2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of thallium and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for thallium based on toxicological studies and epidemiological investigations.

Pure thallium exists in nature but is usually found combined with other elements in inorganic compounds. Thallium forms compounds in both the monovalent and trivalent states; however, the monovalent state is the more stable. This document includes nine of the commonly used thallium compounds. Toxicity data were found for five of these compounds (thallium sulfate, thallium oxide, thallium nitrate, thallium acetate, and thallium carbonate).

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing noobserved-adverse-effect levels (NOAELS) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

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Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989c), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

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

2.2.1.2 Systemic Effects

No studies were located in humans or animals regarding the effects on the respiratory, hematological, musculoskeletal, hepatic, renal, and dermal/ocular systems after inhalation exposure to thallium. Limited occupational data show the cardiovascular and gastrointestinal systems were not susceptible to thallium.

Cardiovascular Effects. There are few data in humans on the cardiovascular effects of thallium following inhalation. Data are limited to a study evaluating the health of workers employed in a magnesium sea water battery plant in England (Marcus 1985). There were no statistically significant differences in cardiovascular effects in a cohort of 86 exposed workers compared with 79 unexposed controls in the same factory. However, the authors did not clearly define the cardiovascular parameters measured. Workplace air levels were 0.014 and 0.022 mg/m^3 in machining and alloying operation areas. Occupational exposure is expected to involve multiple compound exposures. However, the authors did not provide data on other chemicals to which workers have been exposed concomitantly.

No studies were located regarding cardiovascular effects in animals after inhalation exposure to thallium.

Gastrointestinal Effects. Based on available medical records, there were no differences in gastrointestinal effects in a cohort of 86 exposed workers in a magnesium sea water battery plant in England compared with 79

unexposed controls (Marcus 1985). Maximum thallium levels in workplace air were 0.014 and 0.022 mg/m^3 during machining and alloying operations, respectively.

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to thallium.

2.2.1.3 Immunological Effects

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

2.2.1.4 Neurological Effects

Human occupational studies indicate that thallium may affect the nervous system following inhalation. Thirty-six workers involved in cement production for 5-44 years (mean of 22.9) exhibited paresthesia, numbness of toes and fingers, the "burning feet" phenomenon, and muscle cramps (Ludolph et al. 1986). Peripheral conduction was impaired and there were changes in somatosensory action potential. Electroencephalographic recordings revealed no abnormalities. This study did not evaluate an unexposed control group. It should be further noted that 50% of the patients suffered concurrent disease including diabetes, obesity, malabsorption syndrome, (alcoholic) liver disease, disorders of joints and connective tissues, and hypertensive vascular disease. These may have contributed to the neurological effects observed.

No studies were located regarding neurological effects in animals after inhalation exposure to thallium.

No studies were located regarding the following effects in humans or animals after inhalation exposure to thallium:

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

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

2.2.2 Oral Exposure

2.2.2.1 Death

There are numerous case reports of human lethality following acute oral exposure to thallium. Death occurred in one individual 9 days following intentional ingestion of a single estimated dose of 54-110 mg thallium/kg (as thallium nitrate) (Davis et al. 1981). Cranial and peripheral nerves showed axonal degeneration with preservation of most of the overlying myelin, suggesting that thallium damaged axons. Two of three subjects who ingested thallium (thallous acetate) also died; however death occurred 1 month after onset of symptoms (Cavanagh et al. 1974). Dose could not be determined since exposure occurred in three divided doses for unspecified durations. Distal peripheral axon degeneration with preserved proximal fibers was reported in one case (Cavanagh et al. 1974). Other studies (de Groot et al. 1985; Heath et al. 1983; Roby et al. 1984) have reported that thallium (as thallium sulfate, dose not specified) is lethal following ingestion, and there was evidence for central-peripheral distal axonopathy (Roby et al. 1984). While the finding of neurological effects was consistent among case reports, death was attributable to cardiac or respiratory failure. No studies were located concerning intermediate or chronic exposures.

In rats, estimates of LD_{50} for thallium compounds were 32 and 39 mg thallium/kg (as thallium acetate and thallic oxide, respectively) (Downs et al. 1960). The lowest oral doses of thallium compounds showing lethality ranged from 12 (guinea pig) to 29 (rat) mg thallium/kg (as thallium acetate) and 5 (guinea pig) to 30 (dog and rabbit) mg thallium/kg (as thallic oxide) (Downs et al. 1960). Rats exposed for 15 weeks to diets containing thallium showed increased mortality at a dose of 4.5 mg thallium/kg/day (as thallic oxide) and 2.3 mg thallium/kg/day (as thallium acetate) (Downs et al. 1960). Continuous administration via drinking water of approximately 1.4 mg thallium/kg/day to rats (as thallium sulfate) resulted in 15%-21% mortality after 40 and 240 days of treatment, respectively (Manzo et al. 1983). When rats were administered up to 0.20 mg thallium/kg/day (as thallium sulfate) by gavage for 90 days, no deaths were reported (Stoltz et al. 1986).

A NOAEL value and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.2 Systemic Effects

No studies were located regarding hematological effects in humans or animals following oral exposure to thallium. Case studies in humans who ingested various thallium compounds show the respiratory and cardiovascular systems as well as the liver, kidney, and muscles are susceptible. Hair loss may also occur. These effects are discussed below. The highest NOAEL values and all reliable LOAEL values for these systemic effects for each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

TABLE 2-1. Levels of Significant Exposure to Thallium and Compounds - Oral

Key to figure[a]	Species		Exposure frequency/ duration	System	NOAEL (mg Tl/kg/day)	LOAEL (effect) Less serious (mg Tl/kg/day)	LOAEL (effect) Serious (mg Tl/kg/day)	Reference	Form
ACUTE EXPOSURE									
Death									
1	Rat	(F)	1x				39 (LD50-7 days)	Downs et al. 1960	Tl_2O_3
2	Rat	(F)	1x				20 (lowest lethal dose)	Downs et al. 1960	Tl_2O_3
3	Rat	(F)	1x				32 (LD50-7 days)	Downs et al. 1960	$TlC_2H_3O_2$
4	Gn pig	(F)	1x				5 (lowest lethal dose)	Downs et al. 1960	Tl_2O_3
Systemic									
5	Rabbit	(F)	1x	Cardio		56 (electrocardial alterations)		Grunfeld et al. 1963	Tl_2SO_4
Developmental									
6	Rat	(G)	4 d 1x/d Gd 6,7,8,9			0.08 (performance deficit)		Bornhausen and Hagen 1984	Tl_2SO_4
INTERMEDIATE EXPOSURE									
Death									
7	Rat	(F)	15 wk				4.5 (increased mortality)	Downs et al. 1960	Tl_2O_3
8	Rat	(F)	15 wk				2.3 (increased mortality)	Downs et al. 1960	$TlC_2H_3O_2$
9	Rat	(G)	90 d 1x/d		0.2			Stoltz et al. 1986	Tl_2SO_4
10	Rat	(W)	36 wk				1.4 (increased mortality)	Manzo et al. 1983	Tl_2SO_4

