kg). At 25 days postdosing, excretion in urine and feces amounted to 26.4% and 51.4% of the radioactive dose, respectively; and 10.3% of the dose was recovered from the carcass as nonexcreted material. To study biliary excretion of thallium, the common bile duct was severed between ligatures, thus preventing secretion of bile into the GI tract. The rats were then dosed subcutaneously with ^{204}Tl, as thallous sulfate, at a dose of 3 mg/kg (2.4 mg Tl/kg). By day 8 postdosing, rats with severed bile ducts excreted 13.4 and 16.7% of the dose in urine and feces, respectively. Control rats, with intact bile ducts, excreted 13.1 and 19.0% of the same radioactive dose in urine and feces, respectively. The authors concluded that Tl was not excreted in bile to any great extent. To study intestinal secretion of thallium, rats were dosed subcutaneously with ^{201}Tl, as

thallous sulfate, at a dose level of 2.2 mg/kg (1.8 mg Tl/kg). The contents of portions of the GI tract were analyzed for radioactivity at various times for up to 80 hours after dosing. Radioactivity was found in the contents of stomach, ileum, colon, and rectum throughout the 80-hour observation period.

Gregus and Klaassen (1986) studied the excretion of thallium in male Sprague-Dawley rats. The animals were intravenously administered ^{201}Tl-labeled thallium nitrate plus nonradioactive Tl-nitrate at a dose of 10 mg Tl/kg. Over a 4-day period, excretion of thallium in urine and feces amounted to 10.2 and 34.4% of the dose, respectively. During the first day after dosing, excretion in urine and feces amounted to 3.58 and 14.3% of the dose, respectively. To study biliary excretion, bile duct-cannulated rats were administered intravenously ^{204}Tl-labeled thallium nitrate plus thallium chloride at dose levels of 1, 3, 10, and 30 mg Tl/kg. Two hours after dosing, 0.15 to 0.16% of the dose was excreted in bile independently of dose. The authors estimated that the 24-hour excretion of thallium in bile was only one-seventh of that excreted in feces on the first day (i.e., 14.3% of the dose). Thus, they concluded, biliary excretion accounted only partly for fecal excretion of thallium.

Talas and Wellhoner (1983) studied the excretion of thallium in rabbits. Two rabbits were injected intravenously with a tracer dose of ^{201}Tl, as thallium chloride (less than 2 μg Tl/kg), plus 5.5 μmol of thallium acetate/kg (1.1 mg Tl/kg). At 48 hours after dosing, excretion in urine and feces averaged 10.5 and 9.8% of the dose, respectively. Thallium levels in the contents of stomach plus small and large intestines averaged a total of 19.4% of the dose. Contents at the time of sacrifice averaged only 0.02% of the dose.

Henning and Forth (1982) studied the excretion of thallium into the gastrointestinal tract of rats _in situ_. The rats were dosed intravenously with ^{204}Tl, as thallous sulfate, at a dose level of 1.85×10^{-2} mmol/kg (7.5 mg Tl/kg). The stomach and 7-cm-long segments of jejunum, ileum, colon ascendens, and colon descendens were perfused _in situ_ to measure excretion of

thallium into the gastrointestinal tract. By 1 hour after dosing, excretion of thallium in the jejunal segment amounted to about 0.55% of the dose, and excretion in the ileal and colonic segments was in the range of 0.3 to 0.5% of the dose. Thallium excretion via the stomach was very small, amounting to less than 0.05% of the dose.

E. BIOACCUMULATION AND RETENTION

Several single-dose studies (discussed above, Sections III.B, Distribution, and III.D, Excretion) provide estimates for the biological half-life of thallium in mammals.

Lie et al. (1960) calculated a biological half-life of 3.3 days for thallium in rats, following dosing of the animals by the oral and five other routes. Except for hair, other tissues were considered to have similar half-lives for thallium. Based on the half-life of 3.3 days, the author estimated that with daily dosing, the body burden of thallium would reach equilibrium in 20 days. With five daily exposures per week, excluding weekends, it was estimated that the body burden of thallium would reach equilibrium in 30 days. Likewise, Lehmann and Favari (1985) and Rade et al. (1982) have reported half-lives in rats of 7.3 and 2.7 days, respectively.

Atkins et al. (1977) conducted retention studies, using whole-body counting, in normal human volunteers dosed intravenously with a single unspecified dose of ^{201}Tl. These studies indicated a mean whole-body disappearance half-life of 9.8 days for the isotope, with a range of 7.4 to 12.4 days.

F. SUMMARY

In an oral dosing study in rats, it was estimated that 100% of the labeled thallous nitrate was absorbed from the GI tract. In the dog, it was estimated that at least 61.6% of an oral dose of thallous nitrate was absorbed by the GI tract. Toxic signs in humans and mortality in guinea pigs have

followed the cutaneous application of thallium salts, indicating dermal absorption of thallium.

Several studies indicate that thallium is extensively distributed in the tissues following absorption. In oral-dosing studies with thallous salts, the tissue distribution of thallium was found to be uneven, with a strong preference for kidneys. The tissue distribution appeared to be somewhat dependent on the species and duration of dosing.

In a single-dose study in rats, highest levels of thallium were found in kidney, followed in decreasing order by salivary glands, testes, muscle, bone, GI tract, spleen, heart, liver, hair, skin, and brain. A similar tissue distribution was found when the rats were dosed by five other routes. In another study with rats fed thallous acetate for 63 days, highest levels were found in kidneys, followed by liver, bone, spleen, lung, and brain. However, in a female cancer patient, highest levels were found in scalp hair, followed by kidney, heart, and spleen. Lower levels were found in the brain.

Autoradiographic and compartmental modeling studies after parenteral dosing confirm the extensive tissue distribution of thallium observed in the oral studies. Furthermore, it was found that in rats dosed intraperitoneally with ^{201}Tl-labeled thallous sulfate at levels in the range of 0.00021 to 10,256 μg Tl/kg, the pattern of tissue distribution of radioactivity was essentially independent of dose.

Autoradiographic examination of mice dosed intraperitoneally with ^{204}Tl-labeled thallous nitrate revealed accumulation of thallium in bone and kidney by 1 hour, and in the epididymis and deferens ducts at 24 hours after dosing. Subchronic studies of rats administered thallium in drinking water confirm that thallium accumulates preferentially in the kidney and testes.

In another study, the total volume of distribution for thallium after intravenous dosing of human adults was found to be 4.23 L/kg, which is much

larger than the total body water volume in humans. This result is consistent with a migration of thallium into the intracellular space.

Several authors have studied the transplacental transfer of thallium, which appears to be rapid and yields fetal concentrations that are lower than those observed in the mother. After oral dosing, thallium was present in maternal brain and kidney, and in fetal tissue, within 30 minutes after pregnant mice and rats were orally administered thallous sulfate. Thallium levels in fetal tissue, at their maximum level, were about 10% of those observed in maternal tissues for both species. In another study in which pregnant rats were dosed orally with thallous sulfate on day 17 of gestation, fetal levels of thallium in liver and brain were approximately 50% of the respective maternal levels.

In studies of transplacental transfer after parenteral dosing, it was observed that thallium appears in fetal tissues by 15 minutes after intraperitoneal administration of thallous sulfate in mice. In another study, in pregnant rats dosed intraperitoneally with thallous sulfate, peak thallium levels were seen at 4 hours in most maternal tissues, in fetuses, and in placenta. Maternal, fetal, and placental levels of thallium appeared to decrease with half-lives of the same magnitude. Continuous venous infusion of thallous sulfate into pregnant rats at doses in the range of 0.16 to 5.2 mg Tl/kg/min resulted in maternal thallium levels that were 15 to 30 times higher than those in fetal blood, respectively.

The comparative tissue distribution of Tl^{1+} and Tl^{3+} has been studied in rats. In rats dosed orally with Tl^{1+} or Tl^{3+} salts, or the organometallic compound dimethylthallium bromide, the tissue distribution of thallium was very similar in the case of the two salts. It was also observed that the intracellular distribution of thallium for the three compounds was very similar. These observations have led to the suggestion that there is a biochemical conversion of Tl^{1+} and Tl^{3+} into a single species.

III-16

Several authors have studied the excretion of thallium in rats. In one study, after single oral dosing with thallous sulfate, 32% of the dose was eliminated in feces and 21% in urine over an 8-day period. In another study, the ratio of fecal to urinary excretion of thallium ranged from 2 to 5 in rats dosed orally or parenterally regardless of the route of administration. Other studies using the intravenous, intraperitoneal, or subcutaneous routes indicate that thallium is excreted into the lumen of the intestinal tract of rats, with little excretion via the bile. In a human female cancer patient dosed orally with radiolabeled thallous sulfate, excretion of thallium amounted to 15.3% in urine over 5.5 days, and to only 0.4% in feces over 3 days.

Based on single oral dosing, the biological half-life of thallium in rats has been reported as 7.3 days in one study and as 3.3 days in another study. A mean whole-body half-life of 9.8 days has been reported in humans dosed intravenously with ^{200}Tl.

IV. HUMAN EXPOSURE

To be provided by Science and Technology Branch, ODW.

V. HEALTH EFFECTS IN ANIMALS

A. SHORT-TERM EXPOSURE

1. Lethality

The acute oral LD_{50} values for various thallium compounds in mice and rats range from 16 to 46 mg Tl/kg. Values for the lowest oral doses of thallium compounds showing any lethality (LD_{LO}) in guinea pigs, rabbits, and dogs are in the range of 5 to 30 mg Tl/kg. These values are summarized in Table V-1.

2. Other Effects

The following studies indicate that acute dosing with thallium produces degenerative changes in mitochondria of the kidney, liver, and brain, and causes deposition of lipofuscin bodies in brain neurons.

Herman and Bensch (1967) studied the acute effects of thallium in Sprague Dawley rats of both sexes. A total of eight rats (sex ratio unspecified) were administered thallous acetate subcutaneously at a dose level in the range of 20 to 50 mg/kg (15.5 to 38.8 mg Tl/kg). The animals were sacrificed at various times up to 5 days after dosing for necropsy and histopathological assessment. Necropsy findings were unremarkable except for mottled kidney in one rat and changes at the corticomedullary junction in two rats. Light microscopy revealed renal casts, moderate enteritis, and moderate to severe colitis. At 58 hours after dosing, renal mitochondria contained electron-dense particles. At 5 days, there were severe degenerative changes in many mitochondria in all renal tubules. These changes included swelling, partial loss of cristae, and formation of myelin-like structures. Mitochondrial changes were also present in the liver, brain, and small intestine. In this study, the authors did not specify all the dose levels or the doses at which the effects were observed; thus, no NOAEL or LOAEL can be derived from this study.

Table V-1. Summary of Lethality Data on Thallium in Laboratory Animals

Species/sex	Route of admin.[a]	Compound	Lethal dose (mg Tl/kg)	Reference
Mouse/M	po	TlCl	20 (LD$_{50}$)	Tikhova (1964)
Mouse/M	po	TlCl	26 (LD$_{100}$)	Tikhova (1964)
Mouse/M	po	Tl$_2$CO$_3$	18 (LD$_{50}$)	Tikhova (1964)
Mouse/M	po	Tl$_2$CO$_3$	22 (LD$_{100}$)	Tikhova (1964)
Mouse/M	po	Tl$_2$SO$_4$	19 (LD$_{50}$)	Tikhova (1964)
Mouse/M	po	Tl$_2$SO$_4$	28 (LD$_{100}$)	Tikhova (1964)
Mouse/M	po	Tl$_2$SO$_4$	46 (LD$_{50}$)	Truhaut (1959)
Mouse/M	po	TlNO$_3$	25 (LD$_{50}$)	NIOSH (1985)
Mouse/NS[b]	po	TlCH$_3$CO$_2$	27 (LD$_{50}$)	NIOSH (1985)
Mouse/NS	ip	TlCl	20 (LD$_{50}$)	NIOSH (1985)
Mouse/NS	ip	TlCH$_3$CO$_2$	29 (LD$_{50}$)	NIOSH (1985)
Mouse/M	iv	Tl$_2$SO$_4$	33 (LD$_{50}$)	Truhaut (1959)
Mouse/M	sc	Tl$_2$SO$_4$	22 (LD$_{50}$)	Danilewicz et al. (1979)
Mouse/M	sc	Tl$_2$SO$_4$	41 (LD$_{50}$)	Truhaut (1959)
Rat/F	po	Tl$_2$O$_3$	39 (LD$_{50}$)	Downs et al. (1960)
Rat/M	po	Tl$_2$SO$_4$	16 (LD$_{50}$)	Danilewicz et al. (1979)
Rat/F	po	TlCH$_3$CO$_2$	32 (LD$_{50}$)	Downs et al. (1960)
Rat/F	ip	TL$_2$O$_3$	72 (LD$_{50}$)	Downs et al. (1960)
Rat/F	ip	TlCH$_3$CO$_2$	23 (LD$_{50}$)	Downs et al. (1960)
Guinea pig/F	po	TlCH$_3$CO$_2$	12 (LD$_{Lo}$)[c]	Downs et al. (1960)
Guinea pig/M,F	po	Tl$_2$O$_3$	5 (LD$_{Lo}$)	Downs et al. (1960)
Rabbit/F	po	TlCH$_3$CO$_2$	19 (LD$_{Lo}$)	Downs et al. (1960)
Rabbit/M	po	Tl$_2$O$_3$	30 (LD$_{Lo}$)	Downs et al. (1960)
Dog/M,F	po	TlCH$_3$CO$_2$	20 (LD$_{Lo}$)	Downs et al. (1960)
Dog/M	po	Tl$_2$O$_3$	30 (LD$_{Lo}$)	Downs et al. (1960)

[a] po = oral; ip = intraperitoneal; iv = intravenous; sc = subcutaneous.
[b] NS = Sex not specified.
[c] LD$_{Lo}$ = Lowest dose showing any lethality.

