TOXICOLOGICAL PROFILE FOR THALLIUM

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

July 1992

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

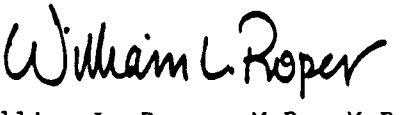
The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about thallium and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). Thallium has been found in at least 18 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for thallium. As EPA evaluates more sites, the number of sites at which thallium is found may change. This information is important for you to know because thallium may cause harmful health effects and because these sites are potential or actual sources of human exposure to thallium.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as thallium, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS THALLIUM?

Pure thallium is a soft, bluish-white metal that is widely distributed in trace amounts in the earth's crust. In its pure form, it is odorless and tasteless. It can be found in pure form or mixed with other metals in the form of alloys. It can also be found combined with other substances such as bromine, chlorine, fluorine, and iodine to form salts. These combinations may appear colorless to white or yellow. Thallium remains in the environment since it is a metal and cannot be broken down to simpler substances.

Thallium exists in two chemical states (thallous and thallic). The thallous state is the more common and stable form. Thallous compounds are the most likely form to which you would be exposed in the environment. Thallium is present in air, water, and soil. We do not know how much time it takes for thallium to move from one medium to another.

Thallium is used mostly in the manufacture of electronic devices, switches, and closures. It also has limited use in the manufacture of special glasses and for medical procedures that evaluate heart disease. Up until 1972 thallium was used as a rat poison, but was then banned because of its potential harm to man. Thallium is no longer produced in the United States.

All the thallium used in the United States since 1984 has been obtained from imports and thallium reserves.

More information on the properties and uses of thallium and how it behaves in the environment may be found in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO THALLIUM?

You can be exposed to thallium in air, water, and food. However, the levels of thallium in air and water are very low. The greatest exposure occurs when you eat food, mostly home-grown fruits and green vegetables contaminated by thallium. Small amounts of thallium are released into the air from coal-burning power plants, cement factories, and smelting operations. This thallium falls out of the air onto nearby fruit and vegetable gardens. Thallium enters food because it is easily taken up by plants through the roots. Very little is known on how much thallium is in specific foods grown or eaten. Cigarette smoking is also a source of thallium. People who smoke have twice as much thallium in their bodies as do nonsmokers. Although fish take up thallium from water, we do not know whether eating fish can increase thallium levels in your body. It has been estimated that the average person eats, on a daily basis, 2 parts thallium per billion parts (ppb) of food. Even though rat poison containing thallium was banned in 1972, accidental poisonings from old rat poison still occur, especially in children.

Thallium is produced or used in power plants, cement factories, and smelters. People who work in these places can breathe in the chemical or it may come in contact with their skin. Information on the amount of thallium in workplace air in the United States could not be found. Hazardous waste sites are also possible sources of exposure to thallium. An average of 23 ppb of thallium in surface water and 11 ppb in groundwater have been found at hazardous waste sites. Since thallium compounds mix easily in water, you can be exposed if you live near a chemical waste site where thallium emissions have contaminated the water. An average of 1.7 parts of thallium per million parts (ppm) of soil was found at hazardous waste sites. Since thallium sticks to soil, you can be exposed at hazardous waste sites if you swallow or touch contaminated soil. Thallium-contaminated dust in the air can also be swallowed after it is cleared from the lungs. Thallium is naturally found in soil at levels from 0.3 to 0.7 ppm.

More information on how you might be exposed to thallium is given in Chapter 5.

1.3 HOW CAN THALLIUM ENTER AND LEAVE MY BODY?

Thallium can enter your body when you eat food or drink water contaminated with thallium, breathe thallium in the air, and when your skin comes in contact with it. When thallium is swallowed most of it is absorbed and rapidly goes to various parts of your body, especially the kidney and

liver. Thallium leaves your body slowly. Most of the thallium leaves your body in urine and to a lesser extent in feces. It can be found in urine within 1 hour after exposure. After 24 hours, increasing amounts are found in feces. It can be found in urine as long as 2 months after exposure. About half the thallium that enters various parts of your body leaves them within 3 days.

The significant, likely routes of exposure near hazardous waste sites are through swallowing thallium-contaminated soil or dust, drinking contaminated water, and skin contact with contaminated soil. More information on how thallium enters and leaves the body is given in Chapter 2.

1.4 HOW CAN THALLIUM AFFECT MY HEALTH?

Thallium can affect your nervous system, lung, heart, liver, and kidney if large amounts are eaten or drunk for short periods of time. Temporary hair loss, vomiting, and diarrhea can also occur and death may result after exposure to large amounts of thallium for short periods. Thallium can be fatal from a dose as low as 1 gram. No information was found on health effects in humans after exposure to smaller amounts of thallium for longer periods. Birth defects observed in children of mothers exposed to small amounts of thallium did not occur more often than would be expected in the general population. The length of time and the amount of thallium eaten by the mothers are not known exactly. As in humans, animal studies indicate that exposure to large amounts of thallium for brief periods of time can damage the nervous system and heart and can cause death. Animal reproductive organs, especially the testes, are damaged after drinking small amounts of thallium-contaminated water for 2 months. These effects have not been seen in humans. No information was found on effects in animals after exposure to small amounts of thallium for longer periods of time. No studies were found on whether thallium can cause cancer in humans or animals.

More information on the health effects of thallium in humans and animals can be found in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO THALLIUM?

Reliable and accurate ways to measure thallium in the body are available. The presence of thallium in the urine and hair can indicate exposure to thallium. Tests of your urine can detect thallium up to 2 months. The normal amount of thallium in human urine amounts to less than 1 ppm and 5-10 ppb in human hair. Although thallium can be measured in blood, this tissue is not a good indicator of exposure since thallium stays there too short a time. We do not know yet whether thallium levels measured in the body can be used to predict possible health effects.

More information on how thallium can be measured in exposed humans is presented in Chapters 2 and 6.

1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has set standards and guidelines to protect individuals from the possible effects of excessive thallium exposure. The EPA has determined a water quality criteria level of 13 ppb in surrounding waters to protect humans from the harmful effects of drinking water and eating food containing thallium.

The Occupational Safety and Health Administration (OSHA) has established an occupational limit of 0.1 mg of soluble thallium compounds per cubic meter of workplace air (mg thallium/m^3/skin) for an 8-hour workday over a 40-hour workweek. "Skin" indicates that measures must be taken to prevent skin exposure to thallium.

Additional information on governmental regulations regarding thallium can be found in Chapter 7.

1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

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.

