CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Thallium is well absorbed following oral exposure; one study suggested 100% absorption.
- Thallium is rapidly distributed throughout the body following oral exposure, with the highest concentrations found in the kidneys.
- Thallium is not metabolized.
- Thallium is primarily excreted in the urine; some is also excreted in feces. A half-life of 21.7 days has been estimated in humans.

3.1.1 Absorption

No quantitative studies were located regarding absorption in humans or animals after inhalation exposure to thallium.

Limited data were located regarding absorption in humans after oral exposure to thallium. Following oral administration of a single tracer dose of 500 microcuries (μCi) of thallium-204 (^{204}Tl) as thallium nitrate and 45 mg daily for 5 days of thallium sulfate in a patient with terminal osteogenic sarcoma, 0.4% of the administered radioactivity was recovered in feces and 11% was recovered in urine during a 72-hour collection period. In 5.5 days, the patient had excreted 15.3% of the administered dose in the urine. These data suggest that most of the thallium was absorbed (Barclay et al. 1953).

Animal studies suggest that thallium is completely absorbed when ingested. Lie et al. (1960) administered a single trace dose of ^{204}Tl as thallium nitrate orally to rats at a dose of 0.767 mg thallium/kg. The body burden of ^{204}Tl, as percent dose, decreased with a single exponential function, which extrapolated to 100% at zero time. The study authors therefore concluded that thallium was completely absorbed from the gastrointestinal tract.

No reliable quantitative studies were located regarding absorption in humans or animals after dermal exposure to thallium.

3.1.2 Distribution

No studies were located regarding distribution in humans or animals after inhalation exposure to thallium.

There is little information on distribution of thallium in humans. Analyses of human tissues indicate that thallium is distributed throughout the body. A female cancer patient was administered a tracer dose of 1.8 mg ^{204}Tl as thallium nitrate orally and thereafter an oral doses of 36 mg thallium as thallium sulfate every 3 days for a total of five doses (Barclay et al. 1953). The thallium tissue levels, reported as percent of average body distribution per gram, were highest in scalp hair (420%), renal papilla (354%), renal cortex (268%), heart (236%), bone tumor (233%), and spleen (200%). Lower levels were found in the brain (39–70%).

In animals, distribution of thallium from the blood stream is rapid and widespread. One study found thallium to accumulate in the kidney (17 µg/g) followed by the heart (7 µg/g), brain (6 µg/g), bone (8 µg/g), skin (3 µg/g), and blood (0.67 µg/g) in rats administered approximately 1.4 mg thallium/kg as thallium sulfate in drinking water (Manzo et al. 1983). In male rats administered 740 µg thallium/kg as thallium sulfate in drinking water, 6.3 µg thallium/g tissue was found in the testes compared to <0.08 µg thallium/g tissue in untreated controls (Formigli et al. 1986). In rats fed 2.3–3.0 mg thallium/kg as thallium I acetate or thallium I oxide, the largest amount of thallium was detected in the kidney (24–31 µg/g wet tissue) with lower levels in the liver (13–16 µg thallium/g) and bone (19 µg thallium/g). Smaller amounts (5–9 µg/g) were found in the brain, lung, and spleen (Downs et al. 1960).

Lie et al. (1960) studied the tissue distribution of thallium in rats administered a single tracer dose of ^{204}Tl as thallium nitrate orally at a dose of 0.76 mg thallium/kg. No day-to-day variation in relative organ content was found with the exception of hair levels, which increased over time; hair thallium levels contained 1.56% of the body burden 7 days post-exposure and 60% of the body burden 21 days post-exposure. Approximately 7 days post treatment, the highest percentage body burden (per gram of tissue) was detected in kidneys (4.7% of the body burden per gram of tissue). Smaller percentages of body burden were detected in salivary glands (1.08%), testes (0.88%), muscle (0.79%), bone (0.74%), gastrointestinal tract (0.62%), spleen (0.56%), heart (0.54%), liver (0.52%), respiratory system (0.47%), hair (0.37%), skin (0.37%), and brain (0.27%). The biological half-life for thallium was 3.3 days.

No studies were located regarding distribution in humans or animals after dermal exposure to thallium.