Woods and Fowler (1986) studied the structural and biochemical changes induced by thallium in rat liver. Male Sprague-Dawley rats were administered thallic chloride tetrahydrate intraperitoneally at doses of 0, 50, 100, or 200 mg/kg (0, 26.7, 53.4, or 106.8 mg Tl/kg). The animals were sacrificed at 16 hours after dosing for ultrastructural and biochemical studies of liver tissue. Ultrastructural studies of hepatocytes showed, at all three doses, mildly swollen mitochondria, increased numbers of electron dense autophagic lysosomes, doserelated loss of ribosomes from the endoplasmic reticulum (ER), and proliferation of the rough ER segment. Surface density measurements of mitochondrial and smooth and rough ER membranes indicated dose-related increases in the surface densities of both the outer and inner mitochondrial membranes, and of the rough ER. Increases in both the outer and inner mitochondrial membranes were associated with increases in the enzymatic activities of monoamine oxidase and ferrochelatase. These two enzymes are integral components of the outer and inner mitochondrial membranes, respectively. In contrast, malate dehydrogenese, which is located in the mitochondrial matrix, was not affected. Similarly, structural changes in the ER were associated with decreased enzymatic activities for microsomal NADPH cytochrome (P-450) reductase, aniline hydroxylase, and aminopyrine demethylase.

Herman and Bensch (1967) studied the subacute effects of thallium in Sprague-Dawley rats of both sexes following subcutaneous administration for up to 16 days. A total of four rats (sex ratio unspecified) were administered two to three weekly doses of thallium acetate, each dose consisting of 10 to 15 mg/kg (7.8 to 11.6 mg Tl/kg). The animals were sacrificed as signs of toxicity appeared, i.e., at days 10, 12, 14, and 16 after the start of dosing. Light microscopy revealed an extensive region of acute necrosis in the mesencephalon of two rats. Mild colitis was present in two animals. Electron microscopy revealed mitochondrial granules in kidney and liver cells. Many dense bodies were seen in the cytoplasm of the cells of the loops of Henle and the distal convoluted tubules. In the brain, lipofuscin bodies were sometimes present in the neuronal cytoplasm. However, the authors did not specify all the dose levels used or the doses at which the effects were observed. Thus, the NOAEL or LOAEL cannot be obtained from this study.

B. LONG-TERM EXPOSURE

1. Subchronic Toxicity

Stoltz et al. (1986) studied the subchronic toxicity of thallium in Sprague-Dawley rats. Groups of 20 male and 20 female rats were dosed daily by gavage for 90 days with thallium sulfate at levels of 0.01, 0.05, or 0.25 mg/kg/day (8.1, 40.5, or 202.4 μg Tl/kg/day, respectively). Two similar groups were used as untreated and vehicle (water) controls. Increased shedding of hair and rough coat were observed in all dose groups. No significant differences in body weight gain or food consumption patterns were observed throughout the study. Increased lacrimation and exophthalmos were present at all dose levels.

Clinical chemistry revealed changes in serum enzymes and electrolytes. In males, apparent dose-related elevations in the enzymatic activities of serum glutamic-oxaloacetic transaminase (SGOT) and lactic dehydrogenase (LDH) were observed. SGOT was significantly elevated above both control groups at the two higher dose levels, whereas LDH was significantly elevated at all dose levels with respect to untreated controls. However, it was not possible to confirm that the increases in SGOT and LDH were dose-related because of scattering ($p \leq 0.05$) of the data points. Serum levels of sodium and calcium were significantly ($p < 0.05$) elevated at all dose levels when compared to untreated controls and at the two higher doses when compared to vehicle-treated controls. Serum glutamic-pyruvic transaminase (SGPT) was unaffected. A slight hypoglycemia, significant with respect to both control groups, was observed at the high-dose level. In females, significant, dose-related increases in serum sodium were observed at 30 and 90 days of treatment; and significant, dose-related increases in SGOT and LDH activities were present at 30 days but not at 90 days. The authors noted that increased activity of SGOT and LDH (about 1.3-fold in males), together with unchanged SGPT activity, is consistent with some degree of extrahepatic damage. The possible site of extrahepatic damage was not identified. However, the authors speculated that

the subtle changes in electrolytes, coupled to increases in enzymatic activities, could reflect an effect on renal function. The kidney is a major target for thallium distribution in rats (Lie et al., 1960; Sabioni et al., 1980), and histopathological effects on rat kidney have been reported at higher doses (Herman and Bensch, 1967).

Alopecia was observed in dosed animals, although it was not clear if it was due to thallium. Histological examination of a skin area showing alopecia in four females revealed hair follicle atrophy in only one case at the highest dose level. No treatment-related gross or light-microscopic findings were reported. Electron microscopic evaluation of tissues was not performed. Based on the absence of gross or histopathologic findings, this study defines a NOAEL of 0.2 mg Tl/kg/day. No LOAEL is defined by this study.

Downs et al. (1960) studied the toxicity of thallous acetate and thallic oxide in rats fed the compounds for approximately 15 weeks. In a first series of experiments, four groups of 10 weanling rats (5 males, 5 females) received dietary levels of thallous acetate at 0, 5, 15, and 50 mg/kg diet for 15 weeks (corresponding to approximately 0, 0.4, 1.2, and 3.9 mg Tl/kg body weight/day for 100-g young rats, respectively, assuming a food consumption of 10 g/kg/day). Two groups of rats added several weeks later were placed on diets containing 0 and 30 mg thallous acetate/kg diet for 63 days (corresponding to 0 and 2.4 mg Tl/kg body weight/day, respectively). Mortality among test animals and controls was high. The highest dose produced 100% mortality by week 12. There was 80% mortality among the animals fed thallous acetate at 30 mg/kg of diet. By week 15, 40% (two/sex) of the control animals died. In the remaining dose groups, mortality amounted to 40% and 20% in animals fed thallous acetate at levels of 1.2 and 0.4 mg/kg of diet, respectively. There was no effect on weight gain at the two lower dose levels, and there was a moderate depression in weight gain with the diet containing thallous acetate at 30 mg/kg diet. The only significant finding at necropsy was moderate to marked alopecia, first seen at 2 weeks of treatment, in rats fed thallous acetate at levels of 15 and 30 mg/kg of diet. No histopathological changes were reported.

Based on alopecia in rats fed thallous acetate at 15 mg/kg diet, a LOAEL of 1.2 mg Tl/kg body weight/day was determined, with a NOAEL of 0.4 mg Tl/kg body weight/day.

In the second series of experiments by Downs et al. (1960), six groups of 10 weanling rats (5 males, 5 females) received thallic oxide in the diet at levels of 0, 20, 35, 50, 100, and 500 mg/kg diet for 15 weeks. These values approximately correspond to 0, 1.8, 3.1, 4.5, 9.0, and 44.8 mg Tl/kg body weight/day for 100-g young rats. All rats fed diets containing 50 mg thallic oxide/kg/day or more died within 8 weeks of treatment. Only one male and three female rats that received thallic oxide at a level of 35 mg/kg/day survived the treatment period. There was marked alopecia by week 4 in rats fed thallic oxide at levels of 20 and 35 mg/kg diet. At termination, necropsy of the survivors revealed a significant elevation in kidney weights for females receiving 20 and 35 mg thallic oxide/kg diet/day and for males receiving 20 mg thallic oxide/kg diet/day. Histologic examination of lung, liver, kidney, and brain showed no effects attributable to thallium ingestion. Histologic examination of skin sections showed considerable atrophy of hair follicles.

Manzo et al. (1983) studied the effects of thallium in 80 female Sprague-Dawley rats administered thallium sulfate in the drinking water at 10 mg Tl/L for 36 weeks. This corresponds to approximately 1.4 mg Tl/kg body weight/day assuming a body weight of 200 g. The mortality rate was 15 and 21% after 40 and 240 days of treatment, respectively. Hair loss appeared after 32 days of treatment and involved about 20% of the animals thereafter. Abnormal electrophysiological parameters were observed in 10 of 16 rats at day 240 posttreatment. These findings included a 44% decrease in the amplitude of motor action potentials (MAP), a 30% decrease in the amplitude of the sensory action potential, and a 25% increase in MAP latency. Histologic examination of sciatic nerve samples from six treated rats revealed morphological changes in three. These changes included Wallerian degeneration of scattered fibers and vacuolization and lamination of the myelin sheath of about 10% of the

fibers. Electron microscopic examination of fibers with Wallerian degeneration showed complete destruction of the axon, with mitochondrial degeneration, neurofilamentous clustering, and evidence of extensive lysosomal activity.

Herman and Bensch (1967) studied the effects of thallous acetate administered by subcutaneous injection to Sprague-Dawley rats for at least 24 weeks. A total of 15 rats (sex ratio unspecified) received an initial subcutaneous injection of thallium acetate in the range of 10 to 20 mg/kg (7.8 to 15.5 mg Tl/kg), followed by weekly subcutaneous injections of the same chemical at 5 mg/kg (3.9 mg Tl/kg), for at least 24 weeks (approximately 0.6 mg Tl/kg/day). The animals were serially sacrificed at various times (4 to 26 weeks) after the initial injection. Light microscopic examination revealed no effects, except mild colitis in one rat 28 days after the initial injection. Electron microscopic examination of the kidneys showed accumulation of debris in the lumen of the convoluted tubules and progressive changes in the mitochondria of the tubule cell. By 12 weeks, many cup-shaped mitochondria were present and, in some mitochondria, partial loss of cristae was evident. In liver cells there were also degenerative changes in mitochondria. In all animals glycogen was abundant, and the endoplasmic reticulum was plentiful and sometimes slightly dilated. In brain, lipofuscin bodies were often numerous in the cytoplasm of neurons. Mitochondrial granules were seen in mucosal cells of the large and small intestines.

2. Chronic Toxicity

No chronic toxicity studies were found in the available literature.

C. REPRODUCTIVE/TERATOGENIC EFFECTS

In a reproductive toxicity study, Formigli et al. (1986) reported that groups of 10 male Wistar rats received 10 ppm thallous sulfate in their drinking water (approximately 740 µg Tl/kg body weight/day, based on a reported thallium consumption of 270 µg Tl/rat and body weight in the range of

350 to 380 g) for 30 or 60 days. Control animals were pair fed. No abnormalities in testicular morphology or biochemistry were observed after 30 days; however, males exposed to thallium for 60 days exhibited epididymal sperm with increased numbers of immature cells and significantly reduced motility. Histological examinations revealed disarrangement of the tubular epithelium; in addition, Sertoli cells had cytoplasmic vacuolization and distension of the smooth endoplasmic reticulum. Testicular beta-glucuronidase activity was significantly reduced in the thallium-treated males. Plasma testosterone levels were unaffected. Testicular thallium concentration was 6.3 μg/g for treated animals and less than 0.08 ng/g in pair-fed controls.

In a teratogenicity study, Claussen et al., (1981) administered thallous acetate or thallous chloride to pregnant Wistar rats, by gavage, at doses of 0 (control), 3, 4.5, or 6 mg/kg on days 6 through 15 of gestation. The administered doses correspond to 0, 2.3, 3.5, and 4.7 mg Tl/kg/day for the acetate, and to 0, 2.6, 3.8, and 5.1 mg Tl/kg/day for the chloride, respectively. Maternal mortality was 100% at 4.5 and 6 mg/kg for both salts. For the control and 3 mg/kg chloride-salt- and acetate-salt-treated groups, 17, 15, and 12 respective litters were delivered by cesarean section and examined for skeletal alterations; 11, 11, and 7 cesarean-delivered litters were examined for visceral alterations; and 14, 14, and 12 litters were maintained for 21 days postpartum. Significantly increased incidences of wavy ribs and dumbbell-shaped sternebrae were noted in both thallium-treated groups at 3 mg/kg when compared to controls. In addition, slightly increased postnatal mortality was noted at this dose level. The NOAEL for developmental toxicity was not established because of the presence of effects at all levels tested.