2. HEALTH EFFECTS

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

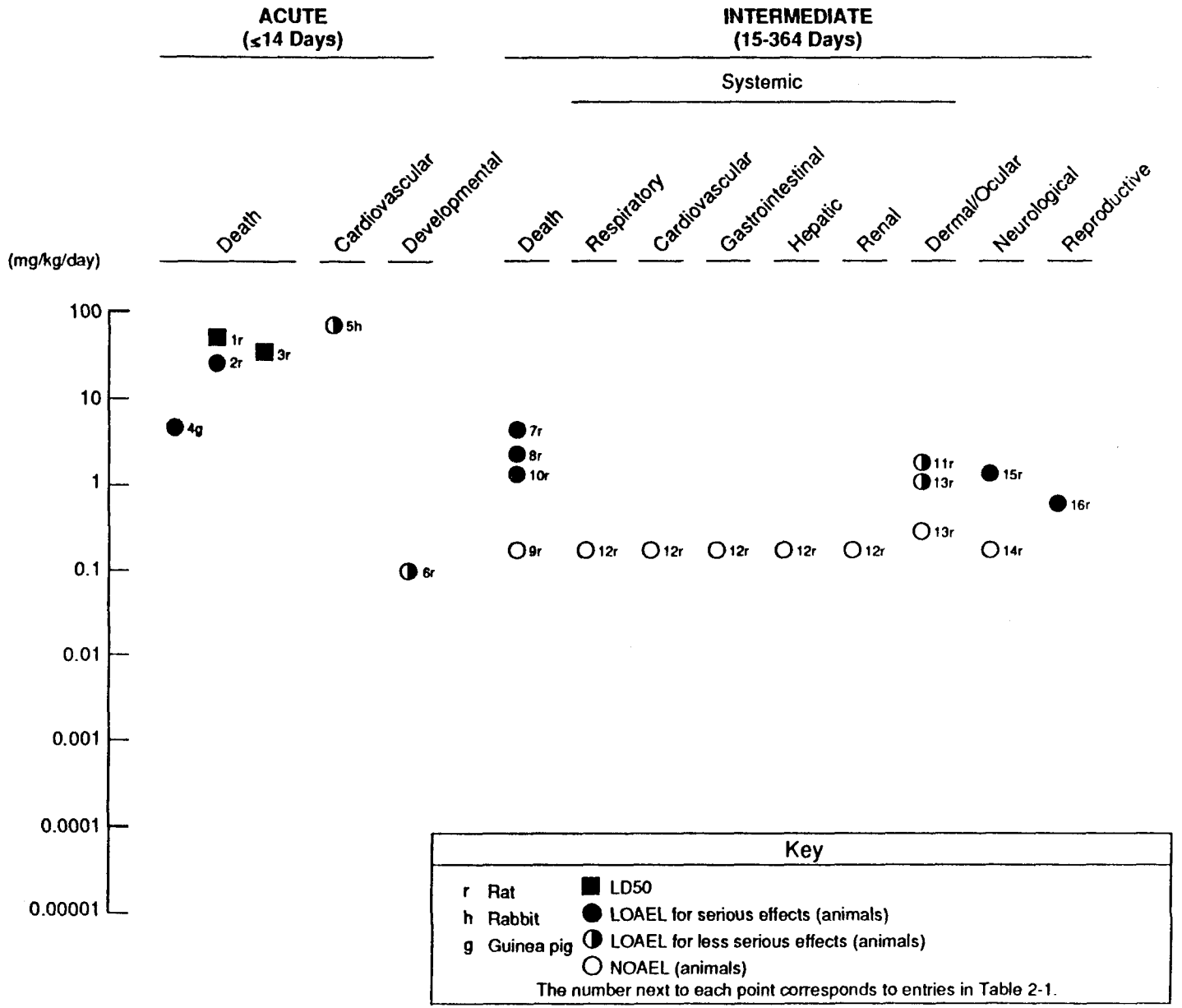
TABLE 2-1 (Continued)

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



2. HEALTH EFFECTS

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 BIOMARKERS 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).

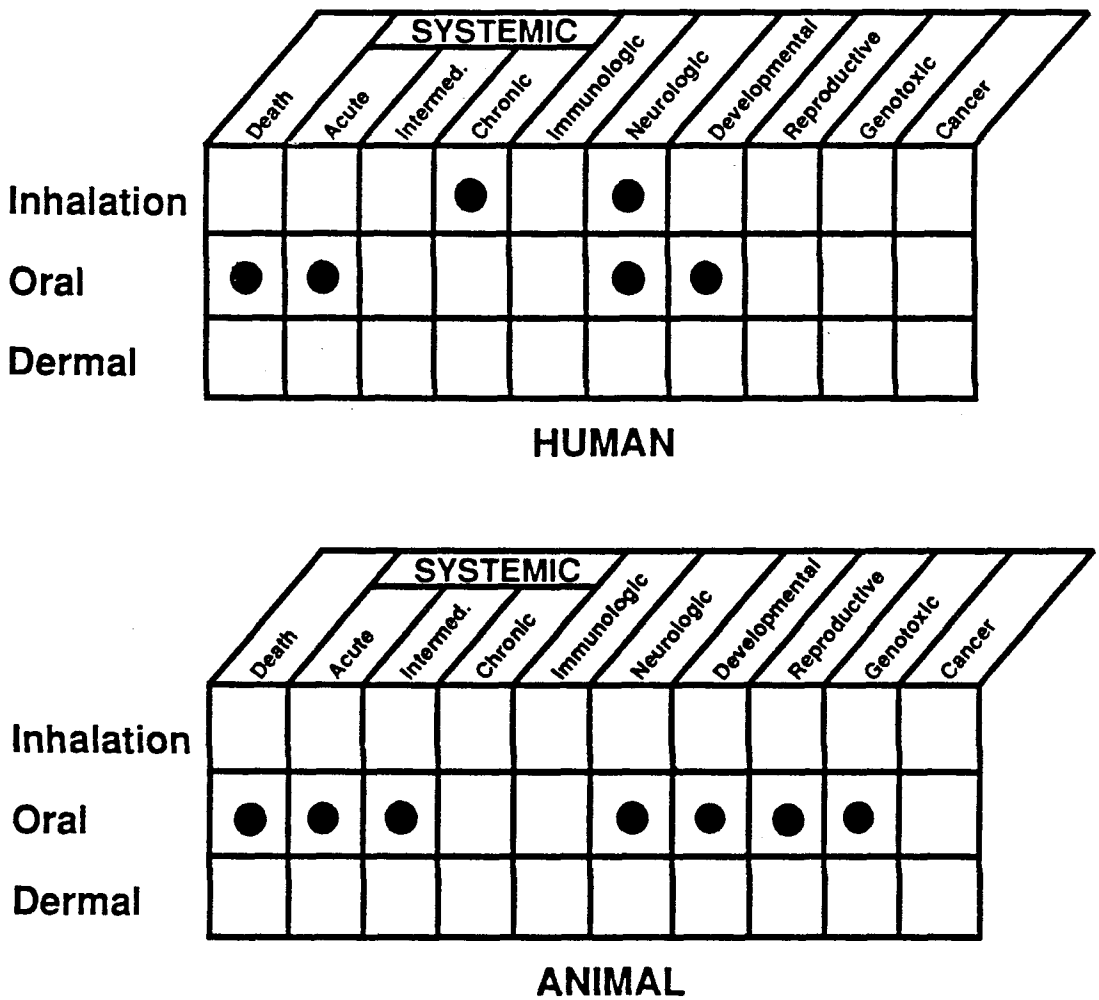
Most of the information concerning the health effects of thallium in humans is found in case reports of accidental or intentional acute ingestion of thallium. No information was found on effects after intermediate and chronic exposures. Reports of chronic inhalation exposure in the workplace exist; however,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

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Table 3-1 lists common synonyms, trade names, and other pertinent identification information for thallium and a number of thallium compounds.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of thallium and selected thallium compounds.