Parenteral studies also indicate extensive tissue distribution of thallium. Adult white mice dosed intraperitoneally with ^{204}Tl at a dose of 4 mg thallium/kg as thallous sulfate showed high thallium concentrations in bone tissue, kidney (particularly in the medulla), pancreas, and large intestine approximately 1 hour after dosing (Andre et al. 1960). Thallium levels in bone decreased after ≥10 days, but thallium was still detectable 28 days post treatment. Intraperitoneal administration of ^{204}Tl mixed with thallium nitrate resulted in peak concentrations in the brain, spinal cord, spleen, liver, and kidney (Ducket et al. 1983). Some apparent differences in the time to peak concentrations were observed between adult rats (33 days of age) and young rats (17 days of age), with peak levels in nervous system tissues (brain, spinal cord and sciatic nerve) occurring 24 hours post-exposure in the adults and 48 hours post-exposure in the young rats. The respective biological half-times in the brain, spinal cord, and sciatic nerve were 1.4, 2.5, and 1.2 days in young rats and 2.7, 4.0, and 3.0 days in adult rats.

^{204}Tl as thallous sulfate has been shown to cross the placenta and locate in the fetus within 15 minutes following intraperitoneal injection (50 μCi, specific activity not stated) (Olsen and Jonsen 1982) and 32 minutes after intravenous administration (0.16–5.2 mg thallium/min/kg) (Rade et al. 1982). The concentration of thallium in the fetus was substantially lower than that in maternal tissues by both routes of administration.

3.1.3 Metabolism

Thallium is not metabolized because it is an element. No human or animal studies were located to assess whether it is transformed from one valence state to another valence state.

3.1.4 Excretion

There are limited data on the excretion of thallium in humans. Elevated urinary thallium levels have been observed in workers in a magnesium seawater battery plant (Marcus 1985) or a cement factory (Schaller et al. 1980). Elevated thallium levels have also been observed in residents living near a cement plant emitting thallium containing dust (Dolgner et al. 1983); consumption of contaminated home-grown vegetables and fruit was considered to be the main source of exposure. The urinary thallium levels decreased after the subjects were advised to decrease consumption of home-grown produce. In a study of a terminally ill cancer patient, 15.3% of the orally administered radiolabelled thallium nitrate was detected in urine 5.5 days postdosing and 0.4% in feces in 3 days (Barclay et al. 1953). A total of 45% of

the radioactivity remained in the body at the time of her death 24 days post-exposure to the isotope. Using the data from Barclay et al. (1953), EPA (1980) estimated an excretion half-life of 21.7 days.

No studies regarding excretion in animals after inhalation or dermal exposure were located. In rats administered 10 mg thallium/kg as thallium sulfate by gavage, 32% of the administered dose was eliminated in feces and 21% was eliminated in urine (Pedro et al. 1985) by 8 days postdosing. Lie et al. (1960) administered a single tracer dose of ^{204}Tl as thallium nitrate via six exposure routes (oral, intramuscular, intraperitoneal, intratracheal, intravenous, and subcutaneous) to rats at a dose of 767 µg thallium/kg. The ratio of fecal to urinary excretion of thallium increased from about 2 to 5 between days 2 and 16. The biological half-life was 3.3 days regardless of the exposure routes.

In rats injected intraperitoneally with ^{204}Tl mixed with thallium nitrate, the biological half-times were 2.6 and 3.8 days, respectively, for young and adult rats. Thallium concentrated in the cerebral cortex, neurons of the caudate nucleus and putamen, and renal proximal tubules and periglomerular spaces. The 95% elimination times for organs in adult rats were fastest for the nervous system, kidney, and liver (range 11.6–17.4 days) and slowest for the spleen (25.8 days), while in young rats, they were fastest for the nervous system, spleen, and kidney (range 6.1–13.6 days) and slowest for the liver (22.0 days) Ducket et al. (1983).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to extrapolate from animal more accurately to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical

descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

The ICRP developed two thallium models: a Human Respiratory Tract Model (HRTM) (Bailey et al. 2007; ICRP 1994, 1995), and a systemic model (ICRP 2022). The HRTM simulates the deposition, clearance, and absorption of inhaled particulates and has absorption parameter values for thallium. The systemic model simulates the distribution and excretion of thallium absorbed from the respiratory or gastrointestinal tract.

The ICRP (2022) has published HRTM parameter values for absorption of thallium compounds (Table 3-1). The HRTM assumes that absorption into blood occurs at equivalent rates in all parts of the respiratory tract, except in the anterior nasal passages, where no absorption occurs. Absorption is simulated as a two-stage process that begins with particle dissolution, followed by transfer of dissolved material into blood. Dissolution is simulated as a biphasic process, with a rapid phase and a slow phase. Dissolution parameters include fraction f_{rapid} dissolving at rate k_{rapid} (day^{-1}) and fraction, f_{slow} ($1-f_{rapid}$) dissolving at rate k_{slow} (day^{-1}). A fraction of the dissolved material can be bound (f_{bound}) transferred to blood at rate (k_{bound}). The unbound fraction, $1-f_{bound}$, is transferred instantaneously to blood. In the absence of specific estimates for absorption kinetics, compounds are classified into absorption types F (fast), M (medium), and S (slow).