In another series of experiments, Claussen et al. (1981) treated NMRI mice with thallous acetate or thallous chloride by gavage on days 6 through 15 of gestation at doses of 0, 3, or 6 mg/kg. The applied doses correspond to 0, 2.3, and 4.7 mg Tl/kg/day for the acetate, and to 2.6 and 5.1 mg Tl/kg/day for the chloride, respectively. The numbers of control litters examined skeletally and viscerally were 28 and 13, respectively. Postpartum examinations were conducted on 24 litters. For the groups receiving the

chloride salt, 24, 11, and 17 litters were examined at 3 mg/kg, respectively, and 20, 12, and 15 litters were examined at 6 mg/kg. For the groups exposed to the acetate salt, 20 and 9 litters were examined skeletally and viscerally, respectively, at 3 mg/kg, and 24 and 12 respective litters were examined at 6 mg/kg. No adverse effects of thallous chloride were noted at 3 mg/kg; however, slightly increased postimplantation loss was noted at 6 mg/kg for both cesarean-delivered and reared litters. Postnatal mortality was also slightly increased at 6 mg/kg thallous chloride. For groups receiving thallous acetate, a slight reduction in fetal weights was noted at 6 mg/kg, and slightly increased incidences of cleft palate were present at 3 and 6 mg/kg. Based on the above information, the NOAEL and LOAEL for developmental toxicity were 2.3 and 5.1 mg Tl/kg/day, respectively, for thallium.

Gibson and Becker (1970) administered aqueous thallous sulfate intraperitoneally to Sprague-Dawley rats at 2.5 mg/kg (six rats/group) on days 8 to 10 or 12 to 14 of gestation, or at 10 mg/kg (three rats/group) on days 12 to 14 of gestation. The applied doses correspond to 2.0 and to 8.1 mg Tl/kg/day, respectively. On gestation day 21, all thallium-treated groups had significantly reduced fetal weights. Dosing on days 12 to 14 produced significantly increased incidences of missing or unossified vertebral bodies at both dose levels. The incidences of hydronephrosis were increased at 2.0 mg Tl/kg/day in the group dosed on gestation days 8 to 10 when compared with controls, and the differences reached statistical significance for the group dosed with 2.0 mg Tl/kg on gestation days 12 to 14; the incidence of hydronephrosis was comparable to controls at 8.1 mg Tl/kg. The NOAEL for developmental toxicity could not be established because of the presence of effects at all levels tested in this study.

Nogami and Terashima (1973) administered thallous sulfate postnatally to 6- and 9-day-old rat pups at doses of 20 and 40 μg/g ip, respectively. The applied doses correspond to 16 and 32 mg Tl/kg, respectively. Histological examination, at an unspecified dose level, on day 18 revealed severely hypoplastic columnar cartilage of the long bones and defective zones of calcification. The authors also concluded that prenatal exposure to thallous

sulfate inhibits the synthesis of cartilage mucopolysaccharides in rat fetuses.

Anschutz et al. (1981) cultured 10.5-day-old rat embryos for 48 hours in human serum. The embryos were exposed to thallium at concentrations of 3, 10, 30, or 100 μg/mL. Dose-related growth retardation was evident at all levels. Complete growth inhibition was reported at 100 μg/mL. At 3 μg/mL, no gross abnormalities were evident; however, cytotoxicity to the central nervous system was detected microscopically.

D. MUTAGENICITY

Published _in vitro_ and _in vivo_ genetic toxicology assays with thallium compounds have been categorized into gene mutation assays (Category 1), chromosome aberration assays (Category 2), and studies that assess other mutagenic mechanisms (Category 3). The findings from the studies are summarized in Table V-2 and are discussed below.

1. Gene Mutation Assays (Category 1)

a. Reverse mutation in prokaryotes

Three investigators (Dehnen, 1979, as cited in Claussen et al., 1981; Kanemastu et al., 1980) reported that thallium compounds (TlC$_2$H$_3$O$_2$, TlCl, and TlNO$_3$) gave negative responses in _Salmonella thyphimurium_ mammalian microsome reverse mutation assays (Ames tests) in the presence or absence of rat liver S9 activation. _S. typhimurium_ strains TA1535, TA1537, TA1538, TA98, and TA100 were assayed. Although the results were uniformly negative, limitations of the Ames assay for detection of metal-induced mutagenesis make these results inconclusive (McCann et al., 1975). Similar problems are encountered in interpreting the inactivity of TlNO$_3$ in the _Escherichia coli_ tryptophan reverse mutation spot test conducted by Kanematsu et al. (1980).

Table V-2. Genotoxicity of Thallium in Various Test Systems

Genetic endpoint	Organism	Compound	Dose range	Response	Comments	Reference
Gene mutation	Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100 (Ames test)	$Tl(C_2H_3O_2)$	3.1 µg to 29.2 mg Tl/plate	-	Unsuitable test system for metals.	Dehnen (1979, as cited in Claussen et al., 1981).
Gene mutation	Ames test	$Tl(C_2H_3O_2)$ TlCl	NR	-	Unsuitable test system for metals.	Claussen et al. (1981)
Gene mutation	Ames test	$TlNO_3$	NR	-	Unsuitable test system for metals.	Kanematsu et al. (1980)
Gene mutation	Escherichia coli WP2 trp-, WP2 uvrA trp-	$TlNO_3$	NR	-	Assay sensitivity for metal mutagens is very low.	Kanematsu et al. (1980)
Chromosome aberrations (somatic cells)	Rat embryo fibroblasts	$TlCO_3$	10^{-6} to 10^{-3} M	+	Dose-dependent chromosome and chromatid breaks.	Zasukhina et al. (1981)
Chromosome aberrations (germinal cells; dominant lethal assay)	Male rats	$TlCO_3$	5×10^{-4}, 5×10^{-5}, 5×10^{-6} mg/kg bw; daily po doses for 8 months[a]	+	Dose-related effects; highest dose decreased the rate of fertilization.	Zasukhina et al. (1981, 1983)
DNA damage/ repair	Bacillus subtilis H17(rec+), M45(rec-)	$TlNO_3$	0.001 M, -S9	+	DNA damage.	Kanematsu et al. (1980)
DNA damage/ repair (DNA strand breaks)	C57BL/6 and CBA mouse embryo cells; rat embryo fibroblast	Tl_2CO_3	10^{-4}, 10^{-5}, 10^{-6} M	+	Dose-related effect in $C_{57}BL/6$ mouse cells and rat cells.	Zasukhina et al. (1981, 1983)
DNA damage/ repair (viral reactivation)	Cell lines as above preinfected with vaccinia virus	Tl_2CO_3	10^{-4}, 10^{-5}, 10^{-6} M	+	Preferential reserve of viral variants.	Zasukhina et al. (1981, 1983)

Table V-2. (cont.)

Genetic endpoint	Organism	Compound	Dose range	Response	Comments	Reference
Sister chromatid exchange	Chinese hamsters (in vivo)	TlCl	5, 10 mg/kg x 2; po exposure	-	No toxic or cytotoxic dose.	Claussen et al. (1981)
Viral enhanced cell transformation	Syrian hamster embryo cells/SA7	Tl(C₂H₃O₂)	0.025, 0.05, 0.1, 0.2 mM	+	Dose-related effect.	Casto et al. (1979)

aAlthough the doses are reported as mg/kg body weight, it is not entirely clear whether the units are as stated or they are in error.

V-12

No gene mutation assays in higher biological systems were found in the open literature.

2. Chromosome Aberration Assays (Category 2)

a. Somatic cells

Zasukhina et al. (1981) exposed triplicate cultures of rat embryo fibroblasts to 10^{-6} and 10^{-5} M Tl_2CO_3 for 24 hours and analyzed approximately 300 metaphase cells for chromosome aberrations. No cytotoxic effects were reported; however, significant increases in the total number of aberrations and the percent of cells with aberrations were seen at both levels. The effect was clearly dose dependent, and the predominant types of aberrations were chromosome and chromatid breaks. Although this study provides acceptable evidence of an *in vitro* mammalian cell clastogenic effect, the results have not been confirmed.

b. Germinal cells

Zasukhina et al. (1981, 1983) also performed a rat dominant lethal assay with Tl_2CO_3 at dosages of 5×10^{-4}, 5×10^{-5}, and 5×10^{-6} mg/kg body weight. An un-reported number of male rats were administered daily oral doses at these levels for 8 months. Following exposure, males were mated with untreated females (number not specified). Females were sacrificed on the 20th day of pregnancy, and the uterine content of 16 controls and 18 females per dose group were scored for total implants, corpora lutea, live implants, preimplantation loss, and postimplantation loss. These parameters were used to calculate overall embryonic mortality; statistical analyses were not performed. Based on the number of corpora lutea and total implants, 5×10^{-4} mg/kg Tl_2CO_3 had an adverse effect on fertilization. Data presented for other parameters were difficult to interpret because of the inclusion of preimplantation losses in the final calculations and apparent typographical errors in some of the calculations. The results indicated that a dose-related increase in postimplantation loss accompanied exposure to Tl_2CO_3. However,

the report did not contain a statistical analysis of the data, and data were insufficient to perform independent statistical analyses; therefore, the study results could not be verified. Furthermore, it was not possible to verify the accuracy of the dose levels administered.

3. Other Mutagenic Mechanisms (Category 3)

a. DNA damage/repair in bacteria

Kanematsu et al. (1980) exposed the Bacillus subtilis, DNA repair-competent strain H17 (rec⁺), and the DNA repair-deficient strain M45 (rec⁻), to a single dose (0.001 M) of nonactivated TlNO₃; TlNO₃ caused preferential inhibition of M45, indicating that damage to DNA had occurred. This "rec" assay with a single dose is supportive evidence for a genotoxic response.

b. DNA damage/viral reactivation in mammalian cells

Thallium carbonate was evaluated for the potential to cause DNA strand breaks and viral reactivation in three rodent cell lines by Zasukhina et al. (1981, 1983). The initial experiments involved a 24-hour exposure of mouse embryo cells (CBA and C57BL/6) and rat embryo fibroblasts to 10^{-4} through 10^{-8} M Tl₂CO₃, and the compound was reported to be noncytotoxic. Following exposure, aliquots of cells were lysed; the DNA was eluted, precipitated, and counted by liquid scintillation; parallel viable cell aliquots were allowed a 24-hour recovery in the absence of Tl₂CO₃. Although negative control results were not presented, the summarized data indicated that significant and dose-related increases in the formation of single-strand DNA were observed in C57BL/6 cells and rat cells, but not in CBA cells. The damage induced by Tl₂CO₃ was completely repaired by the C57BL/6 cells, within 24 hours of compound removal, showing that the DNA damage was via an identifiable mechanism. The rat fibroblast DNA "rec" repair mechanisms were not as efficient; i.e., cells exposed to 10^{-4} M TlCO₃ repaired <20% of the DNA damage at 24 hours postrecovery.

In a related experiment, the three cell lines were infected with vaccinia virus, treated with similar concentrations of $TlCO_3$ for 24 hours, and assayed for virus survival. A decrease in virus titer was seen in all cultures exposed to 10^{-4} M $TlCO_3$. As expected from the earlier results, the preferential rescue of recombined viral variants was higher in C57BL/6 in rat fibroblast than in CBA cells. In concurrence with the initial experiments, the rat fibroblast exhibiting the least efficient DNA repair systems showed the greatest degree of viral reactivation. The studies were well conducted and provide conclusive evidence that Tl_2CO_2 causes primary DNA damage in mammalian cells.

c. In vivo sister chromatid exchange (SCE)

Claussen et al. (1981) administered 5 and 10 mg/kg TlCl by oral gavage (two dosings in a 24-hour period) to Chinese hamsters and collected bone marrow cells for SCE induction. No appreciable increases in SCEs were observed; however, neither dose was toxic to the animals or was cytotoxic to the target cells.