TABLE 3-1. Chemical Identity of Thallium and Compounds[a]

Characteristic	Thallium	Thallium acetate	Thallium chloride	Thallium nitrate	Thallium oxide	Thallium sulfate
Synonyms	Ramor[b]	Thallous acetate; thallium (1+) salt	Thallic chloride	Thallous nitrate; nitric acid, thallium (1+) salt	Thallic oxide	Thallous sulfate
Trade name	No data	No data	No data	No data	No data	No data
Chemical formula	Tl	$TlC_2H_3O_2$	$TlCl_3$	$TlNO_3$	Tl_2O_3	Tl_2SO_4
Chemical structure	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable
Identification numbers:						
CAS Registry	7440-28-0	563-68-8	13453-32-2	10102-45-1	1314-32-5	7416-18-6
NIOSH RTECS	XG3425000[c]	AJ5425000[c]	No data	XG5950000[c]	XG2975000[c]	No data
EPA Hazardous Waste	No data	V214[b]	No data	V217[b]	P113[b]	No data
OHM/TADS	7216925[b]	7217306[b]	No data	No data	No data	No data
DOT/UN/NA/ IMCO Shipping	UN1707[b] IMCO 6.1[b]	UN1707[b] IMCO 6.1[b]	No data No data	UN2727[b] IMCO 6.1[b]	UN1707[b] IMCO 6.1[b]	No data No data
HSDB	4496[b]	855[b]	No data	No data	6055[b]	No data
NCI	No data	No data	No data	No data	No data	No data

TABLE 3-1 (Continued)

Characteristic	Thallium carbonate	Thallium bromide	Thallium iodide	Thallium fluoride
Synonyms	Thallous carbonate; carbonic acid; dithallium carbonate	Thallium monobromide; thallous bromide	Thallous iodide	Thallum monofluoride; Thallous fluoride
Trade name	No data	No data	No data	No data
Chemical formula	Tl_2CO_3	TlBr	TlI	TlF
Chemical structure	Not Applicable	Not Applicable	Not Applicable	Not Applicable
Identification numbers:				
CAS Registry	6533-73-9	7789-40-0	7790-30-9	7789-27-7
NIOSH RTECS	XG4000000[c]	XG3850000[c]	XG5425000[c]	XG4900000[c]
EPA Hazardous Waste	V215[b]	No data	No data	No data
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/ IMCO Shipping	UN1707[b] IMCO6.1[b]	No data No data	No data No data	No data No data
NCI	No data	No data	No data	No data

[a]All information obtained from EPA 1988a, except where noted.
[b]HSDB 1989
[c]Sax 1984

CAS = Chemical Abstracts Service
DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code
EPA = Environmental Protection Agency
HSDB = Hazardous Substances Data Bank
NCI = National Cancer Institute
NIOSH = National Institute for Occupational Safety and Health
OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System
RTECS = Registry of Toxic Effects of Chemical Substances

TABLE 3-2. Physical and Chemical Properties of Thallium and Compounds[a]

Property	Thallium	Thallium acetate	Thallium chloride	Thallium nitrate	Thallium oxide	Thallium sulfate
Molecular weight	204.38	263.43	310.74	266.39	456.76	504.82
Color	Blush-white	White	White[b]	White[b]	Colorless	Colorless
Physical state	Metal	Solid	Solid	Solid	Solid	Solid
Melting point	303.5°C	131°C	25°C	206°C[c]	717±5°C	632°C
Boiling point	1457±10°C	No data	Decomposes	430°C[c]	-20 at 875°C	Decomposes[c]
Density at 20°C	11.85	3.76 at 137°C	No data	5.5[b]	9.65-10.19 at 21°C	6.77
Odor	Odorless[d]	Odorless[d]	No data	Odorless[d]	No data	No data
Odor threshold:						
Water	No data	No data	No data	No data	No data	No data
Air	No data	No data	No data	No data	No data	No data
Solubility:						
Water at 20°C	Insoluble	Very soluble	Very soluble	95.5 g/L	Insoluble	48.7 g/L
Organic solvents	Soluble in nitric or sulfuric acid,	Very soluble in alcohol; insoluble in acetone	Soluble in alcohol and ether	Insoluble in alcohol; Soluble in acetone	Soluble in acids; Insoluble in alkalies	No data
Partition coefficients:						
Log octanol/water	No data	No data	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data	No data	No data
Vapor Pressure at 1000°C	10 mmHg[c]	No data	No data	No data	No data	No data
Henry's law constant	No data	No data	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data	No data	No data

TABLE 3-2 (Continued)

Property	Thallium carbonate	Thallium bromide	Thallium iodide	Thallium fluoride
Molecular weight	468.78	284.29	331.29	223.38
Color	Colorless	Yellowish-white	Yellow red (at 170°C)	Colorless
Physical state	Solid	Solid	Solid	Solid
Melting point	273°C	480°C	440°C[c]	327°C
Boiling point	No data	815°C	824°C[c]	655°C
Density at 20°C	7.11	7.56 at 17.3°C	7.29	8.23 at 4°C
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 20°C	40.3 g/L at 15.5°C	0.5 g/L at 25°C	0.006 g/L	786 g/L at 15°C
Organic solvents	Insoluble in alcohol, ether, and acetone	Soluble in alcohol, insoluble in acetone	Insoluble in alcohol, slightly soluble in nitric acid	Slightly soluble in alcohol
Partition coefficients:				
Log octanol/water	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor Pressure at 1000°C	No data	10 mmHg at 517°C[c]	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data

[a]All information obtained from Weast 1985, except where noted.
[b]Windholz 1983
[c]EPA 1988a
[d]HSDB 1989

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

The domestic production of thallium ceased in 1981. Prior to this, thallium had been recovered as a byproduct from the flue dust and residuals that resulted from the smelting of zinc, copper, and lead ores through treatment by electrolysis, precipitation, or reduction (HSDB 1989; Sax and Lewis 1987; U.S. Bureau of Mines 1983, 1988). Based upon the estimated thallium content of zinc ores, United States mine production of thallium was 0.45 metric tons in 1986 and 1987 and 14.06 metric tons in the rest of the world (U.S. Bureau of Mines 1983, 1988). No data were located regarding the production of thallium acetate, thallium nitrate, thallium chloride, thallium sulfate or thallium oxide.

There are six facilities in the United States that either import thallium, use thallium and its compounds in manufacturing processes, or produce them as byproducts. These facilities are listed in Table 4-1.

4.2 IMPORT/EXPORT

Currently all thallium used in the United States is obtained from thallium reserves or is imported. The combined import of thallium and thallium compounds ranged from 1.27 metric tons in 1983 to 2.04 metric tons in 1987. Between 1983-1986 the countries from which thallium and thallium compounds were imported were Belgium (54%), the Netherlands (16%), the Federal-Republic of Germany (14%), the United Kingdom (6%), and other sources (10%) (U.S. Bureau of Mines 1988).

No information was located regarding the export of thallium or thallium compounds.

4.3 USE

Today's primary user of thallium is the semiconductor industry which in 1987 used 60%-70% of total U.S. thallium imports in its production of switches and closures. The remainder of thallium used was in the pharmaceutical industry to produce thallium for cardiac imaging, and to manufacture highly refractive optical glass (HSDB 1989; U.S. Bureau of Mines 1988; Windholz 1983).

Thallium compounds have a variety of uses. Thallium sulfate is used in the semiconductor industry and in low range thermometers, optical systems, and photoelectric cells, and as a chemical intermediate for other thallium compounds and thallium metals (HSDB 1989). Thallium acetate is used to prepare solutions of high specific gravity for use in separating ore constituents by flotation (HSDB 1989). Thallium chloride is used as a catalyst in chlorination (Windholz 1983). Thallium nitrate is used with other

TABLE 4-1. Facilities That Manufacture or Process Thallium and Compounds[a]

Facility	Location	Maximum Amount on site (lbs)	Use
Philips Industries, Inc., Dexter Axle Div	Albion, IN	10,000-99,999	Import; as a manufacturing aid
Tenneco Oil Company	Chalmette, LA	0-99	As a processing aid
Koch Refining Company	Saint Paul, MN	1,000-9,999	As an impurity
River Cement Company	Festus, MO	100,000,000-499,999,999	As a reactant
Sohio Oil Company Toledo Refinery	Oregon, OH	100-999	As an impurity
Dana Corporation	Reading, PA	0-99	As an impurity

[a]Derived from TRI 1989

compounds and resins for use as signals at sea. It is also used in the production of low melting glass, photocells, fireworks and as an oxidizing agent in organic syntheses (HSDB 1989; Weast 1985). Thallium oxide is used in the manufacture of highly refractive glass and for the production of artificial gems (Windholz 1983). Thallium and compounds were once used as a pesticide for control of rodents and insects, but the use of thallium as a pesticide was banned in 1972 (EPA 1985b).