Table 3-1. ICRP (2022) Absorption Parameters for the Human Respiratory Tract and Systemic Models

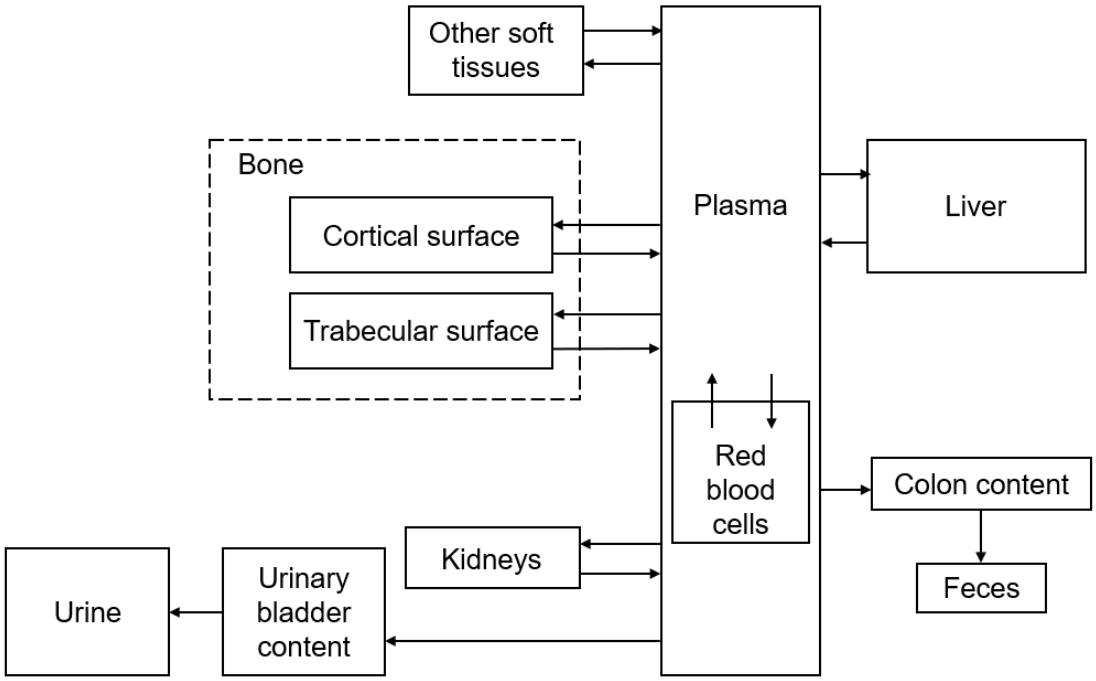
Inhaled thallium							
Type	Rapid fraction	Slow fraction	Rapid Rate (day^{-1})	Slow rate (day^{-1})	Bound fraction	Bound rate (day^{-1})	GI tract absorption fraction[a]
Fast (F)	1.0	0	30	NA	0	NA	1
Medium (M)[b]	0.2	0.8	3	0.005	0	NA	0.2
Slow (S)	0.01	0.99	3	$1X10^{-4}$	0	NA	0.01
Ingested thallium							
All compounds							1

[a]Thallium cleared from the respiratory tract to the gastrointestinal tract.
[b]Type M: default for all thallium compounds in the absence of specific estimates for absorption kinetics.

GI = gastrointestinal; HRTM = Human Respiratory Tract Model; ICRP = International Commission for Radiological Protection; NA = not applicable

The ICRP (2022) systemic model includes compartments representing plasma (central distributing compartment), red blood cells, bladder, bone, colon, kidney, liver, other soft tissues (Figure 3-1). The bone compartment includes sub-compartments representing cortical and trabecular bone surfaces. Transfers of thallium between blood and tissues occurs to and from the plasma compartment. Transfers between compartments are governed by first-order rate coefficients (day^{-1}). Transfer coefficients are presented in Table 3-2. Absorption from the gastrointestinal tract into the plasma is simulated with an absorption fraction. ICRP (2022) assigned an absorption fraction of 1 (100%) for all thallium compounds.