d. In vitro cell transformation

Casto et al. (1979) evaluated 38 metal salts including $Tl(C_2H_3O_2)$ for the potential to enhance simian adenovirus (SA7) transformation of Syrian hamster embryo cells (HEC). Primary HECs were pretreated with four concentrations of $Tl(C_2H_3O_2)$ ranging from 0.025 to 0.2 M for 18 hours, infected with SA7, and plated for survival and transformation. Thallous acetate at 0.1 and 0.2 mM induced significant (p <0.01) and dose-related enhancement of viral transformation. The 4.3-fold increase in transformed foci at 0.2 mM was accompanied by a 51% reduction in cell survival. The 0.1 mM concentration was not cytotoxic; however, the transformation frequency was increased by a factor of 2.2 as compared to the negative control. The lower concentrations (0.025 and 0.05 mM) were biologically inactive.
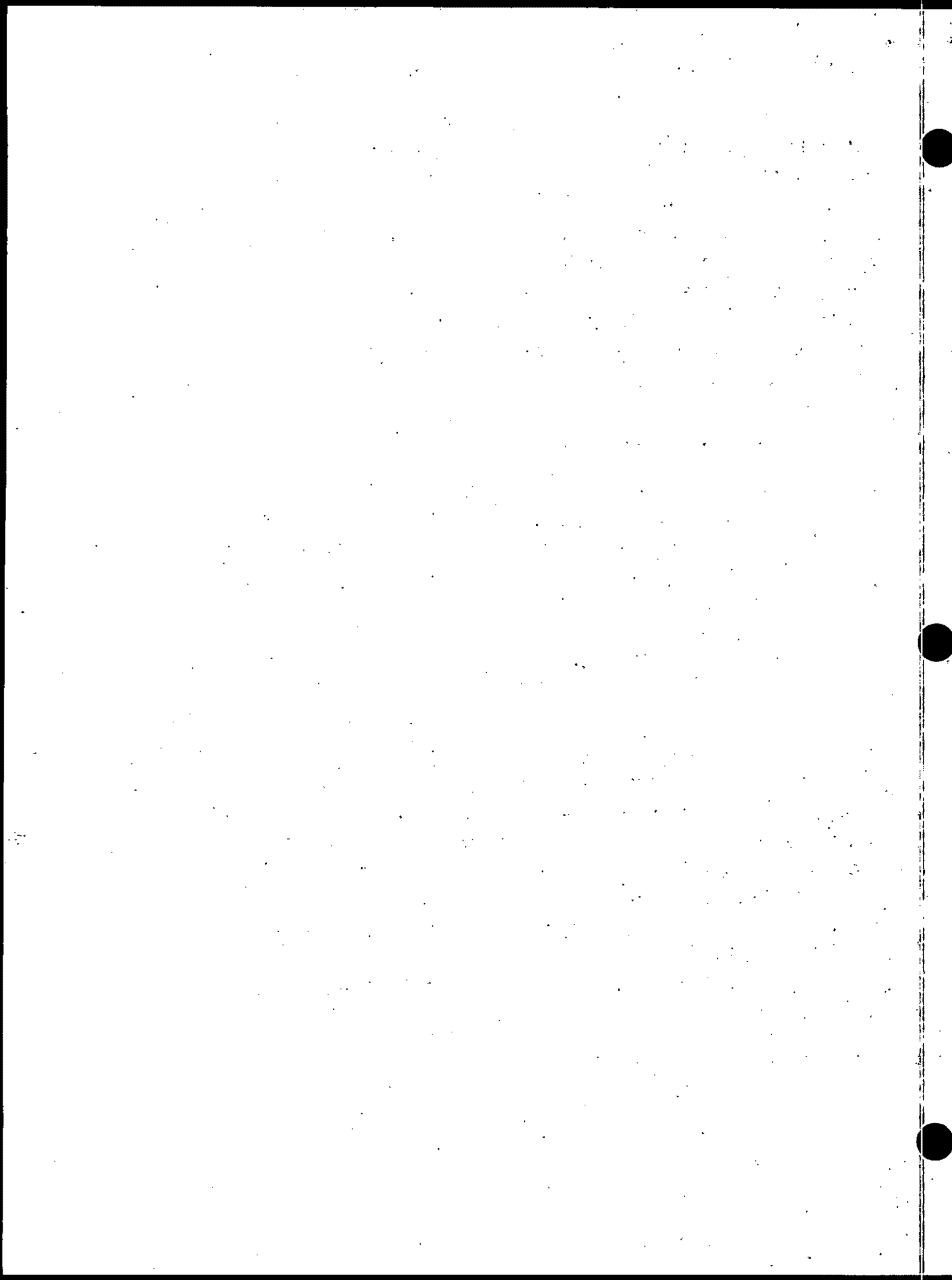
E. CARCINOGENICITY

No carcinogenicity studies for thallium were found.

F. SUMMARY

The acute lethality of thallium has been characterized in several animal species. The oral LD_{50} of thallium compounds in mice and rats ranges from 16 to 46 mg Tl/kg. The oral LD_{50} value for thallic oxide in rats is reported to be 39 mg Tl/kg. The lowest oral dose showing any lethality in guinea pigs, rabbits, and dogs is in the range of 5 to 30 mg Tl/kg.

In acute experiments involving subcutaneous dosing in rats, thallous acetate (15.5 to 38.8 mg Tl/kg) produced degenerative changes in mitochondria of kidneys, liver, brain, and intestines. These changes included swelling, partial loss of cristae, and formation of myelin-like structures. Intraperitoneal injection of thallic chloride (26.7 to 106.8 mg Tl/kg) produced ultrastructural changes in mitochondria, increased numbers of autophagic lysosomes, and changes in the endoplasmic reticulum (ER) in liver of rats. Enzymatic activities associated with the mitochondrial membranes and the ER were increased and decreased, respectively.

In subacute studies with rats, subcutaneous administration of two to three weekly doses of thallous acetate (7.8 to 11.6 mg Tl/kg/dose) produced histopathological changes in brain, kidney, liver, and intestines. Acute necrosis was observed in the mesencephalon of two out of four rats. Electron microscopy showed mitochondrial granules of kidney and liver cells.

In long-term exposure studies, female rats were administered thallium sulfate in the drinking water for up to 36 weeks (approximately 1.4 mg Tl/kg body weight/day). Reported findings included alopecia, abnormal electrophysiological parameters, and histopathologic changes in the sciatic nerve. The histopathological changes included Wallerian degeneration of scattered fibers, vacuolization and lamination of the myelin sheath, and degenerative changes in mitochondria.

In another study, rats were administered thallous sulfate by gavage at doses of 8.1, 40.5, or 202.4 μg Tl/kg/day for 90 days. Moderate, but significant, elevations of serum glutamic-oxaloacetic transaminase (SGOT) and of Na⁺ and Ca²⁺ were reported for males at the two higher dose levels. Although lactate dehydrogenase (LDH) was increased on the average, the increase was not statistically significant. In females, both SGOT and LDH were moderately, but significantly, elevated at 30 days at the two higher doses, but not at 90 days. Sodium was moderately, but significantly, elevated at all dose levels, both at 30 days and 90 days. No histopathologic effects were observed. In the absence of histopathological effects, this study defines a NOAEL of 0.2 mg Tl/kg/day. No LOAEL is defined by this study.

In a dietary administration study, in rats fed diets containing thallous acetate for up to 15 weeks (initial dose of 0.4 to 3.9 mg Tl/kg body weight/day), alopecia was observed after 2 weeks on the diet in rats initially dosed with 1.2 mg Tl/kg bw/day or higher. This study defines a LOAEL of 1.2 mg Tl/kg bw/day and a NOAEL of 0.4 mg Tl/kg bw/day. In a parallel study, rats received thallic oxide in the feed for up to 15 weeks (initial dose of 1.8 to 44.8 mg Tl/kg bw/day). There was 100% mortality at the three higher dose levels. Alopecia and a significant elevation in kidney weights were observed at the lowest dose level.

Subcutaneous administration of an initial dose of thallous acetate (7.8 to 15 mg Tl/kg), followed by weekly doses of 3.9 mg Tl/kg for up to 24 weeks, produced histological changes in kidney, brain, and liver of rats. These changes included progressive degeneration in the mitochondria of liver and kidney and lipofuscin granules in neurons. No chronic toxicity studies were found in the available literature.

In reproductive toxicity studies, male Wistar rats exposed to thallium sulfate (740 μg Tl/kg/day) in drinking water for 60 days exhibited adverse effects on sperm cell maturation and motility. In addition, histological examinations revealed alterations in the epithelium of seminiferous tubules and in Sertoli cells.

In teratogenicity studies, pregnant Wistar rats dosed by gavage at levels of 3.5 to 5.1 mg Tl/kg/day on days 6 through 15 of gestation suffered 100% mortality. Lower doses of 2.3 to 2.6 mg Tl/kg/day were associated with developmental effects including wavy ribs and dumbbell-shaped sternebrae in fetuses, and postnatal mortality.

Pregnant NMRI mice dosed by gavage with thallous acetate or chloride at levels of 2.3 to 5.1 mg Tl/kg/day on days 6 through 15 of gestation had increased postimplantation losses, decreased fetal body weights, and increased incidences of cleft palate and postnatal mortality in their litters.

Pregnant Sprague-Dawley rats given ip injections of thallous sulfate at 2.0 to 8.1 mg Tl/kg/ day on days 12 to 14 of gestation had litters with reduced fetal body weight, increased incidences of unossified vertebral bodies, and hydronephrosis.

Thallium compounds have not been evaluated in gene mutation assays that are suitable for the detection of metal mutagens. However, assays in the remaining categories of genetic endpoints suggest that the Tl_2CO_2 is clastogenic in both rat somatic and germinal cells, $TlNO_3$ causes DNA damage in bacteria, Tl_2CO_3 induces primary DNA damage in rodent cell cultures, and $Tl(C_2H_3O_2)$ enchances in vitro viral transformation of hamster cells. All of the assays demonstrating a positive response require independent confirmation before definitive conclusions can be drawn. When viewed collectively, however, the weight of evidence suggests that thallium is genotoxic and has the potential to interfere with a wide variety of mechanisms that maintain genetic integrity. No studies on the carcinogenic potential of thallium were found.

VI. HEALTH EFFECTS IN HUMANS

Thallium, a slow but persistent systemic poison, is absorbed rapidly from the gastrointestinal tract (Gosselin et al., 1984). Gosselin et al. (1984) give thallium a toxicity rating of 5, i.e., extremely toxic. Cases of thallium poisoning have decreased in the United States since thallium was banned as an ingredient in pesticides and rodenticides in 1972. Thallium toxicity is one of the most complex known to man, with symptomatology being nonspecific owing to multiorgan involvement. Symptoms may appear rapidly, but more commonly are delayed. Gradual development of mild gastrointestinal disturbances, polyneuritis, encephalopathy, tachycardia, skin eruptions, stomatitis, amorphic changes of the skin, and skin hyperesthesia (mainly in the soles of the feet and tibia) are commonly seen. The hallmark of thallium poisoning in humans is the onset of alopecia (Saddique and Peterson, 1983).

A. CLINICAL CASE STUDIES

Table VI-1 briefly outlines various case studies dealing with thallium poisoning. In addition, several studies are included in which human health effects and symptomatology are presented in more detail to give a better understanding of the complexity of thallium poisoning.

Bank et al. (1972) described five case studies involving patients suffering from thallium intoxication as determined by urinary analysis. All five patients exhibited neurologic symptoms ranging from mild peripheral neuropathy to irreversible coma and death. Alopecia, a relatively late manifestation of thallium poisoning, was observed in four of the five patients. In the first two cases, a 27-year-old man and his 25-year-old wife were admitted to the hospital within 5 days of one another. Both patients complained of severe pain in the legs, feet, thighs, abdomen, and the anterior portion of the chest, as well as malaise, and subjective dysesthesias of the hands. Thallium poisoning was suspected after the appearance of marked alopecia of the scalp and body after approximately 3 weeks. Exposure levels to thallium were not determined. To facilitate thallium excretion in urine,

Table VI-1. Case Studies Involving Thallium Poisoning

Case No.	Sex	Age (years)	Dose	Source of Intoxication	Symptoms	Outcome	Reference
1	F=35 M=37	<12	NR[a]	Tl₂SO₄	Cardiovascular problems, mental disorders, abnormal reflexes, neuropathy.	9 died (M=4, F=5); 22 perfect health (M=11, F=11); 26 abnormalities (M=12, F=14); 15 NR.	Reed et al. (1963)
1	F	18	0.53 g Tl; approximately 7.5 mg Tl/kg	Ingestion of contents of 1 tube of Zelio, a rodenticide containing 28 g of a 2.33% thallus sulfate paste/tube	Severe epigastric pain, anorexia, constipation, dehydration, ataxia, agitation, restlessness, alopecia.	Discharged 28 days after ingesting thallium, with mild ataxia and total alopecia; lost to followup.	Grunfled and Hinostroza (1964)
2	M	25	0.53 g Tl; approximately 7.6 mg Tl/kg	Ingestion of 1 tube of Zelio	Abdominal pain, vomiting, paresthesias, pain in limbs, insomnia, ataxia, constipation, alopecia, skin desquamation, nail dystrophy, high blood pressure.	Discharged 48 days after ingestion; admitted to mental hospital due to prior history of schizophrenia.	
1	M	3	NR	Ingestion of thallium-coated peanuts	Ptosis, dysarthria, restricted movement of the left leg; alopecia of the scalp.	Recovery. The only apparent residual effect was a slightly winded gait and minimal left ankle weakness.	Taber (194)
1	M	27	NR	Not determined	Pain in legs, feet, thighs, abdomen, and anterior portion of chest. Alopecia of scalp, beard, and body hair.	Sensory symptoms cleared and hair regrowth after 10 weeks from onset of symptoms.	Bank et al. (1972)

(continued)

Table VI-1. (continued)

Case No.	Sex	Age (years)	Dose	Source of Intoxication	Symptoms	Outcome	Reference
2	F	25	NR	Not determined	Pain in legs and thighs; malaise and subjective dysesthesias in hands; alopecia of scalp.	Total recovery after 10 weeks.	Bank et al. (1972) (continued)
3	M	44	1/2 tsp.	Unspecified "rat poison"	Diffuse abdominal and limb pain, nausea and vomiting. auditory hallucinations. delirium, and profuse sweating.	Spontaneous recovery 8 weeks after ingestion.	
4	M	7	NR	NR	Pain in left lower leg, irritability, right-sided focal motor seizure, alopecia, coma.	Death following respiratory arrest; 74 days after onset of coma.	
5	F	3	1/4 of a	Food thallium-impregnated cookie	Bloody stool, mild dysmetria, irritability, photophobia.	Complete recovery after 6 months.	
1	M	60	0.72 g Tl in two divided doses at unspecified intervals	Thallous acetate solution poured in tea or coffee	Vomiting. weakness, paresthesia of hands and feet; facial nerve weakness, respiratory difficulty, neurological signs.	Death within 1 month of developing symptoms.	Cavanagh et al. (1974)
2	M	56	0.72 g Tl in three divided doses at unspecified intervals	Thallous acetate solution poured in tea or coffee	Vomiting, diarrhea, pain in toes and tingling in fingers: visual impairment; neurological signs	Death within 1 month of developing symptoms.	