4.4 DISPOSAL

Thallium is listed as a hazardous substance, therefore, disposal of waste thallium is controlled by a number of federal regulations, including land disposal restrictions (see Chapter 7). Industries producing or using thallium reported off-site waste transfers of about 40,000 pounds of thallium in 1987 (TRI 1989). Land disposal restrictions were implemented by EPA in 1987. Prior to this time disposal of pesticides had been to municipal and industrial landfills. Since thallium is relatively stable in the environment, we can assume that landfills, as well as other superfund sites, contain thallium or thallium-containing products.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Thallium is a heavy metallic element that exists in the environment mainly combined with other elements (primarily oxygen, sulfur, and the halogens) in inorganic compounds. Thallium is quite stable in the environment, since it is neither transformed nor biodegraded.

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

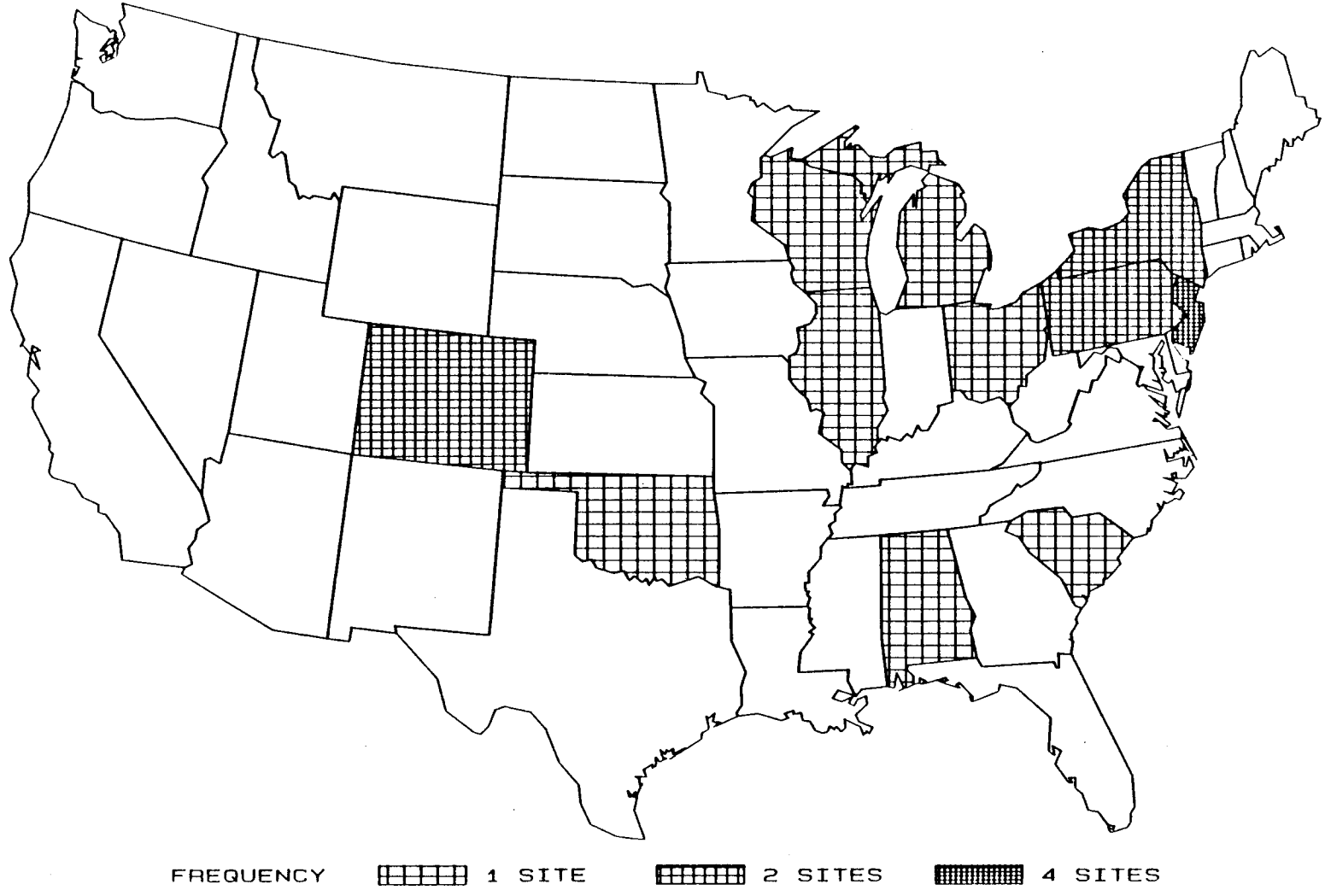
Major releases of thallium to the environment are from processes such as coal-burning and smelting, in which thallium is a trace contaminant of the raw materials, rather than from facilities producing or using thallium compounds. Humans may be exposed to thallium by ingestion, inhalation, or dermal absorption. However, the general population is exposed most frequently by ingestion of thallium-containing foods, especially home-grown fruits and green vegetables. Inhalation of contaminated air near emission sources or in the workplace may also contribute to thallium exposure of some individuals.

The EPA has identified 1,177 NPL sites. Thallium has been found at 18 of the sites evaluated for this chemical. However, we do not know how many of the 1,177 sites have been evaluated for this chemical. As more sites are evaluated, these numbers may change (View 1989). The frequency of these sites within the United States can be seen in Figure 5-1. Seventeen sites are located in the United States and 1 site is located in the commonwealth of Puerto Rico (not shown).

5.2 RELEASES TO THE ENVIRONMENT

Manufacturers, processors, and users of thallium and thallium compounds are required to report quantities of releases of these substances to environmental media annually (EPA 1988c). According to the SARA Section 313 Toxics Release Inventory (TRI), an estimated total of 56,511 pounds of thallium were released to the environment from manufacturing and processing facilities in the United States in 1987 (Table 5-1) (TRI 1989). The TRI data should be used with caution since the 1987 data represent first-time reporting by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list. However, the major sources of

FIGURE 5-1. FREQUENCY OF NPL SITES WITH THALLIUM CONTAMINATION *



* Derived from View 1989

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process Thallium and Compounds[a]

Facility	Location	Total (lbs)						
		Air	Underground injection	Water	Land	Environment	POTW[b] transfer	Off-site transfer
Philips Industries, Inc., Dexter Axle Div	Albion, IN	54,411	0	0	0	54,411	0	39,639
Tenneco Oil Company	Chalmette, LA	0	No Data	0	0	0	No Data	3
Koch Refining Company	Saint Paul, MN	0	0	1,100	0	1,100	No Data	0
River Cement Company	Festus, MO	250	0	0	0	250	0	0
Sohio Oil Company Toledo Refinery	Oregon, OH	0	0	750	0	750	0	0
Dana Corporation	Reading, PA	No Data	No Data	No Data	0	No Data	0	250
Totals		54,661	0	1850	0	56511	0	39892

[a]Derived from TRI 1989
[b]POTW -- publicly-owned treatment works

thallium releases to the environment are not from facilities that produce or use thallium and its compounds, but from processes such as coal-burning or smelting in which thallium is a trace element of the raw materials (Schoer 1984). Data on thallium emissions from these sources are not included in the TRI.