Figure 3-1. Structure of ICRP (2022) Thallium Systemic Model



Source: ICRP 2022, with permission from the International Commission on Radiological Protection

Table 3-2. ICRP Transfer Coefficients for the Human Systemic Model

From	To	Transfer coefficient (day^{-1})
Plasma	Liver	10
Plasma	Kidneys	10
Plasma	RBCs	5
Plasma	Trabecular bone surface	15
Plasma	Cortical bone surface	15
Plasma	Other soft tissues	140

Table 3-2. ICRP Transfer Coefficients for the Human Systemic Model

From	To	Transfer coefficient (day^{-1})
Plasma	Urinary bladder	1.5
Plasma	Colon	3.5
RBCs	Plasma	3.7
Liver	Plasma	2.5
Kidneys	Plasma	2.5
Trabecular bone surface	Plasma	2.5
Cortical bone surface	Plasma	2.5
Other soft tissues	Plasma	2.5

ICRP = International Commission for Radiological Protection; RBC = red blood cell

Source: ICRP 2022, with permission from the International Commission on Radiological Protection

3.1.6 Animal-to-Human Extrapolations

Based on limited available data, the toxicity and toxicokinetic properties of thallium appear to be similar between humans and animals and support extrapolations from animals to humans.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to thallium are discussed in Section 5.7, Populations with Potentially High Exposures.

There are limited data available to identify whether children or other populations are unusually susceptible to the toxicity of thallium. Case series reports of thallium poisoning do not identify differences between adults and children (for example, Sun et al. 2012). A toxicokinetic study in rats administered thallium nitrate suggests some differences in the half-lives of tissue thallium between adult and young rats (Ducket et al. 1983), with longer half-lives in nervous system tissue of the adults. In the liver, a longer half-time was observed in the young rats, as compared to the adult rats.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 2006).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for thallium from this report are discussed in Section 5.6, General Population Exposure.

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 2006). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to thallium are discussed in Section 3.3.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 2006). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by thallium are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Thallium levels in urine, blood, and hair have been used as indications of exposure to thallium. The determination of thallium in urine has been the most widely used of biological indicators of thallium exposure, often expressed in terms of urinary creatinine levels. Higher values have been detected in areas where thallium is used or emitted.

While thallium can be detected in blood, it is cleared from the blood very rapidly. In one case in which a patient with osteogenic sarcoma was administered oral doses of 1.8 mg ^{204}Tl as thallium nitrate (approximately 4 ng thallium/kg), 3% of the administered dose was detected in blood within 2 hours post treatment while 1.6% was detected within 24 hours (Barclay et al. 1953). Since measurements of blood thallium reflect only recent exposures, it is not generally considered to be a reliable means of monitoring human populations for exposure to thallium.

Thallium is excreted in hair and measurement of hair levels may be an indicator of thallium exposure. The normal concentration range of thallium in human hair is approximately 5–10 ng/g. Seven percent of the administered radioactivity was detected in scalp hair of a cancer patient who had been administered 1.8 mg ^{204}Tl as thallium nitrate (Barclay et al. 1953). It should be noted that thallium may adsorb to hair and become incorporated into the hair matrix, making it difficult to distinguish between thallium incorporated into the hair from the body burden and external deposition of thallium.

3.3.2 Biomarkers of Effect

Neurological damage is the primary toxic effect associated with exposure to thallium. Various effects on the nervous system of people exposed to thallium can be detected by monitoring the incidence of signs and symptoms such as ataxia, lethargy, painful extremities, and numbness of toes and fingers. Electromyographic measurements of nerve conduction velocity and amplitude can be monitored to detect early signs of neurotoxicity. However, since neurological damage occurs with other compounds, these

tests are not specific for thallium exposure. Thallium also accumulates in hair. Dark pigmentation of the hair roots and hair loss are common diagnostic features (Gastel 1978). Depletion and inhibition of several enzymes in the brain have been associated with thallium exposure. Hasan et al. (1977a, 1977b) reported depletion of succinic dehydrogenase and guanine deaminase in the rat cerebrum after parenteral administration of 5 mg thallium/kg (as thallium acetate) as well as depletion of monoamine oxidase, acid phosphatase, and cathepsin activity (Hasan et al. 1977b). The significance of this finding as a biomarker of effect is not known.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Studies have shown that trace metals can influence the toxicity of thallium. Potassium has been shown to increase renal excretion of thallium (Gehring and Hammond 1967; Lund 1956a), decrease the degenerative effects of thallium on epiphysial cartilage in mouse limb bud cultures, decrease placental transport of thallium (Sabbioni et al. 1980), and increase the lethality of thallium in animals (Gehring and Hammond 1967). Other interactions can influence thallium toxicity through accelerated elimination. Potent diuretics such as furosemide enhanced the urinary excretion of thallium in rats (Lameijer and van Zwieten 1977, 1978; Pedro et al. 1985). Oral administration of activated charcoal and Prussian blue accelerated the elimination of orally administered thallium in rats (Lund 1956b; Pedro et al. 1985). These agents adsorb thallium in the gastrointestinal tract, and are themselves unabsorbed, thus reducing gastrointestinal absorption of thallium.