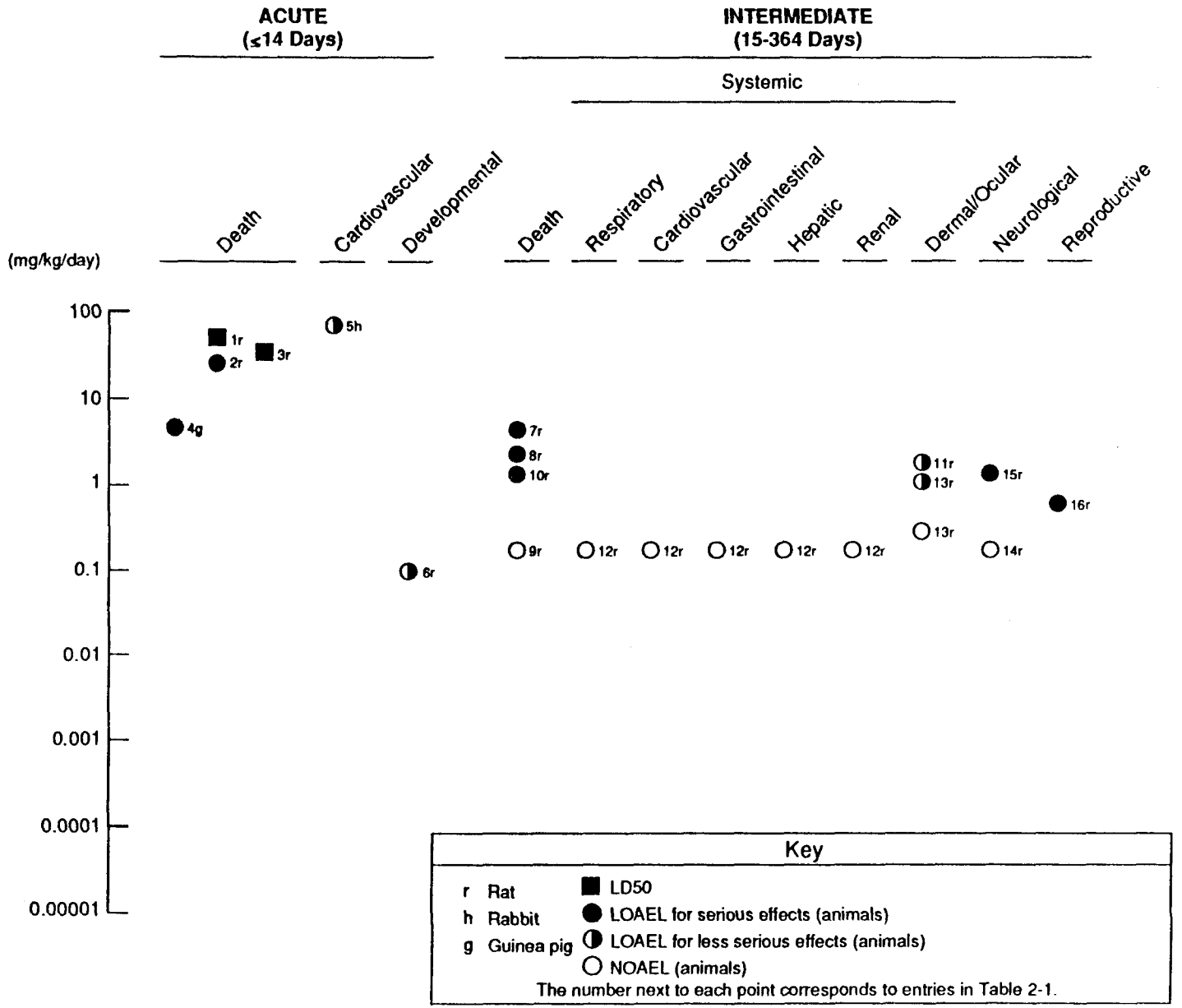
TABLE 2-1 (Continued)

Key to figure[a]	Species		Exposure frequency/ duration	System	NOAEL (mg Tl/kg/day)	LOAEL (effect) Less serious (mg Tl/kg/day)	LOAEL (effect) Serious (mg Tl/kg/day)	Reference	Form
Systemic									
11	Rat	(F)	15 wk	Derm/oc		1.8 (hair loss)		Downs et al. 1960	Tl_2O_3
12	Rat	(G)	90 d 1x/d	Hepatic Renal Cardio Gastro Resp	0.2 0.2 0.2 0.2 0.2			Stoltz et al. 1986	Tl_2SO_4
13	Rat	(F)	15 wk	Derm/oc	0.4	1.2 (hair loss)		Downs et al. 1960	$TlC_2H_3O_2$
Neurological									
14	Rat	(G)	90 d 1x/d		0.2			Stoltz et al. 1986	Tl_2SO_4
15	Rat	(W)	36 wk				1.4 (peripheral nerve damage)	Manzo et al. 1983	Tl_2SO_4
Reproductive									
16	Rat	(W)	30-60 d				0.7 (histological alteration of testis)	Formigli et al. 1986	Tl_2SO_4

[a]The number corresponds to entries in Figure 2-1.

Cardio = cardiovascular; d = day(s); Derm/oc = dermal/ocular; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; Gn = guinea; LD50 = lethal dose, 50% mortality; LOAEL = lowest-observed-adverse-effect level; mg thallium/kg/day = milligram thallium per kilogram body weight per day; NOAEL = no-observed-adverse-effect level; Resp = respiratory; Tl_2SO_4 = thallium sulfate, Tl_2O_3 = thallium carbonate, $TlC_2H_3O_2$ = thallium acetate

FIGURE 2-1. Levels of Significant Exposure to Thallium – Oral



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Respiratory Effects. Limited data in humans show that thallium can cause respiratory damage. Lungs showed diffuse alveolar damage with hyaline membrane and focal organization in one case following acute ingestion of an estimated 54-110 mg thallium/kg (as thallium nitrate). Bronchopneumonia was also reported in this study (Davis et al. 1981). Similar findings were reported after ingestion of thallium acetate; however, the doses that produced these effects were not clearly defined (Cavanagh et al. 1974; de Groot et al. 1985; Roby et al. 1984).

One study was located in animals. No adverse effects were observed on the respiratory system of rats administered 0.20 mg thallium/kg/day (as thallium sulfate) by gavage for 90 days (Stoltz et al. 1986).

Cardiovascular Effects. Cardiovascular damage was reported in humans after ingestion of a single estimated lethal dose of 54-110 mg thallium/kg (as thallium nitrate) (Davis et al. 1981). There was extensive damage of the myocardium with myofiber thinning, accumulation of lipid droplets, myocardial necrosis, and inflammatory reaction (Davis et al. 1981). Sinus bradycardia, ventricular arrhythmias, and T-wave anomalies were reported in two additional case reports; however, the authors did not provide data on dose and duration (Roby et al. 1984).

Limited studies were located regarding cardiovascular effects in animals after oral exposure to thallium. Electrocardiographic changes were observed in rabbits administered 56 mg thallium/kg/day (as thallous sulfate), which was also lethal (Grunfeld et al. 1963). Abnormalities reported included T-wave fluttering, prolonged Q-T intervals, heart block, atria1 and ventricular ectopic rhythms, and ST-segment depression or elevation (Grunfeld et al. 1963). While thallium was detected in heart tissue (16-45 μg/g tissue), histological examination did not reveal damage to the myocardium. When rats were administered up to 0.20 mg thallium/kg/day (as thallium sulfate) by gavage for 90 days, no cardiovascular effects were observed (Stoltz et al. 1986).

Gastrointestinal Effects. In humans, acute ingestion of thallium sulfate caused gastroenteritis, diarrhea or constipation, vomiting, and abdominal pain (Davis et al. 1981; de Groot et al. 1985; Grunfeld and Hinostroza 1964). Gastrointestinal disturbances were also reported in 189 cases of thallium poisoning which occurred in China from 1960 to 1977 (Dai-xing and Ding-nan 1985). High levels of thallium were detected in urine and hair samples. The authors attributed exposure to ingestion of cabbage from contaminated gardens.

Data in animals are sparse. When rats were administered up to 0.20 mg thallium/kg/day (as thallium sulfate) by gavage for 90 days, no adverse effects were observed on the gastrointestinal system (Stoltz et al. 1986).

Musculoskeletal Effects. Data are sparse regarding the muscular effects in humans. Histopathological examination of muscle biopsies from two cases revealed myopathic changes associated with thallium poisoning (Limos et al. 1982). Fiber necrosis, central nucleation, and fiber splitting were reported. No data were provided on exposure levels.