5.2.1 Air

Thallium is released to the atmosphere mainly from coal-burning power plants, cement factories, and ferrous and nonferrous smelting operations (EPA 1988a; Ewers 1988; Sharma et al. 1986). Thallium emissions in the United States were estimated at 140 tons/year each from coal-burning power plants and from iron and steel production (Ewers 1988; Schoer 1984; Smith and Carson 1977). Total air releases reported from industrial sources were about 27 tons in 1987 (TRI 1989).

Davison et al. (1974) reported concentrations of thallium on airborne fly ash emitted from a coal-burning power plant ranging from 29 to 76 μg/g, the thallium concentration increasing with decreasing particle size. The highest concentrations (greater than 60 μg/g) were on particles less than 7.3 μm in diameter. The authors reported that these concentrations were representative of eight other United States power plants burning various types of coal. The highest thallium concentrations were also found on the smaller diameter (0.2 – 0.8 μm) particles of fly dust emitted from a West German cement plant (Ewers 1988).

No quantitative estimates of thallium emissions from other domestic sources were located. However, additional sources of airborne thallium may include manufacturers of alloys, artificial gems, electronics equipment, optical glass, and domestic heating plants (EPA 1987a; Sharma et al. 1986; Valerio et al. 1988).

5.2.2 Water

The major sources of thallium releases to water include nonferrous metals, iron and steel manufacturers and various mining, inorganic chemicals, refining, and ore-processing industries (EPA 1980a, 1983c; Ewers 1988). Thallium concentrations in raw or treated waste waters from these industries ranged up to 2 g/L (EPA 1983c). Thallium has been detected in urban waste waters, apparently from commercial and industrial sources (Callahan et al. 1979a; Levins et al. 1979). Total water releases reported from industrial sources were 1,850 pounds in 1987 (TRI 1989). Thallium has been detected in both surface and groundwater samples at hazardous waste sites. Data from the Contract Laboratory Program (CLP) Statistical Database indicate that thallium occurred in surface water at 1% of sites at a geometric mean concentration of 23 ppb in positive samples and in groundwater at 7% of sites at a mean concentration of 11 ppb in positive samples (CLPSD 1989). Note that the Contract Laboratory Program (CLP) Statistical Database includes data from both

NPL and non-NPL sites. No other quantitative estimates of total thallium releases to water were located.

5.2.3 Soil

Thallium releases to soil are mainly solid wastes from coal combustion and smelting operations (Ewers 1988). Thallium was detected at a geometric mean concentration of 1.7 ppm in positive soil samples from 3.5% of an unspecified number of hazardous waste sites (CLPSD 1989). Although direct soil releases are likely to be small, since thallium-containing wastes are subject to EPA land disposal restrictions, atmospheric thallium pollution may contribute to soil contamination in the vicinity of thallium emission sources (Brockhaus et al. 1981). It should be noted that land disposal restrictions were implemented by EPA in 1987. Prior to this time disposal of pesticides had been to municipal and industrial landfills. Since thallium is relatively stable in the environment, we can assume that landfills, as well other Superfund sites, contain thallium or thallium-containing products.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Thallium is a nonvolatile heavy metal, and if released to the atmosphere by anthropogenic sources, may exist as an oxide (thallium oxide), hydroxide (TlOH), sulfate (thallium sulfate), or as the sulfide Tl_2S (EPA 1988a). These thallium compounds are not volatile (EPA 1983c; Weast 1970). It has been speculated that thallium sulfate and TlOH will partition into water vapor (such as clouds and rain drops) because they are soluble in water and thus, precipitation may remove these forms of thallium from the atmosphere (EPA 1988a). Thallium oxides are less soluble in water, and may be subject to only atmospheric dispersion, and gravitational settling. No corroborative information was located. The atmospheric half-life of suspended thallium particles is unknown.

Thallium exists in water primarily as a monovalent ion (thallium$^+$); thallium may be trivalent (Tl^{3+}) in very oxidizing water (Callahan et al. 1979b). Tl^+ forms complexes in solution with halogens, oxygen, and sulfur (Lee 1971). Thallium may precipitate from water as solid mineral phases. However, thallium chloride, sulfate, carbonate, bromide, and hydroxide are very soluble in water. For example, the solubility of thallium sulfate at 0°C is about 27 g/L (EPA 1980a). In extremely reducing water, thallium may precipitate as a sulfide (Tl_2S), and in oxidizing water, Tl^{3+} may be removed from solution by the formation of $Tl(OH)_3$ (Lee 1971). Stephenson and Lester (1987a, 1987b) argued that the partial removal of thallium from water was the result of precipitation of unknown solids during the treatment of sewage sludge.

5. POTENTIAL FOR HUMAN EXPOSURE

Thallium may partition from water to soils and sediments. Mathis and Kevern (1975) presented indirect evidence that thallium was adsorbed by lake sediments. Furthermore, thallium may be adsorbed by micaceous clays in solution (Frantz and Carlson 1987).

Partition coefficients such as adsorption constants describe the tendency of a chemical to partition to solid phases from water. Adsorption constants for inorganic ions such as Tl+ cannot be predicted a priori, but must be measured for each adsorbent. Thallium adsorption data in Magorian et al. (1974) for a hectorite clay (a rare montmorillonite clay mineral) at pH 8.1 suggest that an adsorption constant for this specific system may be approximately 19 L/g. No other information on the adsorption of thallium by earth materials was located.

Thallium may be bioconcentrated by organisms from water. A bioconcentration factor (BCF) relates the concentration of a chemical in the tissues of aquatic animals or plants to the concentration of the chemical in the water in which they live. Experimentally-measured BCF values have been reported: 18.2 for clams and 11.7 for mussels (Zitko and Carson 1975). Bioconcentration factors for the muscle tissue of juvenile Atlantic salmon have ranged from 27 to 1,430 (Zitko et al. 1975). The maximum BCF for bluegill sunfish was 34 in the study of Barrows et al. (1978). Thallium is absorbed by plants from soil and thereby enters the terrestrial food chain (Ewers 1988; Sharma et al. 1986). Cataldo and Wildung (1983) demonstrated that thallium could be absorbed by the roots of higher plants from the rhizophere.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Metallic thallium oxidizes slowly in air (Lee 1971), and thallous chloride is photosensitive (Cotton and Wilkinson 1980). However, there was no evidence that thallium is transformed significantly by photochemical reactions in the atmosphere (Callahan et al. 1979b).

5.3.2.2 Water

Little is known about thallium transformation in water by either abiotic or biotic processes (EPA 1988a). Pertinent data regarding the photolysis or hydrolysis of common thallium compounds were not located.

5.3.2.3 Soil

Callahan et al. (1979b) concluded that there was no evidence that thallium is biotransformed in the environment. No other information was located.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Data on thallium levels in ambient air are sparse. In six United States cities, the thallium concentrations ranged from 0.02 to 0.1 ng/m^3, with a typical concentration of 0.04 ng/m^3 (EPA 1980a, 1988a). Concentrations of thallium in Chadron, Nebraska reportedly ranged from 0.04 to 0.48 ng/m^3 (EPA 1980a, 1988a), and geometric mean concentrations measured during 1985-1986 in Genoa, Italy were about 0.015 μg/m^3 (Valerio et al. 1988). The estimated thallium concentration near a coal-burning power plant was 0.7 μg/m^3 (EPA 1988a).