Table VI-1. (continued)

Case No.	Sex	Age (years)	Dose	Source of Intoxication	Symptoms	Outcome	Reference
3	M	26	0.241 g Tl in one dose; approximately 3.4 mg Tl/kg	Thallous acetate solution poured in tea or coffee	Paresthesia in both feet and some chest pain; 8 days later, vomiting and weakness; difficulty in walking; alopecia by 19 days after onset of symptoms.	Gradual improvement; within several weeks, hair regrowth was seen and health returned to normal.	Cavanagh et al. (1974) (continued)
1	F	17	NR	NR	Black pigmentation in roots of hair, alopecia.	NR (at time of case study).	Moeschlin (1980); Moeschlin and Condrau (1950)
2	M	36	NR	NR	Lesions on hair follicles and sebaceous glands, necrotic acne.	NR (at time of case study).	Moeschlin and Condrau (1950)
3	M	20	485-567 mg Tl; approximately 6.9-8.1 mg Tl/kg	Tl₂SO₄	Praecoma, ptosis, partial opticus atrophy, acne, and dry anhydrosis alopecia.	Death.	Moeschlin (1980); Moeschlin and Condrau (1950)
4	M	20	405 mg Tl; approximately 5.8 mg Tl/g	Ingestion of thallous sulfate	Severe epileptiform convulsions, alopecia, dry skin.	Full recovery.	Moeschlin (1980)

(continued)

Table VI-1. (continued)

Case No.	Sex	Age (years)	Dose	Source of Intoxication	Symptoms	Outcome	Reference
5	F	35	607 mg Tl₂; approximately 1.2 mg Tl/kg	Ingestion of thallous sulfate	(7 months pregnant); NR fate	Newborn: peculiar alopecia, nail growth disturbance.	Moeschlin (1980) (continued)
1	M	19	3.8-7.6 g Tl; approximately 54-109 mg Tl/kg	Ingestion of thallous nitrate (USP grade)	Nausea, vomiting, slurred speech, burning paresthesias of hands and feet, paralysis of all eye, face, tongue, and neck muscles.	On day 8 of hospitalization, cardiac arrest occurred. Patient remained comatose for 24 hours until death.	Davis et al. (1980)
1	M	52	12.3 g Tl; approximately 176 mg Tl/kg	Ingestion of thallous iodide	Abdominal colic, constipation, motor weakness in lower extremities, postural hypotension, confusion, short-term memory loss, alopecia of the scalp.	Recovery from all symptoms except continuing abnormal neurological parameters, still present 1 year after ingestion.	Koshy and Lovejoy (1981)
1	F	58	NR	Milk laced with thallous sulfate	Vomiting, coughing, weakness, nausea, parahyperesthesia, ataxia, hyperalgesia, paresis, low blood pressure, respiratory problems.	Death.	Heath et al. (1983)
2	M	58	NR	Milk with Tl₂SO₄	Paresthesias of limbs, parahyperesthesia, anhydrosis, drowsiness, hyperalgesia, abnormal vibration perception, alopecia.	Numbness of feet remained; abnormal vibration perception threshold remained in hands and feet.	

(continued)

Table VI-1. (continued)

Case No.	Sex	Age (years)	Dose	Source of Intoxication	Symptoms	Outcome	Reference
3	M	28	NR	Milk with Tl₂SO₄	Hyperesthesia, aching legs, hyperalgesia, reduced vibration perception, alopecia.	Uneventful recovery.	Heath et al. (1983) (continued)
1	M	50	NR	NR	Abdominal pain, weakness, pain in legs, paresthesias, alopecia.	Rapid recovery.	McCormack and McKinney (1983)
2	M	34	NR	NR	Abdominal pain, paresthesias, weakness and pain in legs, behavioral disturbances, confusion, personality change, reduction in sensation in limb, alopecia.	Perfect health.	
3	M	46	NR	NR	Abdominal pain, weakness, paresthesia, pain in legs, alopecia, muscle tenderness, lack of reflexes.	Complete recovery.	
1	M	24	1.2 g Tl; approximately 17 mg Tl/mg	Accidental ingestion of 300 mL aqueous solution containing 5 g thallous sulfate/L	Inability to walk, renal function severely impaired, nausea, vomiting, severe pain in feet, hypertension, tachycardia, and restlessness.	Coma on 5th day. after ingestion, also development of pneumonia was observed. Death on the 9th day after ingestion.	DeGroot et al. (1985)

(continued)

Table VI-1. (continued)

Case No.	Sex	Age (years)	Dose	Source of Intoxication	Symptoms	Outcome	Reference
1	F	51	NR	NR	Chest and abdominal pain, numbness and weakness of legs and hands, alopecia, encephalopathy, peripheral neuropathy.	Remains neurologically disabled, 2 years after thallium intoxication.	Roby et al. (1984)
2	M	45	NR	NR	Burning pain in feet, inability to walk, alopecia, blindness, choreiform disorder of movement.	Continues to have severe bilateral visual impairment, at an unspecified time after thallium intoxication.	
3	F	61	NR	Possibly through ingestion of coffee containing Tl	Generalized paresthesia, difficulty in speaking and swallowing, inability to walk, irregular heartbeats.	Coma and death on 7th day of hospitalization.	
4	F	80	NR	NR	Vomiting, paresthesias, alopecia.	Coma, death on 62nd day of hospitalization following myocardial infarction.	

^aNR = Not reported.

^bDoses per weight have been approximated by assuming a body weight of 50 kg for females and 70 kg for males.

^cThe dose of thallous sulfate was incorrectly reported in Moeschlin (1980) as 0.5 mg (i.e., 0.405 mg Tl). This value has been corrected to 0.5 g thallous sulfate, according to Moeschlin and Condrau (1950). These authors' original publication of the case study states that the dose was 0.5 g thallous sulfate.

^dThis value has been corrected to 0.75 g of thallous sulfate (i.e., 607 mg Tl), under the assumption that the value of 0.75 mg appearing in Moeschlin (1980) is a typographical error.

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the husband was given potassium chloride (15 mEq) orally three times daily, and his wife was given orange juice as a form of potassium supplementation. Both treatments were discontinued due to the resulting increase in the patients' subjective symptoms. Approximately 10 weeks after the onset of intoxication, all sensory symptoms cleared and hair began to grow. Although a thorough search was conducted, no exogenous source of thallium was detected. The remaining cases are summarized in Table VI-1.

Cavanagh et al. (1974) cite three cases of thallium poisoning due to ingestion of crystalline thallous acetate. The crystals were dissolved in water and poured into each victim's beverage. Two of the victims, 56- and 60-year-old males, each ingested a total dose of approximately 0.93 g of thallous acetate in three and two divided doses, respectively. The third victim, a 26-year-old male, ingested approximately 0.31 g of thallous acetate in a single dose (approximately 3.4 mg Tl/kg, assuming a body weight of 70 kg). All three were hospitalized with complaints of diarrhea, vomiting, weakness, and paresthesia of the hands and feet.

The first two victims (the 56- and 60-year-old males) developed bilateral facial nerve weakness and poor palatal motion, muscle deterioration, and increasing respiratory difficulty. Both died of cardiac arrest within 1 month following the onset of symptoms. Postmortem examination revealed edema and early bronchiopneumonia in the lungs and necrosis in the liver and kidney cortex in one of the victims and hemorrhagic bronchiopneumonia and edema in the lungs and centrilobular congestion in the second victim. Primary damage was to the central and somatic nervous system. The third victim gradually improved, although alopecia developed, diarrhea remained, and numbness with sensory loss was noted. Within several weeks, hair regrowth was seen and health returned to normal.

Roby et al. (1984) report four cases indicating (contrary to previously reported descriptions of acute thallium poisoning) that cardiac and pulmonary distress may dominate the acute stages of this illness. Prior to this report,

most case descriptions of myocardial distress were limited to electrocardiographic (ECG) abnormalities and sinus tachycardia.

A 51-year-old woman was referred to the hospital after complaining of chest and abdominal pains of 1 day's duration. Numbness and weakness of legs and hands were also noted. Upon admission, an electrocardiogram revealed frequent ventricular ectopic beats. Pulse and blood pressure fluctuated with periods of bradycardia (20 beats/min) and hypotension (to 70/40 mmHg). Serial electrocardiograms showed flattening of T-waves, prominent U-waves, a prolonged QT interval, and frequent ectopic beats, but no evidence of myocardi⁻ ⁻nfarction. One week after admission, the ECG showed that 16% of all beat ⁻e ventricular ectopic beats. Thallium poisoning was suspected after sev⁻ weeks upon onset of alopecia, encephalopathy, and peripheral neuropathy. Two years after the poisoning, the patient still showed persistent ventricular ectopy. She remains neurologically disabled and is in the care of a nursing home. The remaining three cases are outlined in Table VI-1.

According to several authors, the minimum lethal dose for thallium in adult humans is 0.2 to 1.0 g (Grunfeld and Hinostroza, 1964; Clayton and Clayton, 1981; Heath et al., 1983; Moeschlin, 1980).

Major Target Organs

a. Cardiopulmonary effects

In many cases, cardiac manifestations constituted the primary nonneurological problem encountered in thallium poisoning. Problems such as T-wave abnormalities and refractory atrial fibrillation have been reported in individuals with no prior history of cardiac disease. It has been concluded that the similarity of thallium to potassium causes interference with the sodium-potassium cellular interaction in reference to T-wave abnormalities (Roby et al., 1984).

b. Neurologic effects

Thallium behaves much like potassium in the body (see Chapter VII). It substitutes for potassium and depolarizes nerve membranes, causing demyelinization and axonal destruction. Effects from thallium poisoning are also seen in the cranial and autonomic nerves, spinal ganglia, posterior columns, anterior horn cells, and areas of cortex and basal ganglia (Gastel, 1978). Neurologic symptoms usually appear within 2 to 5 days after ingestion of thallium.

c. Gastrointestinal effects

Excretion of thallium is primarily through the feces. However, thallium toxicity causes paralysis of the small intestine, and fecal excretion therefore becomes almost impossible (Saddique and Peterson, 1983).

In severe cases of thallium poisoning, hypoacidity or anacidity of the gastric juices usually occurs. This is probably due to the direct damage of acid-secreting epithelium. It might also occur directly upon absorption of the poison or on secondary secretion of the metal into the gastrointestinal tract (Moeschlin, 1980).

B. EPIDEMIOLOGICAL STUDIES

Three medical surveys were conducted between 1979 and 1981 in a population living near a cement plant that emitted dust containing thallium. To determine thallium levels of individuals in that population, 24-hour urine samples (TIU) were analyzed for thallium content. The majority of the population had significantly elevated urinary thallium levels (range: <0.1-76.5 mg/L) as compared with an "unexposed" reference population (mean TIU: 0.3 mg/L). Using 0.8 mg/L as the upper normal limit of TIU level for "nonexposed" subjects, the following was determined: 84.5% of the test population in the first survey exceeded the TIU upper normal limit. In the second and third surveys, approximately 62 and 78%, respectively, had TIU

levels exceeding the upper normal limit. The decrease in thallium intake was achieved, through advise of authorities, because the population largely avoided the consumption of homegrown, potentially contaminated foodstuffs (Dolgner et al., 1983).

Other available studies, such as Munch et al. (1933) and Reed et al. (1963), deal with thallium poisoning outbreaks due to the ingestion of thallium-containing rodenticides or medicine. An outbreak of thallium poisoning (thallotoxicosis) was observed in 1932. A Mexican laborer illegally obtained a 100-pound sack of thalgrain (thallium-laden barley) and distributed it to two families. In all, approximately 31 persons were exposed, 14 were hospitalized, and 6 died from acute thallium poisoning (Munch et al., 1933).