Hepatic Effects. Case reports in humans demonstrate that the liver is susceptible to thallium toxicity. Centrilobular necrosis with fatty changes has been reported (Cavanagh et al. 1974; Davis et al. 1981). It was not clear whether the effects observed were a result of a direct effect on the liver or secondary to other effects. Serum glutamic oxaloacetic transaminase, serum pyruvic oxaloacetic transaminase, and alkaline phosphatase levels were elevated.

Data in animals are sparse. No adverse effects were observed on the liver when rats were administered 0.20 mg thallium/kg/day (as thallium sulfate) by gavage for 90 days (Stoltz et al. 1986).

Renal Effects. Human case studies report that thallium can affect the kidneys (Cavanagh et al. 1974; Gastel 1978). Histological examination of the kidneys in one case revealed extensive recent necrosis of the cortex (Cavanagh et al. 1974). The authors reported that the effects were probably the result of infarction. Renal function is also impaired following thallium exposure. Diminished creatinine clearance, a raised blood urea, and proteinuria are common (Cavanagh et al. 1974).

In animals, there were no adverse renal effects in rats administered 0.20 mg thallium/kg/day (as thallium sulfate) by gavage for 90 days (Stoltz et al. 1986).

Dermal/Ocular Effects. Ingestion of thallium has been associated with hair loss in humans. Loss can occur as early as 8 days after exposure (Grunfeld and Hinostroza 1964). Several cases have reported loss of body hair, full beard, and scalp hair (Grunfeld and Hinostroza 1964). In other instances, body and pubic hair have been spared (Gastel 1978; Grunfeld and Hinostroza 1964). Hair loss is temporary, and no local skin changes have been reported.

In animals, hair loss was observed in rats exposed to ≥ 1.2 mg thallium/kg/day (as thallium acetate or thallium oxide) for 15 weeks (Downs et al. 1960). Histological examination revealed that 1.8 mg thallium/kg/day (as thallium oxide) caused atrophy of the hair follicles and there was a decrease in size of sebaceous glands.

No studies were located regarding the direct effects of thallium on the eyes of humans. However, thallium caused damage to certain cranial nerves which lead to eye disturbances. Decreased visual acuity due to bilateral central scotomas and progressive optic atrophy have been associated with optic.

nerve damage (Moeschlin 1980). Also, there are degenerative changes in cranial nerves which innervate the extraocular muscles. Ptosis and disconjugate eye movements are common manifestations of eye disturbances (Cavanagh et al. 1974; Davis et al. 1981).

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to thallium.

2.2.2.4 Neurological Effects

Human case studies revealed that the nervous system is susceptible *to* thallium toxicity after acute oral exposure at high doses. Severe cranial and peripheral neuropathy were reported following ingestion of a single estimated dose of 54-110 mg thallium/kg (as thallium nitrate), which was also lethal (Davis et al. 1981). Examination of nerves obtained on days 7 and 9 demonstrated axonal degeneration with secondary myelin loss. Axons were swollen and contained distended mitochondria and vacuoles (Davis et al. 1981). Distal peripheral axonal degeneration with preserved proximal fibers was observed in another case in which death occurred; however, reliable exposure data (dose and duration) were not reported (Cavanagh et al. 1974; Roby et al. 1984).

No studies were located regarding neurological effects in humans after intermediate oral exposure to thallium. Peripheral neuropathy was reported in 189 cases of thallium poisoning in China from 1960 to 1977 (Dai-xing and Ding-nan 1985). Thallium was detected in urine samples of the exposed group at higher levels (0.6-2.25 mg/L, $P>0.01$) than in the unexposed individuals (0.14-0.31 mg/L). Similarly, levels in the hair were 21.8-31.5 mg/kg ($P>0.01$) compared to 5.80-11.3 mg/kg in the unexposed group. The authors attributed exposure to ingestion of cabbage grown in thallium-contaminated gardens. No other details were provided.

In animals, structural and functional changes were observed in peripheral nerves in rats at 240 days, following treatment with 1.4 mg thallium/kg/day (as thallium sulfate), but effects were not found at 40 days (Manzo et al. 1983). There was a 44% decrease in the amplitude of motor action potential (MAP), a 30% decrease in the amplitude of the sensory action potential, and a 25% increase in MAP latency. Wallerian degeneration of scattered fibers and vacuolization and delamination of the myelin sheath of 10% of the fibers were reported in 50% of the test animals (Manzo et al. 1983). Ultrastructural examination of fibers with Wallerian degeneration showed complete destruction of the axon, with mitochondrial degeneration, neurofilamentous clustering, and evidence of extensive lysosomal activity

(Manzo et al. 1983). However, when rats were administered up to 0.20 mg thallium/kg (as thallium sulfate) by gavage for 90 days, light microscopic examination did not reveal neurological effects (Stoltz et al. 1986). No electron microscopic evaluations were performed in this study.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.5 Developmental Effects

Thallium can cross the human placenta; however, data are limited regarding the developmental effects. A retrospective study was conducted to assess the teratogenic potential of thallium in 297 children born to mothers living in the vicinity of a cement plant in Germany that discharged thallium into the atmosphere (Dolgner et al. 1983). Maternal intake was presumed to have been due to consumption of home-grown vegetables and fruits contaminated with thallium. Levels of thallium in 24-hour urine samples were determined to assess the degree of past thallium exposure, s!nce there were no relaible data on exposure during pregnancy. Maternal urinary levels were 0.6-2.2 μg/L compared to less than 1 μg/L for the general population. In the absence of reliable exposure data, no firm conclusions can be made about the developmental toxicity of thallium in humans. The incidence of congenital malformations and anomalies in the exposed group did not exceed the number of expected birth defects in the general population.

Data in animals are sparse. Rats were administered 0, 0.08, 0.4 or 1.6 mg thallium/kg/day as thallium sulfate on days 6-9 of gestation to determine the effect of prenatal exposure on learning ability. The study involved a conditioning program in which lever pressing was rewarded with a food pellet (Bornhausen and Hagen 1984). Rats showed impairment of learning after prenatal exposure at doses of 0.08 mg thallium/kg/day or greater but no dose-response relationship was observed. The LOAEL of 0.08 mg thallium/kg/day is recorded in Table 2-l and plotted in Figure 2-1. While performance deficits suggest impairment of brain function, no structural alterations were reported at any dose tested.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to thallium.

In animals, abnormalities in testicular morphology, function, or biochemistry were evident in rats which received an average daily intake of 0.27 mg thallium/day (approximately 0.7 mg/thallium/kg/day, as thallium sulfate) during a 60-day treatment period (Formigli et al. 1986). Males exposed to thallium for 60 days exhibited epididymal sperm with increased number of immature cells and significantly reduced motility. Histological

examination revealed disarrangement of the tubular epithelium. In addition, Sertoli cells showed cytoplasmic vacuolization and distension of the smooth endoplasmic reticulum. Testicular ,β-glucuronidase activity was reduced significantly ($p<0.01$) in the thallium-treated males, but plasma testosterone levels were unaffected. Abnormalities in testicular morphology, function, or biochemistry were not observed in rats exposed for 30 days (Formigli et al. 1986); however, thallium levels were not measured in this dose group. The LOAEL of 0.7 mg thallium/kg/day is recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to thallium. However, thallium caused dominant lethal mutations in rats after oral exposure at a dose of 0.04 pg thallium/kg/day as thallium carbonate (Zasukhina et al. 1983). Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer effects in humans or animals after oral exposure to thallium.

2.2.3 Dermal Exposure

2.2.3.1 Death

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

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular effects in humans or animals after dermal exposure to thallium.

No studies were located regarding the following health effects in humans or animals after dermal exposure to thallium:

2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

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

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

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

2.3.1.2 Oral Exposure

Limited data show direct gastrointestinal tract absorption in humans. Indirect oral exposure may also occur through breathing contaminated airborne dust. The mucociliary clearance mechanism moves most particulates with a mass median aerodynamic diameter (MMAD) of 1-5 μm out of the lungs and into the gastrointestinal tract. Larger particles (greater than 5 μm) impacting in the nasopharyngeal region would also be eventually ingested.