Thallium levels have also been measured in workplace air. Marcus (1985) reported maximum thallium levels in workplace air at 0.014 and 0.022 mg/m^3 during machining and alloying operations, respectively, of a magnesium alloy used in batteries at a plant in England. Air samples in two cement plants and two foundries in Italy had thallium concentrations of less than 1 μg /m^3 (Apostoli et al. 1988).

5.4.2 Water

Since thallium is a naturally-occurring element, it may be present in ambient waters in trace amounts. However, monitoring data indicate elevated thallium concentrations near industrial and commercial sources and hazardous waste sites.

A survey of tap water from 3,834 homes in the United States detected thallium in 0.68% of samples at an average thallium concentration of 0.89 μg/L (EPA 1980a, 1988a). Thallium was detected in 10% of urban stormwater runoff samples at concentrations ranging from 1 to 14 μg/L (Cole et al. 1984). Thallium has been measured in seawater at 0.01-14.00 μg/L (Sharma et al. 1986).

Water concentrations of thallium in rivers in the United States and Canada that receive mining operations effluents ranged from 0.7 to 88.3 μg/L (EPA 1980a, 1988a; Zitko et al. 1975).

5.4.3 Soil

Estimates of thallium concentration in the earth's crust range from 0.3 to 0.7 ppm (EPA 1988a), so thallium is likely to be present in soils in trace amounts. The limited data available indicate that soil thallium levels may be increased near thallium-emitting industrial sources and at hazardous waste sites. Measured thallium concentrations in lake sediments ranged from 0.13 to 0.27 μg/g in four remote Rocky Mountain lakes (Heit et al. 1984) to 2.1-23.1 mg/kg (mean value 13.1 mg/kg) in a Michigan lake reportedly polluted by airborne particulate matter (EPA 1988a). Up to 5 mg/kg thallium was

reported in stream sediments near metal industry runoff areas (Wallwork-Barber et al. 1985).

5.4.4 Other Environmental Media

Trace amounts of thallium are found in most foods (Ewers 1988), but few foods, except vegetables grown in thallium-polluted soil, are likely to have significant thallium concentrations (Ewers 1988; Sharma et al. 1986).

Data on thallium content of specific foods grown and consumed in the United States were not located. However, a recent study of the thallium content of food in the United Kingdom reports levels of thallium in meat, fish, fats, and green vegetables (Sherlock and Smart 1986).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Human exposure to thallium may occur by inhalation, ingestion, or dermal absorption. The general population is exposed most frequently by ingestion of thallium-containing foods (EPA 1980a, 1988a; Ewers 1988). From the very limited data available, EPA estimated daily intakes for the general adult population from drinking water, air, and food (EPA 1980a). More recent data on thallium concentrations in food and dietary intake of the general population (Sherlock and Smart 1986) confirm that food (green vegetables in particular) is probably the major source of thallium exposure. Although these data are from the United Kingdom, it is not likely that the thallium content of the food supply of the United States would be significantly different. Limited data on thallium concentrations in cigars and cigarettes suggest smoking may be a source of thallium. The extent of exposure from this source is not clear since thallium levels in cigarette smoke are not known. Table 5-2 summarizes the estimated typical daily intakes from water, food, and air.

Occupational exposure to thallium may be significant for workers in smelters, power plants, cement factories, and other industries that produce or use thallium compounds or alloys. Exposure may occur by dermal absorption from handling thallium-containing compounds, ores, limestone, or cement or by inhalation of workplace air (Ewers 1988; Marcus 1985; Schaller et al. 1980).

Urinary thallium levels are considered the most reliable indicator of thallium exposure. Although data on exposure levels in workplace air are rare (see Section 5.4.1), studies associating workplace exposure and elevated urinary thallium confirm the occurrence of industrial exposures in Europe (Apostoli et al. 1988; Marcus 1985; Schaller et al. 1980). Similar data were not located for U.S. workplaces. However, NIOSH estimated that more than

TABLE 5-2. Summary of Typical Human Exposure to Thallium[a]

Parameter	Exposure medium		
	Water	Air	Food
Typical concentration in medium	0.89 μg/L	0.48 ng/m^3	ND-50 μg/kg
Assumed intake of medium by 70-kg adult	2 L/day	20 m^3/day	1.5 kg
Assumed absorption fraction	1.0	0.35	1.0
Estimated daily intake by 70-kg adult	≈2 μg	3.4 ng	5 μg

[a]Adapted from EPA 1980a, 1988a; Sherlock and Smart 1986

ND = not detected

1,600 people are occupationally exposed to thallium in the United States (NOES 1989). The NOES database does not contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. This survey provides only estimates of the number of workers potentially exposed to chemicals in the workplace.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Populations with potentially high exposures are those living near coal-Burning power plants, metal smelters, or cement plants (Sharma et al. 1986). The airborne particulate emissions from these plants may have high thallium levels, especially on the small-diameter, respirable particles (Davison et al. 1974; Ewers 1988). Human populations living in the vicinity of these plants may be exposed by inhalation or by ingestion of fruits and vegetables homegrown in contaminated soils (Brockhaus et al. 1980, 1981; EPA 1988a; Sharma et al. 1986).

Workers in industries producing or using thallium-containing materials also have potentially high exposures as noted above (Section 5.5).

Limited data suggest that smokers may have potentially high exposure to thallium. Although recent authoritative evaluations of cigarette smoke constituents do not include thallium, thallium was detected at 0.057-0.170 μg/g in cigar stubs and 0.024 μg/g in cigarette tobacco (EPA 1980a; Smith and Carson 1977). One study indicates that the urinary excretion of thallium in smokers is about twice that of nonsmokers (EPA 1980a; Smith and Carson 1977).

5.7 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 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.

5.7.1 Data Needs

Physical and Chemical Properties. Additional measurements of the aqueous solubility of environmentally relevant thallium compounds would provide a more accurate basis for applying mineral equilibria to predict the fate of thallium in water (EPA 1988a).

Production, Import/Export, Use, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Data on production, use, and disposal (HSDB 1989; TRI 1989; U.S. Bureau of Mines 1988) are adequate. Additional information is unlikely to significantly affect estimates of human exposure.

Environmental Fate. Little information is available on partitioning of thallium in the atmosphere (EPA 1988a). This lack of data is not important since thallium is nonvolatile. The reaction mechanisms controlling the fate of thallium in water are not well known. Adsorption-desorption reactions with soils and sediments (Frantz and Carlson 1987; Magorian et al. 1974; Mathis and Kevern 1975) suggest that movement of thallium can be reduced. Additional research would provide a more accurate basis for predicting the fate of thallium in water. Very little is known about potential transformation mechanisms for thallium in air, water, or soil (Callahan et al. 1979b; EPA 1988a), but this lack of detailed data may not be a major limitation because many transition metals are not susceptible to transformation or degradation-type processes.

Bioavailability From Environmental Media. Thallium can be absorbed following inhalation of contaminated workplace air, ingestion of contaminated food, or dermal contact (Dai-xing and Ding-nan 1985; Dolgner et al. 1983; Marcus 1985). The most significant routes of exposure near hazardous waste sites are likely to be through drinking thallium-contaminated water and skin contact with or ingestion of thallium that is attached to soil particles. Information on the percent of thallium taken into the body from environmental media that is actually absorbed or bioavailable would be useful in clarifying the toxic potential of thallium in humans. The relative absorption of different species/forms of thallium from inorganic and biological matrices would also be useful.