C. HIGH-RISK POPULATIONS

No population has been identified as being at high risk for thallium toxicity. Increased thallium body burdens from environmental exposures have been shown for individuals living near one particular cement plant.

D. SUMMARY

There is an extensive body of literature concerning thallium poisoning (thallotoxicosis) from accidental or suicidal ingestion of pesticides or rodenticides that contain thallium. The number of cases involving thallium poisoning in humans has dramatically decreased since its use was banned in 1972. Several authors conclude that the minimum lethal dose for humans is 0.2 to 1.0 g.

Thallium is a complex poison because of its multiorgan involvement. Neurologic symptoms, which predominate thallotoxicosis, may range from mild peripheral neuropathy to irreversible coma and death. It is now suggested that cardiac and pulmonary distress may dominate the acute stages of this illness.

It was found that thallium can arise as a by-product in the dust from zinc and lead smelting processes or cement refineries. Medical surveys were conducted near a cement refinery in an attempt to determine if individuals in that area were being exposed to abnormally high levels of thallium. It was concluded that the "test" population had urine thallium concentrations 62 to 84% higher than the upper normal limit (0.8 μg/L) of a "nonexposed" reference population.

No population has been identified as being at high risk for thallium toxicity. Increased thallium body burdens can result from environmental exposure as evidenced by residents living in close proximity to one particular cement plant.

VII. MECHANISMS OF TOXICITY

The studies discussed in the following sections of this chapter indicate that thallium may substitute for potassium in activation of the (Na^+-K^+)-dependent ATPase and may be taken up by mitochondria where it disrupts oxidative phosphorylation. These effects may be related to some of the in vivo and in vitro effects on the nervous system reviewed below.

A. EFFECTS ON ION TRANSPORT

Britten and Blank (1968) reported that thallium (administered as thallous acetate) replaced potassium ion in the activation of the (Na^+-K^+)-dependent ATPase of rabbit kidney in vitro. Both thallium and potassium produced comparable maximal activities. However, thallium ion had a tenfold higher affinity for the enzyme (half-maximal ATPase activities were observed in the ranges of 0.16×10^{-3} to 0.20×10^{-3} M and 1.2×10^{-3} to 3.0×10^{-3} M for thallium and potassium, respectively).

Cavieres and Ellory (1974) studied the effect of thallium on the sodium pump in human erythrocytes. Incubation of $^{24}Na^+$-loaded erythrocytes in the presence of varying concentrations of thallous chloride in a potassium-free medium resulted in a concentration-dependent efflux of sodium into the medium. Half-maximal activity was seen between 0.03 and 0.05 mM external thallium. In another series of experiments, 0.05 to 0.15 mM thallous chloride competitively inhibited the ouabain [a(Na^+-K^+)-dependent ATPase inhibitor]-sensitive influx of $^{42}K^+$ into human erythrocytes incubated in the presence of 0.06 to 0.39 mM K^+. It appeared that more than one thallium ion must bind for the competitive inhibition to occur. The relative Tl^+/K^+ affinity ratio for the K^+ sites of the sodium pump was estimated to have a value of 3 to 5.

Gehring and Hammond (1964) studied the uptake of thallium by rabbit erythrocytes in vitro. When the erythrocytes were incubated in the presence of ^{204}Tl, as thallium nitrate at a concentration of 0.0938 mmol/L, uptake of thallium was biphasic with half-lives of 9.8 and 165 minutes. The ratio of

internal to external thallium concentrations averaged 8.7 at the end of a
2-hour period. When ouabain (0.1 mmol/L) or potassium (5 mmol/L) was added,
the fast component of uptake was eliminated and the half-life of the slow
component increased to 289 minutes for ouabain and to 277 minutes for
potassium. The uptake of thallium was also reduced by lowering the incubation
temperature to 4°C and by adding fluoride, an inhibitor of glycolysis. The
inhibitory effect of potassium suggested to the authors that there is an
interrelationship between potassium and thallium with regard to the uptake of
thallium by rabbit erythrocytes.

Barrera and Gomez-Puyou (1975) studied the effect of thallium on the
movement of potassium ion across the mitochondrial membrane in vitro. Leakage
of potassium ion from rat liver mitochondria was reduced by about 50% in the
presence of thallous sulfate at a concentration of 8 mM. The uptake of
potassium ion by potassium-depleted rat liver mitochondria was also found to
be inhibited by thallium; the extent of the inhibition depended on the
relative concentrations of thallium and potassium in the incubation medium.
Using 8 mM thallous sulfate, inhibition of potassium uptake amounted to about
75 and 50% with potassium concentrations of 25 mM and 50 mM, respectively.
The observation that the inhibitory effect of thallium is more marked at the
higher thallium to potassium ratio suggested to the authors that competition
exists between the two cations. Binding of thallium to mitochondrial protein
was observed in parallel experiments, using [204]Tl as thallous sulfate. At
8 mM thallous sulfate, about 12 nmol of thallium were bound per mg of
mitochondrial protein.

B.   EFFECTS ON MITOCHONDRIA

Melnick et al. (1976) reported that thallous acetate uncoupled oxidative
phosphorylation in rat liver mitochondria in vitro. The effect was observed
with half-maximal intensity at 6.5 mM thallium. The effect was attributed to
active accumulation of thallium by energized mitochondria. The mechanism of
the effect was not elucidated.

C. EFFECTS ON THE NERVOUS SYSTEM

1. In vivo effects

Hasan et al. (1977) studied the effects of thallium on the corpus striatum of the rat. To assess biochemical parameters, male albino rats were injected intraperitoneally with thallous acetate (5 mg Tl/kg) daily for 7 days. At sacrifice, brain weights of the treated rats did not differ significantly from controls. Succinic dehydrogenase (SDA), monoamine oxidase (MAO), acid phosphatase (AP), guanine deaminase, and protease (cathepsin) activities were significantly decreased in the corpus striatum of the treated animals. Protein content of the corpus striatum was significantly increased, presumably because of decreased lysosomal activity, which was evidenced by the decreases in activities of cathepsin and AP. To assess the electrophysiologic effects of thallium, the firing rate of 27 neurons in the caudate nucleus was recorded in five rats prior to intravenous administration of thallium acetate (10 mg Tl/kg), followed by the recording of neuronal activity for 3 to 4 hours after dosing. Similar recordings were conducted in controls before and after dosing with physiological saline. Thallium acetate caused a significant increase in the firing rate of 79% of the investigated neurons in the caudate nucleus. This increase could have been due to a direct stimulation of caudate neurons or to an imbalance of neurotransmitters, as suggested by the decrease in MAO activity.

Marwaha et al. (1980) studied the effect of thallium on catecholaminergic transmission in the rat cerebellum. Adult male Sprague-Dawley (SD) rats were injected intraperitoneally with thallous acetate (4 mg/kg) daily, for 1 week. (It was not clear whether the dose referred to thallium or to thallous acetate.) Recordings of electrophysiological activity of single neurons revealed a significant increase in the spontaneous discharge rate of Purkinje neurons in the thallium-treated rats. In parallel experiments, the authors observed that neither direct stimulation of the locus ceruleus, which is linked to the Purkinje neurons by a norepinephrine-containing pathway, nor administration of amphetamine, haloperidol, or

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6-hydroxydopamine had any effect on spontaneous discharge rate of Purkinje neurons of the thallium-treated rats. Based on these observations, the authors concluded that thallium exposure disrupts central catecholaminergic transmission in central neurons.

Hamilton et al. (1985) investigated the correlation between levels of lipid peroxidation in various regions of the brain and behavioral pattern changes in rats treated with thallium. Male rats were injected intraperitoneally with thallous acetate, 6 mg/kg/day (4.7 mg Tl/kg/day) for 7 days. At days 4, 8, 12, and 21, groups of rats were sacrificed for assessment of lipid peroxidation in the brain. Lipid peroxidation was found in various regions of the brain and decreased in the following order: cerebellum, brain stem, corpus striatrum, hippocampus, cortex, and midbrain. Changes in motor activity observed after dosing were consistent with cerebellar injury.

Hasan et al. (1978) also reported ultrastructural changes in rat cerebellar neurons. The animals were dosed intraperitoneally with thallous acetate (5 mg Tl/kg/day) for 7 days. Electron microscopic examination of cerebellar neurons revealed abnormally shaped mitochondria, electron dense bodies (often vacuolated), well-developed Golgi zones, and multilamellar bodies (some of these within mitochrondria). The authors speculated that thallium-induced alterations in the mitochondrion might be associated with the formation of the multilamellar bodies.

2. **In vitro effects**

Spencer et al. (1973) studied the ultrastructural changes in nerve tissue exposed to thallium **in vitro**. Combination cultures for dorsal root ganglia, spinal cord, peripheral nerve, and muscle from fetal mice were exposed to either thallous acetate (10 μg/mL) or to thallous sulfate (5 to 10 μg/mL) for up to 4 days. Exposure to thallous sulfate for 24 hours produced vacuolization in peripheral nervous system (PNS) fibers of both dorsal roots and their distal outgrowths. Longer exposure led to increased vacuolization, progressive fiber distortion, and retraction of myelin from the nodes of

Ranvier. Nerve impulses, however, were still able to propagate along the nerve fibers. Electron microscopic examination of axons of PNS fibers revealed a sequential pattern of mitochondrial destruction. After 2 to 8 hours of exposure to thallous salts, the mitochondria were enlarged. Within 24 to 48 hours, the mitochondrial matrix became a vacuole bounded by the original mitochondrial membrane. Comparable but less severe changes were seen in dorsal root ganglion neurons and in central nervous system fibers.

Wiegand et al. (1984) studied the effect of thallium on spontaneous transmitter release at the rat neuromuscular junction. Changes in the frequency of spontaneous miniature endplate potentials (MEPPs) were used as an indicator of the effect of thallium on spontaneous release of transmitter quanta from presynaptic nerve terminals. Recordings of MEPPs were done from neuromuscular junctions of the rat phrenic nerve-diaphragm preparation in vitro. Incubation with thallous acetate at concentrations of 1 and 0.5 mM resulted in a tenfold increase in the frequency of MEPPs within 30 and 180 minutes, respectively. The authors concluded that thallium increased the spontaneous release of transmitter quanta from presynaptic terminals. The mechanism of the effect was not elucidated.

Windebank (1986) studied the inhibitory effect of thallium on neurite outgrowth from dorsal root ganglion (DRG) neurons. DRG explants from E15 rat pups were cultured in the presence of thallous nitrate at concentrations in the range of 10^{-2} to 10^{-7} M. Neurite outgrowth was measured for up to 80 hours of incubation. Complete inhibition and 50% inhibition of neurite outgrowth occurred at 4.8×10^{-4} and 1.3×10^{-4} M thallous nitrate, respectively.

D.   CYTOTOXICITY

Cavanagh and Gregson (1978) studied the effect of thallium on the proliferation of hair follicle cells in rats. Wistar rats (aged 4 of 7 days) were administered thallous sulfate subcutaneously at a dose of 30 mg/kg (24 mg Tl/kg) and were sacrificed at various times thereafter. There was a marked decline in mitotic rate of hair follicle cells over a 48-hour period after

treatment. In parallel studies with 7-day-old pups, at the same thallium dose, no significant effects were observed on cell cycle parameters of hair follicle cells.

Tan et al. (1984) examined the cytotoxicity of thallium and other metal ions in Chinese hamster ovary (CHO) cells $\underline{in}$ $\underline{vitro}$. The cloning efficiency of CHO cells was reduced by 50% (CD_{50}) when cultured in the presence of 150 μM thallous nitrate.

E.   EFFECTS ON CARTILAGE FORMATION

Nogami and Terashima (1973) studied $\underline{in}$ $\underline{vivo}$ the incorporation of ^{35}S into mucopolysaccharides in thallium-treated rats. SD rats were administered intraperitoneal injections of thallous sulfate at dose levels of 16 and 32 mg Tl/kg, respectively, on days 6 and 9 after birth. On day 18 after birth, the rats were injected with an unspecified dose of $^{35}SO_4$ and were sacrificed 3 hours later for removal of cartilage from long bones. Histological examination revealed severely hypoplastic columnar cartilage of the long bones and defective zones of calcification. Incorporation of ^{35}S into cartilage mucopolysaccharides in the thallium-treated rats was found to be reduced to 50% of that observed in controls.

F.   INTERACTIONS

1.   Interactions With Potassium

In addition to the direct interactions of thallium with potassium ion at the molecular level, reviewed above, other authors have studied thallium/potassium interactions at the organismal level. These interactions, reviewed below, are reported to result in alterations in the acute toxicity and $\underline{in}$ $\underline{vitro}$ teratogenic potential of thallium depending on the relative thallium/potassium levels.