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 thalliumz^{204} (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% 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 thallium^{204} (as thallium nitrate) orally to rats at a dose of 0.767 mg thallium/kg. The body burden of thallium^{204}, as percent dose, decreased with a single exponential function which extrapolated to 100% at zero time. The authors, therefore, concluded that thallium is completely absorbed from the gastrointestinal tract.

2.3.1.3 Dermal Exposure

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

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

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

2.3.2.2 Oral Exposure

There is little information on distribution of thallium in humans. Analysis of human tissues indicate that thallium is distributed throughout the body. A female cancer patient was administered a tracer dose of 1.8 mg thallium^{204} (as thallium nitrate) orally and thereafter an oral dose of 36 mg thallium/kg (as thallium sulfate) (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 (45%-70%).

In animals distribution of thallium from the blood stream is rapid and widespread. Thallium was found 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 less than 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 acetate or thallic 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 thallium^{204} (as thallium nitrate) orally at a dose of 0.76 mg thallium/kg. Approximately 7 days post-treatment, the highest level of thallium was detected in kidneys (4.7% of the body burden per gram of tissue). Lesser amounts 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.

2.3.2.3 Dermal Exposure

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

2.3.2.4 Other Exposure

Parenteral studies also indicate extensive tissue distribution of thallium. Adult white mice dosed intraperitoneally with thallium^{204} 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 or more, but thallium was still detectable 28 days posttreatment. Parenteral administration of thallium resulted in peak concentrations in the brain, spinal cord, spleen, liver, and kidney. Half-lives for depletion from several tissues in rats were estimated at 2.7 days for the brain to 6.0 days for the spleen (Ducket et al. 1983).

Thallium^{204} 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.

2.3.3 Metabolism

No studies were located regarding metabolism of thallium in humans or animals.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

In humans, thallium urinary levels ranging from ≤50 μg/L to 236 μg/L were found in 39 workers exposed to thallium in a magnesium seawater battery plant (Marcus 1985). Workers employed in a cement factory showed urinary levels between 0.3-6.3 μg thallium/g creatinine (Schaller et al. 1980).

No studies were located regarding excretion in animals after inhalation exposure to thallium.

2.3.4.2 Oral Exposure

In humans, 15.3% of the administered radioactivity was detected in urine 5.5 days postdosing and 0.4% in feces in 3 days (Barclay et al. 1953). An excretion half-life of 21.7 days was estimated (EPA 1980a).

In rats administered 10 mg thallium/kg (as thallium sulfate) by gavage, 32% of the administered dose was eliminated in feces and 21% in urine (Lehman and Favari 1985) by 8 days postdosing.

Lie et al. (1960) administered a single tracer dose of thallium^{204} (as thallium nitrate) orally 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.

2.3.4.3 Dermal Exposure

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

2.4 RELEVANCE TO PUBLIC HEALTH

As discussed in Section 2.2, estimates of levels of exposure to thallium posing minimal risk to humans (MRLs) were to have been made, where data were believed reliable, for the most sensitive noncancer effect for each route and exposure duration. Because no data were located on effects of acute-duration or intermediate-duration inhalation exposure to thallium in humans or animals, and because available information concerning effects of chronic-duration inhalation exposure in humans was not quantitative, no inhalation MRLs were derived. Limited data on human and animal acute oral exposure to thallium suggests that the nervous system may be the target organ, but reliable doseresponse data were not available (Bornhausen and Hagen 1984; Cavanagh et al. 1974; Davis et al. 1981; Roby et al. 1984). Data on effects of intermediateduration oral exposure in animals do not reliably identify the most sensitive target organ or the threshold for adverse effects. No data on effects of chronic-duration oral exposure to thallium were located. Therefore, acuteduration, intermediate-duration, and chronic-duration oral MRLs were not derived. Acute-duration, intermediate-duration, and chronic-duration dermal MRLs were not derived for thallium due to the lack of an appropriate methodology for the development of dermal MRLs.

Inhalation and oral studies in humans and oral studies in animals demonstrate that thallium compounds such as thallium oxide and thallium sulfate can be lethal at relatively low doses (about 1 gram). However, these doses are high compared to exposure levels that would be expected from thallium at NPL sites. Thallium compounds can affect the respiratory, cardiovascular, and gastrointestinal systems, liver, kidneys, and the male reproductive system. Temporary hair loss has also been associated with ingestion of thallium in humans. Thallium compounds can also affect the peripheral and central nervous systems. The rate of congenital malformations among children of mothers exposed to thallium did not exceed the rate expected for the general population. No studies have been located regarding thallium exposure and development of cancer in humans or animals.

Death. Thallium was lethal in humans following acute oral exposure at doses of 54-110 mg thallium/kg of body weight as thallium sulfate (Davis et al. 1981). The estimated lethal dose for the average adult for thallium is 1 g (approximately 14-15 mg/kg) (Gosselin et al. 1984). No studies were

located concerning intermediate and chronic exposures in humans by oral, inhalation, or dermal route.

Death has been reported in animals exposed to low doses for brief periods. The lowest doses showing lethality ranged from 5 to 30 mg thallium/kg for several species (Downs et al. 1960). Exposure to low doses of thallium (1.4 mg thallium/kg/day, as thallium sulfate) for longer durations (40-240 days) can also cause death (Manzo et al. 1983). No studies were located on chronic oral exposures or inhalation or dermal exposure for any duration in animals.

Mortality data of exposed humans and results of studies in several animal species suggest that humans are at risk of death from exposure to high concentrations of thallium. Neurological damage was a consistent feature among humans who died following thallium exposure. However, death was regularly attributed to cardiac or respiratory failure. Ingestion of lethal doses readily resulted in cardiac and respiratory depression which generally overshadowed the characteristic manifestation of neuropathy.

Systemic Effects.

Respiratory Effects. Human case studies reported respiratory effects following acute oral exposure. Alveolar damage, hyaline membrane formation, and pulmonary edema have been reported (Davis et al. 1981; Roby et al. 1984). It has been suggested that thallium may have a direct effect on pulmonary epithelial and endothelial cells. Alveolar damage suggests that respiratory effects may be an area of concern following thallium exposure.

Cardiovascular Effects. Studies in humans demonstrated cardiovascular effects following oral exposure to thallium. Myocardial damage and electrocardiographic changes were observed (Davis et al. 1981; Roby et al. 1984). Following a single oral dose (56 mg thallium/kg as thallium sulfate), rabbits showed electromyographic abnormalities without changes in the myocardium (Grunfeld et al. 1963). The precise mechanism of thallium-induced cardiovascular injury is not clear. However, parenteral injection of thallium causes a direct effect on the cardiovascular system. Intravenously applied thallium caused a significant dose-dependent decrease in mean arterial pressure and heart rate, the maximum fall in blood pressure occurring within 3-5 minutes (Lameijer and van Zwieten 1976). The authors presumed a direct influence of thallium on the sinus node. Based on human and animal data, cardiovascular effects may be an area of concern following thallium exposure.

Musculoskeletal Effects. Very little information was found on the effects of thallium on muscles. Myopathic changes included fiber necrosis, fiber splitting, and central nucleation (Limos et al. 1982). It should be noted that these effects occurred in cases involving axon degeneration of the nerve. It is, therefore, not clear if the effects observed were due to a

direct toxic effect on muscle or were the result of rapid atrophy of the paralyzed muscle secondary to severe axonal degeneration.

Hepatic Effects. Oral studies in humans suggest that the liver is susceptible to thallium toxicity. Necrosis, fatty changes, and altered serum enzyme levels were reported. No studies were located demonstrating that thallium causes liver toxicity in humans or animals by inhalation or dermal exposure. Parenteral injection in animals has been observed to cause liver effects. Single intraperitoneal doses of 33-132 mg thallium/kg/day (as thallium chloride) were associated with ultrastructural.and biochemical changes in the liver consistent with injury to the membranes of subcellular organelles in the hepatocytes (Woods and Fowler 1986). In rats administered subcutaneous injections of thallium (7.8-15.5 mg thallium/kg, as thallium acetate), there were degenerative changes in mitochondria and increased glycogen deposits (Herman and Bensch 1967). The precise mechanism for liver toxicity is not known; however, thallium may combine with the sulfhydryl groups of mitochondria, interfering with oxidative phosphorylation. Because these effects occurred under conditions not likely to result in human exposure, it is not clear whether similar effects on subcellular organelles will occur in humans following relevant routes of exposure.