Food Chain Bioaccumulation. There are no specific data on the bioaccumulation of thallium or its potential to be transferred from lower trophic levels to higher organisms. Because thallium can be bioconcentrated, it may be that it can also be accumulated in living tissues. We know that

thallium may be bioconcentrated by aquatic plants, invertebrates, and fish (Barrows et al. 1978; Zitko and Carson 1975; Zitko et al. 1975). Information on biotransformation in aquatic biota would provide further insight into the extent of chemical speciation and forms of thallium to which humans could be exposed near hazardous waste sites. Terrestrial plants absorb thallium from soil (Cataldo and Wildung 1983). Additional measurements of the bioconcentration of thallium by plants and animals and information on soil types and conditions which enhance thallium uptake by plants would be helpful to better define the tendency of thallium to partition to living tissues. Detectable levels of thallium have been found in many foods (Ewers 1988; Sharma et al. 1986; Sherlock and Smart 1986). However, no data were located on biomagnification of thallium in the food chain. Information on food chain bioaccumulation would be useful in assessing the potential for human exposure to thallium from food.

Exposure Levels in Environmental Media. Data on thallium levels in all environmental media are sparse (EPA 1988a). More research using sensitive analytical methods for all media, especially in the vicinity of potential thallium pollution sources and waste sites, and specific data on the thallium content of the American diet would increase the accuracy of human exposure estimates.

Exposure Levels in Humans. Thallium has been detected in human urine and urinary thallium excretion is used as a measure of thallium absorption (Dai-xing and Ding-nan 1985; Dolgher et al. 1983; Marcus 1985). Reliable data on urinary thallium in unexposed individuals and correlating urinary thallium levels with environmental exposures at hazardous waste sites would help to identify populations at risk in the vicinity of these sites from thallium exposure.

Exposure Registries. No exposure registries for thallium were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

Remedial investigations and feasibility studies conducted at the 18 NPL sites known to be contaminated with thallium will add to the available database on exposure levels in environmental media, exposure levels in humans, and exposure registries.

No other information was located on any on-going studies on the fate, transport, or potential for human exposure for thallium.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring thallium in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify thallium. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect thallium in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

Thallium is almost always determined as total metal, rather than specific thallium compounds. Among the wide range of techniques that can be used to measure thallium are spectrophotometry, mass spectrometry, voltammetry, neutron activation analysis, and x-ray fluorimetry (Sharma et al. 1986). However, direct aspiration atomic absorption analysis is the most widely used and straightforward method for determining thallium; furnace atomic absorption analysis is used for very low analyte levels and inductively coupled plasma atomic emission analysis for multianalyte analyses that include thallium.

6.1 BIOLOGICAL MATERIALS

Methods for detection of thallium in biological materials are summarized in Table 6-1. Normally, for determination in biological samples, the sample is digested in an oxidizing acid mixture, such as 3:1:1 (v/v/v) nitric:perchloric:sulfuric acid mixture (Kneip and Crable 1988), followed by atomic spectrometric determination. Alternatively, thallium can be extracted from biological samples such as blood or urine by chelating agents such as diethylthiocarbamate in methylisobutylketone and measured by atomic absorption analysis.

6.2 ENVIRONMENTAL SAMPLES

Methods for the determination of thallium in environmental samples are summarized in Table 6-2. Thallium is readily measured in multielement analyses of air, water, and solid waste samples by inductively coupled plasma atomic emission spectroscopy. For individual analyses of thallium, direct aspiration atomic absorption spectroscopy is a very convenient method of analysis; if lower detection limits are needed, furnace atomic absorption analysis can be employed. Other sensitive means of measuring thallium include anodic stripping voltammetry and laser-excited atomic fluorescence spectroscopy, which have been used for biological samples (see Table 6-2).

TABLE 6-1. Analytical Methods for Determining Thallium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Biotic materials	Combustion in oxygen stream	ASV and AAS	No data	No data	Kaiser and Tolg 1986
Blood and tissue	Acid digestion	ICP/AES	No data	131% recovery at 10 mg/sample	Kneip and Crable 1988
Blood and urine	Extraction into methyl-isobutylketone with diethyldithiocarbamate chelating agent	AAS	<3 µg/L[a]	No data	Baselt 1988
Blood and tissue	Acid digestion	ICP/AES	1 µg/100g blood, 0.2 µg/g tissue	106% 4.9% RSD	NIOSH 1984a
Bovine liver, mouse brain tissue	No data	LEAFS	No data	No data	Dougherty et al. 1988
Liver, kidney	Digestion by proteolytic enzyme	AAS	No data	No data	Carpenter 1981
Urine	Acid digestion	ASV	1 µg/L	95% recovery at 16 µg/L	Angerer and Schaller 1985
Urine	Extraction into toluene with sodium diethylthio-carbamate chelting agent	AAS	0.1 µg/L	95%-98% 3.5%-4.4% RSD	Chandler and Scott 1984
Urine	Dilution	AAS	0.5 µg/L	No data	Paschal and Bailey 1986

[a]Estimated from cited values of normal blood thallium concentration.

AAS = atomic absorption spectroscopy; ASV = anoidc stripping voltammetry (inverse voltammetry); ICP/AES = inductively coupled plasma atomic emission spectroscopy; LEAFS = laser excited atomic fluorescence spectroscopy; RSD = relative standard deviation

TABLE 6-2. Analytical Methods for Determining Thallium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection on filter, workup in acid	AAS	No data	No data	Sittig 1985
Air	Collection on filter; workup in acid	ICP/AES	1 µg per sample	103% recovery at 2.5 µg per sample	NIOSH 1984b
Water	Acidify with nitric acid	AAS (direct aspiration)	0.1 mg/L	98±1.7% at 3 mg/L	APHA 1985
Water	Acidify with nitric acid	AAS (direct aspiration)	0.1 mg/L	No data	EPA 1983a
Water	Acidify with nitric acid	AAS (furnace technique)	1 µg/L	No data	EPA 1983b
Water	Digestion for total thallium, filtration through 0.45 micron filter followed by digestion for dissolved thallium	AAS	No data	No data	Sittig 1985
Wastewater	Acid digestion	ICP/AES	40 µg/L	No data	EPA 1985a
Solid waste	Acid digestion	AAS (direct aspiration)	0.1 mg/L[a]	98±1.7% at 3 mg/L	EPA 1986a
Solid waste	Acid digestion	AAS (furnace technique)	1 µg/L[a]	No data	EPA 1986b
Solid waste	Acid digestion	ICP/AES	40 µg/L[a]	No data	EPA 1986c
Solid environmental samples	No data	AAS (electrothermal)	No data	No data	DeRuck et al. 1989

[a]Detection limit for thallium in liquid sample digestate.

AAS = atomic absorption spectroscopy; ICP/AES = inductively coupled plasma atomic emission spectroscopy

6.3 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 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.

6.3.1 Data Needs

Methods for Biomarkers of Exposure and Effect. The only means available to indicate exposure to thallium is detection of thallium in tissue and biological fluids. Sensitive, specific, readily used atomic spectrometric techniques are available for the detection and quantitative measurement of thallium after the sample matrix in which it is contained has been digested with oxidant acids or after thallium has been extracted with methylisobutylketone (Baselt 1988). The determination of specific compounds that contain thallium are relatively unimportant because of the uncomplicated chemistry of this element and there is no evidence in the literature for the production of metabolites. If such metabolites do in fact exist, methods for their determination would be useful in monitoring exposure to thallium. Studies are needed to determine whether solid tissues provide a "matrix effect" biasing the accuracy of determinations from tissues. Thallium exists in both stable univalent (I) and trivalent (III) states. Additional studies would be useful in clarifying if relative concentration of thallium in various tissues would be affected by the valence or if there is a biochemical conversion of Tl^{+} and $T1^{3+}$ into a single species.