Gehring and Hammond (1967) studied the interaction between thallium and
potassium in rats and dogs. Sprague-Dawley male rats were maintained on low
potassium commercial diets supplemented with either 0, 15.5, or 25 mEq
potassium per 100 g of diet for at least 3 days prior to thallium dosing.
Groups of five rats from each of the above three groups were dosed
intravenously with ^{204}Tl, as thallium nitrate, at tracer level (<0.1 mg Tl/kg)
or at 10 mg Tl/kg. Urine and feces were collected for 14 days to assess
excretion of thallium. Total excretion of thallium increased with an increase
in potassium intake. In the animals dosed with tracer levels of thallium,
total excretion of thallium amounted to 65.0, 83.3, and 86.0% of the dose, for
the low, medium, and high potassium diets, respectively. In the animals
administered the high thallium dose, total excretion of thallium amounted to
52.7, 64.7, and 79.2% of the dose, for the low, medium, and high potassium
diets. The increased thallium excretion was due solely to an increase in
urinary excretion of thallium. In parallel experiments in rats, it was
observed that the intravenous LD_{50} for thallium nitrate increased from 12.5 to
14.5 mg Tl/kg for rats maintained on diets containing 15.5 and 25 mEq
potassium per 100 g of diet, respectively.

The interaction between potassium and thallium was further studied in
dogs. The dogs were fed diets containing potassium at 0.3 or 25.3 mEq/100 g
of diet and were dosed intravenously with ^{204}Tl, as thallium nitrate at a dose
level of 5 mg Tl/kg. Urinary excretion of thallium was 30 to 40% of the dose
for the low-potassium diet and 80 to 90% of the dose for the high-potassium
diet at 2 weeks postdosing. The authors also found that infusion of potassium
increased the renal clearance of thallium and increased the mobilization of
thallium from tissues. The above observations, together with their finding
that 1 to 4 mM thallous ion may substitute for potassium in activating rat
erythrocyte (Na^+-K^+)-dependent ATPase in vitro, suggested to the authors that
the uptake and release of thallium and potassium may be interrelated.

Neubert and Bluth (1985) studied the effect of varying concentrations of
thallium and potassium on mammalian limb development in culture. When limbs
of 11-day-old embryos of an unspecified mammalian species were incubated in

the presence of 6 mM potassium and of 15 μM thallium (anion unspecified), differentiation of the cartilaginous bone anlagen was slightly impaired. When the concentration of thallium was raised to 50 μM, clear-cut abnormal development of the scapula and paw skeleton occurred. The effect was partly prevented by raising the concentration of potassium ion to 17 mM.

2. Aversion to Saccharin

Peele et al. (1986) studied the aversion to saccharin induced in rats by thallium administration. Male, Long-Evans, 40-day-old rats on a water deprivation schedule received an initial exposure to 0.1% sodium saccharin in water for 30 minutes followed 20 minutes later by oral or intraperitoneal dosing with thallous sulfate at levels of 0, 2.5, 5, 10, or 20 mg/kg (corresponding to 0, 2.0, 4.0, 8.1, or 16.2 mg Tl/kg). Two days later the rats were offered a choice between the saccharin solution and water, followed by oral or intraperitoneal dosing with thallium as above. The cycle choice/thallium dosing was then repeated two more times. Vehicle-treated and nontreated rats consistently preferred the saccharin solution. The rats dosed orally with thallium showed a robust, dose-dependent aversion to saccharin for all three choice trials. The intraperitoneally dosed rats developed only a marginal aversion to saccharin, which occurred only at the highest dose level. The nature of the route specificity for the development of saccharin aversion was not elucidated.

G. SUMMARY

The mechanism of action of thallium has not been elucidated. Some studies indicate that thallium may substitute for potassium in activation of (NA^+-K^+)-dependent ATPase or it may be taken up by mitochondria, where it disrupts oxidative phosphorylation.

Thallous ion replaced potassium in the activation of (Na^+-K^+)-dependent ATPase from rabbit kidney, with a half-maximal activity at 0.16 to 0.20 mM.

Likewise, thallous ion at 1 to 4 mM was found to substitute for potassium ion in activation of the (Na^+-K^+)-dependent ATPase activity from rat erythrocytes.

Thallium uptake into rabbit erythrocytes was reported to be fast and to produce internal to external thallium concentrations in the ratio of 8.7 to 1. Uptake of thallium was inhibited by 5 mM K^+. In experiments with human erythrocytes, 0.03 to 0.05 mM external thallous ion stimulated the efflux of $^{24}Na^+$ into a potassium-free medium and competitively inhibited, at external concentrations of 0.05 to 0.15 mM, the ouabain-sensitive influx $^{42}K^+$ in erythrocytes. The relative Tl^+/K^+ affinity for K^+ sites of the sodium pump was estimated to be in the range of 3 to 5.

In experiments with rat liver mitochondria, 8 mM thallous ion inhibited leakage of potassium by 50% and inhibited potassium uptake (at 25 mM K^+) by 75%. The inhibition of potassium uptake was dependent on the Tl^+/K^+ ratios, indicating competition between the two ions. Binding to mitochondrial protein was also observed at 8 mM thallous ion. Oxidative phosphorylation was found to be inhibited by thallous ion, with a half-maximal activity at 6.5 mM thallium. Several in vivo and in vitro effects of thallium appear to have been related to disturbances at the level of presynaptic events.

In in vivo studies, intraperitoneal dosing of rats with thallous acetate (5 mg Tl/kg) for 7 days produced a decrease in enzyme activities, including monoamine oxidase (MAO) of the corpus striatum. With a single dose of 10 mg Tl/kg, an increase in firing rate of neurons of the caudate nucleus was observed. In another study, an increase in the rate of discharge of Purkinje neurons was observed in rats injected with thallous acetate. The effect was attributed to catecholaminergic transmission in central neurons.

In rats dosed with thallous acetate (4.7 mg Tl/kg/day) for 7 days, lipid peroxidation was found in several brain regions. Changes in motor activity observed after dosing were consistent with cerebellar injury. Likewise, dosing of rats with thallous acetate (5 mg Tl/kg/day) for 7 days resulted in ultrastructural damage to cerebellar neurons.

In in vitro studies, exposure of combination cultures of dorsal root ganglia-spinal cord-peripheral nerve to thallous acetate (0.04 mM) or sulfate (0.01 to 0.02 mM) produced mitochondrial degeneration in central and peripheral neurons. Incubation of rat phrenic nerve-diaphragm preparations with thallous acetate (0.5 to 1 mM) produced an increase in spontaneous release of transmitter quanta from presynaptic terminals. Thallous nitrate (1.3 x 10^{-4} M) produced a 50% inhibition of neurite outgrowth from rat dorsal root ganglion neurons.

Cytotoxic effects have been reported for thallium in vitro and in vivo. Cloning efficiency of CHO cells was inhibited 50% by 150 μM thallous nitrate. Subcutaneous administration of thallous sulfate (24 mg Tl/kg) to 4- or 7-day-old rats produced a marked decline in mitotic rate of hair follicle cells over a 48-hour period after treatment.

Intraperitoneal administration of thallous sulfate to 18-day-old rats inhibited the incorporation of $^{35}SO_4$ into cartilage mucopolysaccharides by 50%.

Besides interactions with potassium at the molecular level, there have been reports of Tl$^+$/K$^+$ interactions at the organ or tissue level. Total excretion of thallium increased with an increase in potassium intake in rats and dogs dosed with thallous nitrate and maintained on low-or high-potassium diets. Furthermore, it was observed in rats that the LD$_{50}$ for thallous nitrate increased with an increase of potassium in the diet. In dogs, it was observed that infusion of K$^+$ increased the renal clearance and the mobilization of thallium from tissues. In in vitro studies of mammalian limb development, it was observed that the extent of thallium-induced teratogenesis was affected by the ratio of Tl$^+$/K$^+$ in the medium.

Dose-dependent aversion to saccharin flavor in drinking water was developed in rats after one exposure to 0.1% sodium saccharin in water followed 20 minutes later by oral dosing with thallous sulfate at levels of 2, 4, 8.1, or 16.2 mg Tl/kg.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of
separate assessments of noncarcinogenic and carcinogenic effects. Chemicals
that do not produce carcinogenic effects are believed to have a threshold dose
below which no adverse, noncarcinogenic health effects occur, while
carcinogens are assumed to act without a threshold.

A. PROCEDURES FOR QUANTIFICATION OF TOXICOLOGICAL EFFECTS

1. Noncarcinogenic Effects

In the quantification of noncarcinogenic effects, a Reference Dose (RfD),
formerly called the Acceptable Daily Intake (ADI), is calculated. The RfD is
an estimate (with an uncertainty spanning perhaps an order of magnitude) of a
daily exposure of the human population (including sensitive subgroups) that is
likely to be without an appreciable risk of deleterious health effects during
a lifetime. The RfD is derived from a No-Observed-Adverse-Effect Level
(NOAEL), or Lowest-Observed-Adverse-Effect Level (LOAEL), identified from a
subchronic or chronic study, and divided by an uncertainty factor(s). The RfD
is calculated as follows:

$$RfD = \frac{(NOAEL \text{ or } LOAEL)}{Uncertainty \text{ } factor(s)} = \underline{} \text{ mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of
the RfD is based on professional judgment while considering the entire data
base of toxicological effects for the chemical. To ensure that uncertainty
factors are selected and applied in a consistent manner, the Office of
Drinking Water (ODW) employs a modification to the guidelines proposed by the
National Academy of Sciences (NAS, 1977, 1980) as follows:

- An uncertainty factor of 10 is generally used when good chronic or subchronic human exposure data identifying a NOAEL are available and are supported by good chronic or subchronic toxicity data in other species.

- An uncertainty factor of 100 is generally used when good chronic toxicity data identifying a NOAEL are available for one or more animal species (and human data are not available), or when good chronic or subchronic toxicity data identifying a LOAEL in humans are available.

- An uncertainty factor of 1,000 is generally used when limited or incomplete chronic or subchronic toxicity data are available, or when good chronic or subchronic toxicity data identifying a LOAEL, but not a NOAEL, for one or more animal species are available.

The uncertainty factor used for a specific risk assessment is based principally on scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations, which may necessitate the use of an additional uncertainty factor of 1 to 10, not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less-than-lifetime study for deriving an RfD, the significance of the adverse health effect, pharmacokinetic factors, and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium-specific (i.e., drinking water) lifetime exposure, at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard.

For ingestion data, the DWEL is derived as follows:

$$\text{DWEL} = \frac{\text{RfD x (body weight in kg)}}{\text{Drinking water volume in L/day}} = \underline{\quad} \text{ mg/L } (\underline{\quad} \mu\text{g/L})$$

where:

Body weight = assumed to be 70 kg for an adult.

Drinking water volume = assumed to be 2 L per day for an adult.

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (One-day, Ten-day, and Longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using an equation similar to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$\text{HA} = \frac{\text{(NOAEL or LOAEL) x (bw)}}{\text{(UF) x } (\underline{\quad} \text{ L/day})} = \underline{\quad} \text{ mg/L } (\underline{\quad} \mu\text{g/L})$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. One-day HA for a 10-kg child ingesting 1 L water per day.
2. Ten-day HA for a 10-kg child ingesting 1 L water per day.
3. Longer-term HA for a 10-kg child ingesting 1 L water per day.
4. Longer-term HA for a 70-kg adult ingesting 2 L water per day.

The One-day HA calculated for a 10-kg child assumes a single acute expo-sure to the chemical and is generally derived from a study of less than 7 days duration. The Ten-day HA assumes a limited exposure period of 1 to 2 weeks and is generally derived from a study of less than 30 days duration. The Longer-term HA is derived for both a 10-kg child and a 70-kg adult and assumes an exposure period of approximately 7 years (or 10% of an individual's

lifetime). The Longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of an animal's lifetime).

2. Carcinogenic Effects

The EPA categorizes the carcinogenic potential of a chemical, based on the overall weight of evidence, according to the following scheme:

- Group A: <u>Human Carcinogen</u>. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.

- Group B: <u>Probable Human Carcinogen</u>. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.

- Group C: <u>Possible Human Carcinogen</u>. Limited evidence of carcinogenicity in animals in the absence of human data.

- Group D: <u>Not Classified as to Human Carcinogenicity</u>. Inadequate human and animal evidence of carcinogenicity or for which no data are available.