Renal Effects. Very little information was found on the effects of thallium on the kidney in humans. Tubular necrosis has been reported in some cases following ingestion. However, these effects were reportedly due to infarction rather than a direct affect on kidney tissue. Thallium did not cause injury to the kidneys of rats following oral exposure. No studies were located regarding renal effects in humans or animals after inhalation or dermal exposure to thallium. Parenteral exposure studies in animals demonstrate that thallium can affect the kidney following subcutaneous administration. Accumulation of debris in the lumen of the convoluted tubules and progressive changes in the mitochondria of the tubule cell were observed (Herman and Bensch 1967). By 12 weeks, many cup-shaped mitochondria were present, and, in some mitochondria, partial loss of cristae was evident. This route of exposure is not likely to result in significant human exposure. Therefore, it is not clear if similar effects will occur in humans by relevant exposure routes.

Dermal/Ocular Effects. Hair loss has been reported in humans following exposure to thallium. However, the effect is reversible. Animal studies confirm human findings. However, these studies should be interpreted with caution since rodent hair does not continue to grow as does cycling human head hair. Animal studies suggest that thallium affects hair follicles directly or that hair loss is the result of effects of thallium on the sympathetic nervous system (Carson et al. 1986). No direct ocular effects of thallium have been reported. However defects of the oculomotor nerve, ocular muscle, and ptosis have been reported (Cavanagh et al. 1974; Davis et al. 1981).

2. HEALTH EFFECTS

Immunological Effects. No studies were located regarding the immunological effects in humans or animals after inhalation, oral, or dermal exposure to thallium. In the absence of histopathologic evaluation and direct tests of immune functions, the potential for thallium to affect the immune system in humans cannot be determined.

Neurological Effects. Human case reports demonstrated that thallium caused disturbances of the peripheral and central nervous systems following acute oral exposure. Ataxia, tremor, and multiple cranial palsies have been reported following oral exposure to thallium as has numbness of toes and fingers, "burning feet" phenomenon, and muscle cramps. Convulsions and death can also occur. While thallium characteristically produces distal, predominantly sensory neuropathy in humans, structural alterations underlying the changes have not been firmly established. Histological evaluations have shown axonal degeneration and myelin loss.

The mechanism by which thallium exerts its effects is not clear. However, parenteral studies in animals suggest that the effects observed may be due in part to the depletion or inhibition of critical enzyme systems. There was depletion of succinic dehydrogenase and guanine deaminase in the rat cerebrum after intraperitoneal injection of 5 mg thallium/kg (as thallium acetate) (Hasan et al. 1977a, 1977b) as well as depletion of monoamine oxidase, acid phosphatase, and cathepsin activity (Hasan et al. 1977b). Adenosine triphosphatase and adenosine deaminase activities were unaffected. At the same dose, sequestrated axons were observed in the hypothalamus, and there were increased Golgi zones and electron dense bodies in the hypothalamus and hippocampus (Hasan et al. 1977a, 1978). Also, the protein content of the corpus striatum was significantly increased (Hasan et al. 1977b). Furthermore, there was a significant increase in the spontaneous discharge rate of cerebellar Purkinje neurons of rats administered intraperitoneal injections of 5 mg thallium/kg/day (as thallium acetate) (Marwaha et al. 1980).

The effects in the hypothalamus, hippocampus, and corpus striatum are consistent with a reported differential distribution of thallium in the brain. In rats that received a single intraperitoneal injection of 13-39 mg thallium/kg/day (as thallium sulfate), the highest thallium concentrations were found in the hypothalamus and the lowest in the cortex (Rios et al. 1989). It was also noted that thallium accumulated more rapidly in the hypothalamus than in other brain regions (Rios et al. 1989). Differential distribution of thallium suggests that some areas of the brain may be affected more severely than others. Brown et al. (1985) provided data suggesting a dose-related selective toxicity between brain regions. Lipid peroxidation rates and P-galactosidase activity were increased in the cerebellum and brainstem following intraperitoneal injections of 3 mg thallium/kg/day (as thallium acetate). However, when 6 mg thallium/kg/day (as thallium acetate) were administered, lipid peroxidation rates were increased in the cerebellum,

brainstem, striatum, and cortex. β-Galactosidase activity was also increased in the cerebellum, cortex, hippocampus, and brainstem.

Developmental Effects. A retrospective study was conducted to compare the incidence of congenital abnormalities in children born to mothers who had been exposed to thallium during pregnancy (Dolgner et al. 1983). The number of anomalies in the exposed group did not exceed the number of expected birth defects for the general population.

Existing evidence suggests that thallium causes alterations in the functional competence of the nervous system. There was impairment of learning in rats prenatally exposed to 0.08 mg thallium/kg/day or greater during gestation but no dose-response relationship was found (Bornhausen and Hagen 1984). No structural alterations in the brain were reported in this study. It should be noted that these effects were reported to occur at dose levels below those at which other neurological effects (e.g. structural and functional alterations of peripheral nerves) have been observed. While existing data suggest, in part, that thallium may be a potential developmental neurotoxicant, additional testing batteries are needed. These studies would be useful in determining the full spectrum of behavioral alterations and for assessing the relative importance of this finding and human health risk.

In animals, cultured rat embryos exposed to thallium at concentrations of 10, 30, or 100 μg/mL showed dose-related growth retardation at all levels, suggesting embryotoxic effects (Anschutz et al. 1981). Complete growth inhibition was reported at 100 μg/mL. At 3 μg/mL (lowest dose tested), the treated and control embryos did not differ significantly. Administration by intraperitoneal injection to pregnant rats at a dose of 2.0 mg thallium/kg/day (as thallium sulfate) during gestation days 8-10 resulted in reduced fetal body weights, hydronephrosis, and the absence of vertebral bodies (Gibson and Becker 1970). While these data suggest that thallium is a developmental toxicant, the evidence is limited and does not allow a conclusive decision about the human health implications.

Reproductive Effects. No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to thallium.

In rats, thallium administered in the drinking water at 0.74 mg/kg/day (as thallium sulfate) for 60 days caused decreased sperm motility, inhibition of β-glucuronidase activity and histopathological alterations of the testes (Formigli et al. 1986). Mutagenicity studies employing dominant lethal assays in mice provide some evidence of the potential reproductive effects of thallium (see Genotoxic Effects). There was increased embryolethality following oral exposure. While there are no human data regarding the reproductive effects of thallium, animal data suggest that the male reproductive system may be susceptible to the toxic action of thallium.

Genotoxic Effects. No studies were located regarding the genotoxic effects of thallium in humans. Results of animal and bacterial assays suggest thallium is genotoxic. Thallium induced dominant lethals in male rats in vivo. The overall embryonic mortality increased at doses of 0.04 μg thallium/kg/day or greater as thallium carbonate (Zasukhina et al. 1983). In vitro DNA damage tests employing rat embryo cells were positive (Table 2-2). Thallium enhanced viral-induced transformations in Syrian hamster embryo cells (Table 2-2). The significance of this response in the overall assessment of the mutagenic potential of thallium is reduced since this end point is not well understood. In vitro tests employing bacterial assays were positive (Table 2-2). Existing data suggest that genotoxicity may be an area of concern for thallium exposure in humans.

Cancer. No studies were located regarding carcinogenicity in humans or animals after inhalation, oral, or dermal exposure to thallium. In the absence of epidemiological studies or long-term animal bioassays, the potential for thallium to cause cancer in humans cannot be determined.

2.5 BIOMARXERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

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 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites 'in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to thallium are discussed in Section 2.5.1.

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 1989). This definition encompasses biochemical or

TABLE 2-2. Genotoxicity of Thallium *In Vitro*

Species (test system)	Compound	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:					
Bacillus subtilis	$TlNO_3$	DNA damage/repair	Not tested	+	Kanematsu et al. 1980
Mammalian cells:					
CBA mouse embryo cells; Rat embryo fibroblast	Tl_2CO_3	DNA damage/repair	Not tested	+	Zasukhina et al. 1981, 1983
Syrian hamster embryo cells/SA7	$TlC_2H_3O_2$	Enhancement of viral transformation	Not tested	+	Casto et al. 1979

+ = positive result; $TlC_2H_3O_2$ = thallium acetate; Tl_2CO_3 = thallium carbonate; $TlNO_3$ = thallium nitrate

cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by thallium are discussed in Section 2.5.2.

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, biologically effective dose,. or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Thallium

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. Typical thallium levels in unexposed individuals are below 1 μg/g creatinine (Schaller et al. 1980). Because of the quantitative renal excretion of creatinine and its rather consistent rate of production, creatinine constitutes an endogenous substance suitable for clearance testing. Higher values have been detected in areas where thallium is used or emitted. Urinary levels in cement workers ranged between <0.3 and 6.3 μg thallium/g creatinine (Schaller et al. 1980). A mean urinary thallium level of 76 μg/L was reported in a population living in the vicinity of a cement production plant (Brockhaus et al. 1981). Apostoli et al. (1988) reported mean urinary thallium levels of 0.38 and 0.33 μg/L in two groups of workers employed in two cement production plants and two cast iron foundries. Unexposed subjects showed lower mean levels CO.22 μg/L). Urinary levels in toxic cases may be 3,100 μg/L (Gastel 1978) and ≥ 5,000 μg/L in fatal cases (Roby et al. 1984).

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 thallium^{204} (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 thallium^{204} (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.

2.5.2 Biomarkers Used to Characterize Effects Caused by Thallium

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. Also, thallium 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). However, the usefulness of the data is reduced since the procedure is highly invasive.

2.6 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 1977a, 1978; Lehman and Favari 1985). Oral administration of activated charcoal and Prussian blue accelerated the elimination of orally administered thallium in rats (Lehman and Favari 1985; Lund 1956b). These agents adsorb thallium in the gastrointestinal tract, and are themselves unabsorbed, thus reducing gastrointestinal absorption of thallium.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Limited toxicity data suggest there are certain subgroups of the general population which may be more susceptible to thallium exposure than other

groups. People with preexisting neurological disease, kidney, and liver damage may be at risk.

Neurological injury is a major effect associated with exposure to thallium in humans (Cavanagh et al. 1974; Davis et al. 1981; Ludolph et al. 1986; Roby et al. 1984). In people with neurological damage of other etiology, thallium may add to or magnify the effect on the nervous system.

Other subgroups that are potentially more sensitive to thallium exposure are individuals with liver and kidney disease. In humans, necrosis of the liver with fatty changes and elevated serum enzymes have been observed (Cavanagh et al. 1974; Davis et al. 1981). Individuals with preexisting liver disease may sustain additional liver damage at lower than usual dose levels producing liver injury. Renal damage has also been associated with thallium exposure. Tubular necrosis and renal failure may occur (Cavanagh et al. 1974; Gastel 1978). In people with renal disease, there may be decreased capacity to excrete thallium. Also, individuals with potassium deficiency may be at risk since potassium has been shown to increase renal excretion of thallium (Gehring and Hammond 1967; Lund 1956a).

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to thallium. This section is intended to inform the public of existing clinical practice and the status of research concerning such methods. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to thallium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Exposure to thallium may occur by inhalation, ingestion, or dermal absorption, but ingestion appears to be the predominant route of exposure for humans (see Chapter 5). Thallium ingestion causes acute gastrointestinal symptoms and multiple systemic effects, including respiratory, neurological, cardiovascular, hepatic, and renal damage and alopecia (see Section 2.2).

Procedures that have been suggested following acute, high-level exposure to thallium consist of measures to reduce or eliminate further absorption. Following inhalation exposure, these measures are removal of the victim and administration of high-flow, humidified oxygen (Bronstein and Currance 1988; Stutz and Janusz 1988). Following dermal exposure, contaminated clothing is removed and skin thoroughly washed. Following ocular exposure, the eyes are. flushed (Bronstein and Currance 1988; Stutz and Janusz 1988). Treatment for acute, high-level oral exposure to thallium is designed to remove thallium from the gastrointestinal tract as quickly as possible, to prevent absorption of any remaining thallium and to increase excretion of thallium (Proctor et al. 1988). However, some of the methods recommended to accomplish these aims

are controversial. Emptying the stomach by gastric lavage or administration of syrup of ipecac has been suggested within the first few hours following exposure, if the victim is alert and has an intact gag reflex. Following gastric emptying, it has been suggested that serial doses of activated charcoal be administered to adsorb residual and rescreted thallium, and a mild cathartic also used to accelerate fecal excretion (Ellenhorn and Barceloux 1988; Stutz and Janusz 1988).

Prussian blue (potassium ferric ferrocyanide) binds with thallium in the intestine and neither the Prussian blue nor its complex with thallium is absorbed systemically. The oral or duodenal administration of this compound effectively prevents absorption and increases fecal excretion (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Proctor et al. 1988). However, this use of Prussian blue has not been approved by the U.S. Food and Drug Administration (FDA), but is approved for use in Europe (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990).

Oral administration of potassium chloride in large doses has been recommended in victims with intact renal function to enhance thallium clearance from tissue storage sites and increase renal excretion. However, there may be a transient worsening of symptoms following this treatment due to the redistribution of thallium from tissue stores into the serum, and there is some controversy concerning the efficacy of potassium chloride administration (Ellenhorn and Barceloux 1988; Proctor et al. 1988).

Hemodialysis or hemoperfusion may be beneficial in cases of severe poisoning. Hemodialysis has been found to be quite effective in reducing thallium concentrations in the blood in some cases and only minimally effective in others. Hemoperfusion may give better results than hemodialysis. These procedures may be used in cases where renal failure and paralytic bowel render other treatments ineffective (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Proctor et al. 1988).

It is unlikely that populations surrounding hazardous waste sites would be exposed to thallium at levels that would result in symptoms requiring any of these measures. Supportive follow-up medical care is likely to be the only treatment for long-term neurological effects of thallium exposure. Additional details regarding the treatment of acute, high-level thallium poisoning may be obtained from the cited references.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of thallium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP),

is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of thallium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Thallium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to thallium are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of thallium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