- Group E: <u>Evidence of Noncarcinogenicity for Humans</u>. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable, or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these estimates usually come from lifetime exposure studies in animals. To predict the risk for humans from animal data, animal doses must be converted to equivalent

human doses. This conversion includes correction for noncontinuous exposure, less-than-lifetime studies, and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg, and that the average water consumption of an adult human is 2 liters of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure via ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit providing a low-dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates also may be calculated using other models such as the one-hit, Weibull, logit, and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any others. Because each model is based on differing assumptions, the estimates that are derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty due to the systematic and random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water; the impact of the experimental animal's age, sex, and species; the nature of the target organ system(s) examined; and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure, not for the lower levels of exposure closer to where a standard may be set. When there is exposure to

more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

B. QUANTIFICATION OF NONCARCINOGENIC EFFECTS FOR THALLIUM

1. One-day Health Advisory

The lethal effects of thallium ingestion have been documented in children, adults, and laboratory animals. In humans, ingestion of doses of about 3 to 15 mg/kg have been shown to cause death. A variety of thallium salts have been tested in rats and mice, with oral LD_{50}s ranging from 16 to 46 mg Tl/kg. No studies were found that identified a NOAEL or LOAEL based on appropriately sensitive endpoints of toxicity suitable for derivation of a One-day HA value. Because of concern for the serious health effects associated with exposure to thallium, it is recommended that the Longer-term HA value for the 10-kg child, 7.0 μg Tl/L, be used as a conservative estimate of the One-day HA value.

2. Ten-day Health Advisory

No suitable toxicity studies following repeated dosing were found in the available literature. Table VIII-1 summarizes two developmental toxicity studies in which rats and mice were administered thallium over a 10-day period. Both studies define a LOAEL of 2.3 mg Tl/kg/day, the lowest dose tested. These studies were not appropriate for determining the 10-day HA; serious developmental effects were observed at this dose, and similar doses (3 to 15 mg/kg) may be fatal to humans. Because of concern for the serious health effects associated with exposure to thallium, it is recommended that the Longer-term HA value for the 10-kg child, 7.0 μg Tl/L, be used as a conservative estimate of the Ten-day HA value.

3. Longer-term Health Advisory

Table VIII-2 summarizes the studies considered for derivation of the Longer-term HA values for thallium. All subchronic studies were done with

Table VIII-1. Summary of Candidate Studies for Derivation of the
Ten-day Health Advisory for Thallium

Species	Route	Exposure duration	Endpoints	NOAEL (mg Tl/kg bw/day)	LOAEL (mg Tl/kg bw/day)	Reference
Rat	Oral	10 days (days 6 to 15 of gestation)	Develop-mental toxicity	ND[a]	2.3	Claussen et al. (1981)
Mouse	Oral	10 days (days 6 to 15 of gestation)	Develop-mental toxicity	ND	2.3	Claussen et al. (1981)

[a]ND = Not determined.

Table VIII-2. Summary of Candidate Studies for Derivation of the Longer-term Health Advisory for Thallium

Route	Exposure duration (weeks)	Endpoints	NOAEL (mg Tl/kg bw/day)	LOAEL (mg Tl/kg bw/day)	Reference
Oral (diet)	13	Enzyme levels and electrolytes in serum	0.2	--	Stoltz et al. (1986)
Oral (diet)	15	Alopecia	0.4	1.2	Downs et al. (1960)
Oral (drinking water)	36	Neurotoxicity, axonal destruction, mortality	--	1.4[a]	Manzo et al. (1983)
Oral (drinking water)	8	Reduced sperm motility, increased numbers of immature epididymal sperm cells, vacuolization of Sertoli cells	--	0.74[a,b]	Formigli et al. (1986)
Subcutaneous	24	Histopathological changes in kidney, liver, brain at the electron microscopic level	--	0.6[c]	Herman and Bensch (1967)

[a]Only one dose level was administered.
[b]Zasukhina et al. (1981, 1983) have also reported reproductive effects of thallium in rats. However, from data present in their report it was not possible to assess the statistical significance of their results or verify the accuracy of the dose levels administered.
[c]An initial subcutaneous injection (in the range of 7.8 to 15.5 mg Tl/kg) was administered, followed by weekly subcutaneous injections at 3.9 mg Tl/kg (approximately 0.6 mg Tl/kg/day for a 7-day week).

rats. Several endpoints of toxicity were noted including increased mortality (Manzo et al., 1983); alopecia (Stoltz et al., 1986; Downs, 1960; Manzo et al., 1983); histopathological changes observed at the light microscopic level in nerve cells (Manzo et al., 1983) and testes (Formigli et al., 1986); and at the electron microscopic level, effects on the liver, brain, and kidney (Herman and Bensch, 1967). It is not possible to determine which of these effects is the most sensitive endpoint of toxicity. Studies performed at the lowest doses failed to test for testicular toxicity of effects at the electron microscopic level. In no study is a range of doses tested that demonstrates a relationship between thallium toxicity and administered dose.

Two subchronic studies have reported on the toxicity of thallium administered in drinking water. Manzo et al. (1983) reported axonal destruction and increased mortality in rats administered 1.4 mg Tl/kg/day in the drinking water for 36 weeks, and Formigli et al. (1986) reported decreased sperm motility, epididymal sperm with increased numbers of immature cells, and Sertoli cells showing cytoplasmic vacuolization in rats administered 0.74 mg Tl/kg/day, in the drinking water, for 60 days. Neither study is suitable for derivation of the Longer-term HA. In both studies, serious effects were observed at the one dose tested, and no data on the dose-response relationship are provided for extrapolating effects to lower doses.

Herman and Bensch (1967) reported histopathological changes in kidney, liver, and brain of rats dosed subcutaneously with thallium. Following an initial subcutaneous injection (precise dose unspecified, in the range of 7.8 to 15.5 mg Tl/kg), rats were administered weekly subcutaneous injections of 3.9 mg Tl/kg, generally once each week (approximately 0.6 mg Tl/kg/day), for up to 24 weeks. The uncertainty in the dosing protocol, the relatively high levels of thallium administered in each weekly dose, and the difficulties in extrapolating between subcutaneous and oral administration make this study unsuitable for derivation of HA values.

In the two remaining studies, thallium toxicity was tested over a range of doses via oral administration. Although both studies identify a NOAEL,

tests for testicular effects and neurotoxicity, which were observed in other studies (Formigli et al., 1986; Herman and Bensch, 1967), were not conducted. The study of Downs (1960) defines a LOAEL of 1.2 mg Tl/kg/day. Based on the appearance of alopecia in Wistar rats maintained for up to 15 weeks on a thallium-containing diet, the NOAEL was 0.4 mg Tl/kg/day. Stoltz et al. (1986) reported moderate changes in blood chemistry in rats dosed, by gavage, with 0.008 to 0.20 mg Tl/kg/day for 13 weeks. These changes included increases in SGOT, LDH, and sodium levels. Although the enzymatic activities were significantly elevated with respect to vehicle controls, it was not possible to ascertain that the effects were dose related owing to the scattering of data points. Furthermore, gross pathologic and light-microscopic evaluation of organs and tissues did not reveal any significant treatment-related effects. The only gross finding at necropsy thought to be treatment related was alopecia; however, light-microscopic examination did not reveal any histopathologic alteration that would indicate damage to hair follicles. Based on the results of this study, in the absence of confirmatory histological evidence, the dose of 0.20 mg Tl/kg/day is considered to be a NOAEL. Based on this study, Longer-term HA values were derived as follows:

$$\text{Longer-term HA}_{child} = \frac{(0.20 \text{ mg Tl/kg/day}) (10 \text{ kg})}{(100) (3) (1 \text{ L/day})} = 6.67 \text{ mg/L } (7 \text{ } \mu g/L)$$

where:

0.20 mg Tl/kg/day = NOAEL, based on the absence of gross or light-microscopic histopathology in rats exposed to thallous sulfate, by gavage, for 90 days.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

3 = extra uncertainty factor to account for inadequate testing of other species, endpoints and uncertainties with the critical study.

10 kg = assumed weight of a child.

1 L/day = assumed water consumption of a 10-kg child.

Longer-term HA_{adult} = $\dfrac{(0.20 \text{ mg Tl/kg/day}) \ (70 \text{ kg})}{(100) \ (3) \ (2 \text{ L/day})}$ = 0.023 mg/L (20 μg/L)

where:

0.20 mg Tl/kg/day = NOAEL, based on the absence of gross or light-microscopic histopathology in rats exposed to thallous sulfate, by gavage, for 90 days.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

3 = extra uncertainty factor to account for inadequate testing of other species, endpoints and uncertainties with the critical study.

70 kg = assumed weight of an adult.

2 L/day = assumed water consumption of a 70-kg adult.

No existing guidelines or standards were located for longer term (subchronic) exposure to thallium.

4. ·Reference Dose and Drinking Water Equivalent Level

Table VIII-2 summarizes studies considered for derivation of the RfD and DWEL for thallium.

Based on the rationale presented in the previous section (Section VIII. B.3), the 90-day study with rats by Stoltz et al. (1986) has been selected for calculation of the RfD and DWEL. A NOAEL of 0.2 mg Tl/kg/day was established, based on the absence of gross and light-microscopic histopathological effects.

Although the study by Stoltz et al. (1986) revealed no histopathological lesions at the light microscopic level, some uncertainty remains as to whether any lesions would have been found at the electron microscopic level, correlating with the blood chemistry changes that suggest some form of extrahepatic damage. In fact, Herman and Bensch (1967) reported absence of light-microscopic histopathology, in the presence of ultrastructural effects in cells of kidney, liver, and brain of rats dosed with weekly intraperitoneal

injections of 3.9 mg Tl/kg (approximately 0.6 mg Tl/kg/day) for at least 24 weeks.

Additional uncertainty is introduced into the NOAEL of 0.2 mg Tl/kg/day defined by the study of Stoltz et al. (1986) by the observations of Formigli et al. (1986). These authors reported that 0.74 mg Tl/kg/day administered in the drinking water for 8 weeks produced reduced sperm motility and vacuolization of Sertoli cells and increased the number of immature epididymal sperm cells. Because the study of Formigli et al. (1986) was performed at only one dose level and thus there is no dose-response curve, it is not possible to rule out whether the testicular effects reported by Formigli et al. (1986) would occur at or below the selected NOAEL value of 0.2 mg Tl/kg/day, especially during long-term exposures.

Thus, in view of the uncertainty associated with the selected NOAEL value of 0.2 mg Tl/kg/day, an uncertainty factor of 3 has been introduced into the following calculations to account for inadequate testing of other endpoints of toxicity. This factor of 3 is in addition to the factor of 1,000 for use with an animal study of less-than-lifetime duration.

Using the study of Stoltz et al. (1986), the DWEL is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.25\ mg\ Tl_2SO_4/kg/day)}{(1,000)\ (3)} = 0.08\ \mu g\ Tl_2SO_4/kg/day$$
$$= 0.07\ \mu g\ Tl/kg/day$$

where:

0.25 mg Tl$_2$SO$_4$/kg/day = NOAEL, based on the absence of gross or light-microscopic histopathology in rats exposed to thallous sulfate, by gavage, for 90 days.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL for an animal study of less-than-lifetime duration.

3 = additional uncertainty factor to account for inadequate testing of other species, endpoints of toxicity, and uncertainties with the critical study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.07 \ \mu g \ Tl/kg/day) \ (70 \ kg)}{2 \ L/day}$$

$$= 2.45 \ \mu g \ Tl/L \ (2.0 \ \mu g \ Tl/L)$$

where:

0.07 μg Tl/kg/day = RfD.

70 kg = assumed weight of an adult.

2 L/day = assumed water consumption of a 70-kg adult.

Thallium salts are designated as a hazardous substance under Section 311(b)(2)(A) of the Federal Water Pollution Control Act and further regulated by the Clean Water Act Amendments of 1977 and 1978. These regulations apply to discharges of these substances (U.S. EPA, 1986a).

The reportable quantity of thallium salts, when discharged into or upon the navigable waters and adjoining shorelines of the United States, is 1,000 pounds (454 kg) (U.S. EPA, 1986b).

C. QUANTIFICATION OF CARCINOGENIC EFFECTS FOR THALLIUM

1. Characterization of Carcinogenic Potential

The carcinogenic potential of thallium has not been evaluated by the U.S. EPA or the International Agency for Research on Cancer (IARC). Thallium has been found to be genotoxic in in vitro assays with mammalian cells (see Table V-2).

2. Quantitative Carcinogenic Risk Estimates

No quantitative assessment of excess cancer risk has been reported.

D. SUMMARY

Table VIII-3 summarizes HA and DWEL values calculated on the basis of noncarcinogenic endpoints. No estimations of excess cancer risk were performed.

Table VIII-3. Summary of Quantification of Toxicological Effects for Thallium

Value	Drinking water concentration (μg Tl/L)	Reference
One-day HA for a 10-kg child	--[a]	--
Ten-day HA for a 10-kg child	--[a]	--
Longer-term HA for a 10-kg child	7.0	Stoltz et al. (1986)
Longer-term HA for a 70-kg adult	20.0	Stoltz et al. (1986)
DWEL (70-kg adult)	2.0	Stoltz et al. (1986)
Excess cancer risk (10^{-6})	--	--

[a]The Longer-term HA for a 10-kg child is recommended as a conservative estimate of the One-day and Ten-day HA values.

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