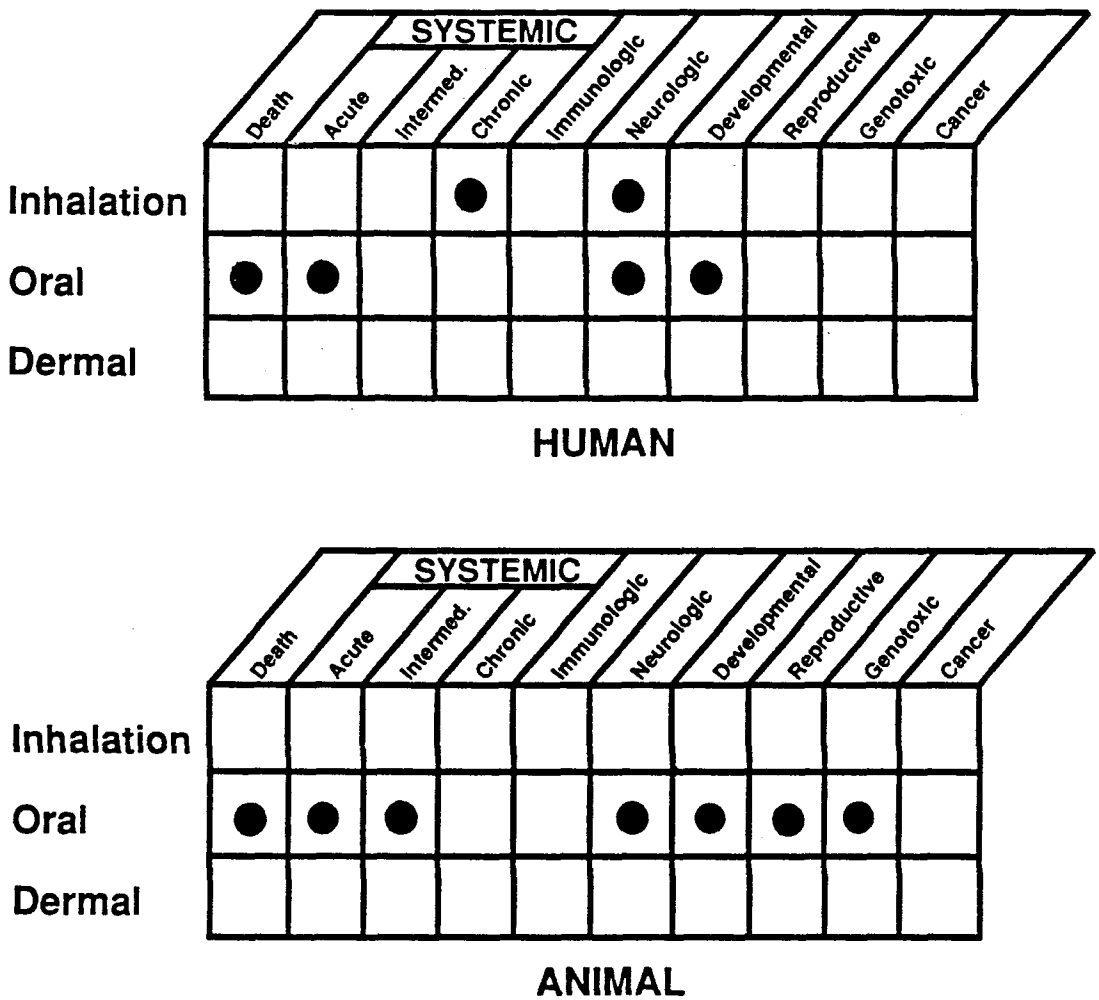
Most of the information concerning the health effects of thallium in humans is found in case reports of accidental or intentional acute ingestion of thallium. No information was found on effects after intermediate and chronic exposures. Reports of chronic inhalation exposure in the workplace exist; however, these are limited to sites outside the United States. No information was found on effects of thallium after acute and intermediate inhalation exposure or on effects after acute, intermediate, or chronic dermal exposures.

In animals, information exists on acute and intermediate oral exposures to thallium in several species. However, no studies were located regarding chronic oral exposures and on effects following acute, intermediate, and chronic inhalation or dermal exposures.

2.9.2 Data Needs

Acute-Duration Exposure. No studies were found on the adverse effects of acute-duration inhalation exposure in humans or animals. Inhalation is not likely to lead to significant exposure of the general population near hazardous waste sites. Thallium and compounds are not volatile and are subject to precipitation washout. The available information on effects of acute-duration exposure to thallium and compounds in humans is limited to case reports that indicate neurological, gastrointestinal, lung, liver, kidney, and heart effects following oral exposure (Cavanagh et al. 1976; Davis et al. 1982; deGroot et al. 1985; Roby et al. 1984). Some studies did not report

FIGURE 2-2. Existing Information on Health Effects of Thallium



reliable exposure data. Estimated dose levels were provided in other cases,but these doses far exceeded those expected to occur in the environment. Human exposure data were not sufficient to derive an acute oral MEL since reliable NOAEL and LOAEL values could not be determined. Since thallium binds tightly to soil particles, dermal contact may be significant, particularly in children who may ingest thallium-contaminated soil. Additional dermal studies would be useful to determine if soil-bound thallium is bioavailable. Acute oral data in animals demonstrated lethal (Downs et al. 1960) and developmental neurological effects (Bornhausen and Hagen 1984) of thallium, but data were not sufficient to derive an acute oral MEL. Additional studies in other species would be useful to identify the most sensitive effect and a doseresponse relationship following acute oral exposure to thallium. Information was not available to derive acute inhalation and dermal MRLs.

Intermediate-Duration Exposure. No studies are available on adverse health effects of intermediate-duration inhalation exposure in humans to thallium and compounds. Since thallium is not volatile, this route may not be a major concern to humans exposed near hazardous waste sites. No information is available on the effects of intermediate-duration inhalation exposure in animals. Limited oral studies in animals demonstrated neurological and reproductive effects (Formigli et al. 1986; Manzo et al. 1983). Data from these studies were not sufficient to derive an intermediate MEL. These studies employed one dose level, precluding dose-response evaluations. Additional oral studies employing other animal species and additional dose levels would be useful in identifying susceptible organs and intermediate-duration threshold for effects. There are no data on intermediate-duration exposure in humans or animals and toxicokinetics data are lacking. Additional studies would be useful in determining potential target organs and critical effects levels.

Chronic-Duration Exposure and Cancer. A few studies are available evaluating the effects on humans chronically exposed to thallium in workplace air (Ludolph et al. 1986; Marcus 1985). One study demonstrated that the nervous system is adversely affected by inhalation exposure (Ludolph et al. 1986); however, no exposure data are provided. In the absence of quantitative exposure data, available studies are not sufficient to derive a chronic-duration MRL. Because thallium is not volatile and is subject to precipitation washout from the atmosphere, exposure by this route may not be a major concern at hazardous waste sites. No studies are available on the effects of chronic oral or dermal exposure in humans or in animals by any route of exposure. Because long-term environmental exposure to thallium can occur in humans at hazardous waste sites, oral chronic animal studies of various species at several dose levels would be useful in identifying susceptible target organs and defining chronic thresholds.

No studies are available on the carcinogenic effects of inhalation, oral, or dermal exposure in humans or animals to thallium and compounds. Considering the positive results of the genotoxicity assays (Casto et al.

1979; Kanematsu et al. 1980; Zasukhina et al. 1981, 1983), studies to assess the carcinogenic potential would be useful. There are some populations in the vicinity of hazardous waste sites that might be exposed to low doses of thallium for long periods of time.

Genotoxicity. No information was available on the genotoxic effects of thallium and compounds in humans. Microbial and in vitro and in vivo mammalian assays evaluating DNA damage and repair were positive (Kanematsu et al. 1980). Additional in vivo studies evaluating structural and numerical chromosomal aberrations would be useful to confirm the genotoxic potential of thallium in humans.

Reproductive Toxicity. No epidemiological studies have been conducted in humans to establish a relationship between thallium exposure and adverse effects on reproduction. Subchronic oral studies in rats suggest that the testes may be susceptible (Formigli et al. 1986). These studies evaluated only one dose level precluding dose-response evaluations. Results of dominant lethal assays (Zasukhina et al. 1983) suggest thallium may act through a genotoxic mechanism resulting in adverse reproductive effects. Subchronic oral studies in other animal species evaluating various dose levels would be helpful in confirming potential reproductive effects and identifying a threshold for this effect.

Developmental Toxicity. No studies were found in humans on the developmental toxicity of thallium and compounds following inhalation exposure. As stated previously, inhalation exposure is not expected to be an important source of exposure in the general population living near hazardous waste sites. There is one human study involving the ingestion of contaminated homegrown vegetables (Dolgner et al. 1983). It failed to clearly establish any relationship between thallium exposure and occurrence of developmental effects. Animal studies show that thallium can cross the placenta by the parenteral route (Olsen and Jonsen 1982; Rade et al. 1982) and suggest that it is a developmental, neurological toxicant by the oral route (Bornhausen and Hagen 1984). While data are limited on thallium-induced alterations on the functional competence of the nervous system, it should be noted that these effects were reported to occur at dose levels below those at which other neurological effects occurred. Additional animal studies involving other species and employing various dose levels by oral exposure during critical developmental periods would be helpful in confirming this effect and determining a threshold level for this effect. Since dermal exposure through soil contact may be a significant source of exposure in children living near hazardous waste sites, studies are needed to determine if soil-bound thallium is bioavailable.

Immunotoxicity. No studies were located regarding immunotoxicity in humans or animals following inhalation, oral or dermal exposures. Since subchronic studies do not suggest the immune system is a target, additional studies are not essential at this time.

Neurotoxicity. Clinical neurological signs as well as histological lesions in cranial and peripheral nerves have been demonstrated in humans following inhalation (Ludolph et al. 1986) or oral (Cavanagh et al. 1974; Davis et al. 1981; Dai-xing and Ding-nan 1985; Roby et al. 1984) exposure. Exposure levels were not provided or if available, levels far exceeded those expected to occur in the environment. No studies are available on effects following dermal exposure. Structural and functional changes in peripheral nerves in animals following oral exposure (Manzo et al. 1983) confirm findings in humans. Since studies evaluated only one dose level and one additional study using multiple doses did not demonstrate neurological effects (Stoltz et al. 1986), data gaps exist relative to dose-response relationships for this target tissue. Additional oral studies would be useful in identifying a threshold for this effect. Further, parenteral studies in animals demonstrated biochemical changes in various parts of the brain suggesting a doserelated selective toxicity between brain regions (Brown et al. 1985; Hasan et al. 1977a,b, 1978; Rios et al. 1989). Additional animal studies to evaluate preferential deposition of thallium in certain brain regions would be useful in confirming the extent of neurological damage induced by thallium.

Epidemiological and Human Dosimetry Studies. Epidemiological studies evaluating the potential health effects of thallium are limited. One study reported peripheral neuropathy in a group of cement workers exposed to thallium (Ludolph et al. 1986). The relative usefulness of this study is limited since an unexposed control group was not evaluated, exposure concentrations were not reported, and the study population was small. Since thallium is nonvolatiie, inhalation exposure may not be a major concern near hazardous waste sites. However, there is potential for oral exposure. Long-term epidemiological studies by the oral route evaluating low-dose exposure would be useful in characterizing the nature of organ changes produced by thallium. Since neurological effects are well characterized, these studies should consider reproductive effects based on animal data suggesting that the male organs are susceptible to thallium toxicity (Formigli et al. 1986).

Biomarkers of Exposure and Effect. The presence of thallium in urine is the most reliable biomarker of exposure. The metal can be detected in urine more than several days after exposure (Brockhaus et al. 1981; Schaller et al. 1980).

Alopecia and changes in the nervous system are characteristic of thallium exposure (Dai-zing and Ding-nan 1985; Gastel 1978; Grunfeld and Hinostroza 1964; Ludolph et al. 1986). Electromyographic measurements of nerve conduction velocity and amplitude can be monitored to detect early signs of neurotoxicity in people exposed to thallium. While such tests are not specific for thallium-induced toxicity, they do identify potential health impairment. Studies to develop more specific biomarkers of thallium-induced effects would be useful in assessing the potential health risk of thallium exposure near hazardous waste sites.

Absorption, Distribution, Metabolism, and Excretion. No quantitative information is available on absorption of thallium in humans or animals by inhalation or dermal exposure. However, animal studies following intratracheal administration suggested that uptake through respiratory epithelium was rapid and complete (Lie et al. 1960). Data regarding absorption in humans are limited. In one study in which a patient with terminal osteogenic sarcoma was given a single oral dose of thalliumzo4, complete absorption was suggested based on an increased urinary radioactivity over a 72-hour period (Barclay et al. 1953). Additional oral studies that provide data on rate and extent of absorption would be useful since this appears to be the primary exposure route. In one study in which rats were administered radiolabel thallium nitrate by oral exposure, body burden of radioactivity was expressed as a percent of administered dose over time, suggesting virtually complete and rapid uptake by this route (Lie et al. 1960).

No information was found on the distribution of thallium following inhalation or dermal exposure. There are a few studies by oral exposure, which indicate that thallium is found in many tissues of the body (Barclay et al. 1953). Data in humans reported tissue levels are highest in the scalp hair, kidney, heart, bone, and spleen. Lower levels were found in the brain (Barclay et al. 1953). Animal studies confirmed that thallium is widely distributed (Downs et al. 1960; Grunfeld et al. 1963; Lie et al. 1960). However, in animals, thallium is chiefly distributed to the kidneys and liver. Additional studies are needed as a basis for understanding species differences in distribution of thallium. Data exist suggesting that thallium can cross the placental barrier by parenteral administration (Olsen and Jonsen 1982; Rade et al. 1982). However, in human studies evaluating developmental toxicity, the increase of congenital malformation and anomalies in the exposed group did not exceed the number of expected defects in the general population (Dolgner et al. 1983). Additional animal studies by the oral route would be useful in confirming that thallium can locate in the fetus and providing a basis for assessing if there is potential human health risk.

No information is available on the metabolism of thallium. Additional studies are needed to determine if thallium is transformed in the body and would provide a basis for understanding target organ toxicity.

No data are available on excretion of thallium in humans or animals by inhalation or dermal exposure. There are data on excretion in humans and animals by oral exposure. In one study in which a patient was administered radiolabel thallium nitrate, one half of the radioactivity was detected in the urine 21.7 days after exposure, suggesting that thallium is slowly excreted from the body (Barclay et al. 1953). In animals, excretion is more rapid (e.g., half in 3.3 days) and occurs primarily via feces (Lehman and Favan 1985; Lie et al. 1960). Additional studies of other animal species by all routes of exposure would be useful in clarifying differences in excretion patterns.

Comparative Toxicokinetics. Since human and animal toxicokinetics data are limited, very little data exist on comparative kinetics across species. Human data are limited to one study (Barclay et al. 1953) and animal data are primarily in rats (Downs et al. 1960; Lehman and Favan 1985; Lie et al. 1960). These data suggest some kinetics differences, particularly in distribution and excretion patterns. Additional studies using other animal species would be useful in clarifying species differences.

Mitigation of Effects. Recommended methods for the mitigation of the acute effects of thallium poisoning involve prevention of thallium absorption from the gastrointestinal tract by administration of emetics, cathartics, and/or binding agents and removal of absorbed thallium from the serum by hemodialysis or hemoperfusion or by administration of potassium chloride (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Proctor et al. 1988). No information was located concerning mitigation of effects of lower-level or longer-term exposure to thallium. Further information on techniques to mitigate such effects would be useful in determining the safety and effectiveness of possible methods for treating thallium-exposed populations surrounding hazardous waste sites.

2.9.3 On-going Studies

A number of research projects are in progress investigating the toxicity of thallium. These projects are summarized in Table 2-3.

TABLE 2-3. On-going Studies on the Health Effects of Thallium

Investigator	Affiliation	Research description	Sponsoring agency
S. J. Adelstein	Shields Warren Radiation Lab	The kinetics of uptake and intracellular microscopic distribution of thallium radiolabeled with Auger emitters will be measured in cell culture and their relationship to biological effects determined. Cytogenetic effects, transformation, and mutagenesis will also be scored in cell cultures exposed to Auger and alpha emitters.	NIH
B. J. Hoffer	University of Colorado, Denver	The effects of chronic perinatal and acute exposure on the histological organization and electrophysiological function in selected areas of the brain will be studied. These studies may provide some insight into the mechanism of thallium-induced neurotoxicity.	NIH, NIEHS
B. Weiss	University of Rochester	Thallium levels in various tissues in rats exposed to thallium in drinking water and subsequently treated with diethyldithiocarbamate will be determined. Behavioral measures, derived from a modified running wheel apparatus, will be used to trace the appearance of neurotoxicity.	NIH

NIH = National Institutes of Health; NIEHS = National Institute of Environmental Health Sciences