Biomarkers for effects of thallium intoxication are alopecia, neurological effects, and albuminuria (Baselt 1988), which are indicative of exposure to many other toxicants as well. Therefore, methods are needed for more specific biomarkers for effects of thallium exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining the parent compound, thallium, in water, air, and waste samples with excellent selectivity and sensitivity are well developed (EPA 1983a,b, 1985a, 1986a, b,c; NIOSH 1984b), so the database in this area is good and undergoing constant improvement.

Sampling methodologies for very low-level elemental pollutants such as thallium continue to pose problems such as nonrepresentative samples, insufficient sample volumes, contamination, and labor-intensive, tedious extraction and purification procedures (Green and LePape 1987).

6.3.2 On-going Studies

Examination of the literature suggests that studies are underway to improve means for determining thallium and other heavy metals in biological samples and environmental media. Improvements continue to be made in detection limits and ease and speed of analysis.

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, a number of regulations and guidelines have been established for thallium by various national and state agencies. These values are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Thallium and Compounds

Agency	Description	Information	Reference
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA (soluble compounds, as Tl)	0.1 mg/m^3	OSHA 1989 (29 CFR 1910.1000) Table Z-1-A
b. Water:			
EPA OWRS	General permits under NPDES	Yes	40 CFR 122, Appendix D, Table II
	General pretreatment regulations for existing and new sources of pollution	Yes	40 CFR 403
	Hazardous substance		EPA 1989a
	Thallium sulfate	Yes	(40 CFR 116)
	Reportable quantity		40 CFR 117.3
	Thallium sulfate	100 pounds	
c. Nonspecific media:			
EPA OERR	Reportable quantity		EPA 1989a (40 CFR 302.4)
	Thallium	1,000 pounds	
	Thallium (1) acetate	100 pounds	
	Thallium (1) chloride	*100 pounds*	
	Thallium (1) nitrate	100 pounds	
	Thallic oxide	100 pounds	
	Thallium (1) sulfate	100 pounds	
	Thallium (1) carbonate	100 pounds	
	Thallium selenite	1,000 pounds	
	Extremely hazardous substance TPQ		EPA 1987b (40 CFR 355)
	Thallium sulfate	100/10,000 pounds	
	Thallous chloride	100/10,000 pounds	
	Thallous sulfate	100/10,000 pounds	
	Thallous carbonate	100/10,000 pounds	
	Thallous malonate	100/10,000 pounds	
EPA OPP	Cancellation of all pesticide products containing thallium *sulfate 03/09/72*	Yes	EPA 1985b
EPA OSW	Hazardous waste constituent (Appendix VIII) (Thallium and Compounds)	Yes	EPA 1980c (40 CFR 261)
	Groundwater monitoring list (Appendix IX)	Yes	EPA 1987c (40 CFR 264)
	Land disposal restrictions	Yes	EPA 1988d, 1987d (40 CFR 264, 268)
EPA OTS	Toxic chemical release reporting	Yes	EPA 1988c (40 CFR 372)
	Health and safety data reporting rule	Yes	EPA 1988e (40 CFR 716)

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	Reference
Guidelines:			
a. Air:			
ACGIH	TLV TWA (soluble compounds as Tl)	0.1 mg/m^3	ACGIH 1986
NIOSH	IDLH (soluble compounds as Tl)	20 mg/m^3	NIOSH 1985
b. Water:			
EPA OWRS	Ambient water quality criteria		EPA 1980a
	Ingesting water and organisms	13 µg/L	
	Ingesting organisms only	48 µg/L	
c. Other:			
EPA	Carcinogenic classification	Group D[a]	EPA 1988a
	Thallium and salts		
	RfD (oral)		IRIS 1989
	Thallium (insoluble salts)	7×10^{-5} mg/kg/day	EPA 1991
	Thallium (I) sulfate	8×10^{-5} mg/kg/day	
	Thallium (I) acetate	9×10^{-5} mg/kg/day	
	Thallium (I) chloride	8×10^{-5} mg/kg/day	
	Thallium (I) nitrate	9×10^{-5} mg/kg/day	
	Thallium (I) carbonate	8×10^{-5} mg/kg/day	
STATE			
Regulations:			
a. Air:	Acceptable ambient air concentration		NATICH 1989
Connecticut		2.0 µg/m^3 (8 hr)	
Florida (Tampa)		0.001 mg/m^3 (8 hr)	
Kansas (Kansas City)		0.238 µg/m^3 (1 yr)	
Nevada		0.002 mg/m^3 (8 hr)	
New York		0.330 µg/m^3 (1 yr)	
North Dakota		0.001 mg/m^3 (8 hr)	
Pennsylvania (Philadelphia)		2.47 µg/m^3 (1 yr)	
		2.40 µg/m^3 (annual)	
Virginia		1.60 µg/m^3 (24 hr)	
Wisconsin		2.4 µg/m^3 (24 hr)	
b. Water:	Drinking water		FSTRAC 1988
Kansas		13 µg/L	
Wisconsin		6.5 µg/L	

[a] Group D = not classified as to human carcinogenicity. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; IDLH = Immediately Dangerous to Life or Health Level; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; OERR = Office of Emergency and Remedial Response; OPP = Office of Pesticide Products; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; TLV = Threshold Limit Value; TPQ = Threshold Planning Quantity; TWA = Time-Weighted Average

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, a number of regulations and guidelines have been established for thallium by various national and state agencies. These values are summarized in Table 7-1.

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9. GLOSSARY

Acute Exposure - Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{OC}) - The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d) - The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) - The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) - The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen - A chemical capable of inducing cancer.

Ceiling Value - A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure - Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity - The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity - Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory - An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

9. GLOSSARY

Immediately Dangerous to Life or Health (IDLH) - The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure - Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity - The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro - Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo - Occurring within the living organism.

Lethal Concentration $_{(LO)}$ (LC_{LO}) - The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration $_{(50)}$ (LC_{50}) - A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose $_{(LO)}$ (LD_{LO}) - The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose $_{(50)}$ (LD_{50}) - The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time $_{(50)}$ (LT_{50}) - A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) - The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations - Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level - An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen - A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

9. GLOSSARY

Neurotoxicity - The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) - The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{OW}) - The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) - An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* - The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) - An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) - The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity - The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) - The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

9. GLOSSARY

Target Organ Toxicity - This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen - A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) - A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) - An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) - A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) - A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people ,living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and end point and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minima1 Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented- below demonstrate the application of these tables and figures. A representative example of LSE Table 2-l and Figure 2-1 are shown. The numbers in the left columrn of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate mute of exposure. When sufficient data exist,

three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

2) Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-1).

5) Species The test species, whether animal or human, are identified in this column.

6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance XI via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

7) System This column further defines the systemic effects. These systems include: respiratory9 cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key nmber 18, one systemic effect (respiratory)was investigated in this study.

8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects, These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to

quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

10) Reference The complete reference citation is given in Chapter 8 of the profile.

11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer9 but the text may report doses which did not cause a measurable increase in cancer.

12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables ate found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See LSE Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

13) Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

14) Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

15) Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

16) NOAEL In this example, 1% NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key numbr 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRI, of 0.005 ppm (see footnote "b" in the LSE table).

17) CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

APPENDIX

18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5 ↓	6 ↓	7 ↓	8 ↓	9 ↓		10 ↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer						11 ↓	
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

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

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

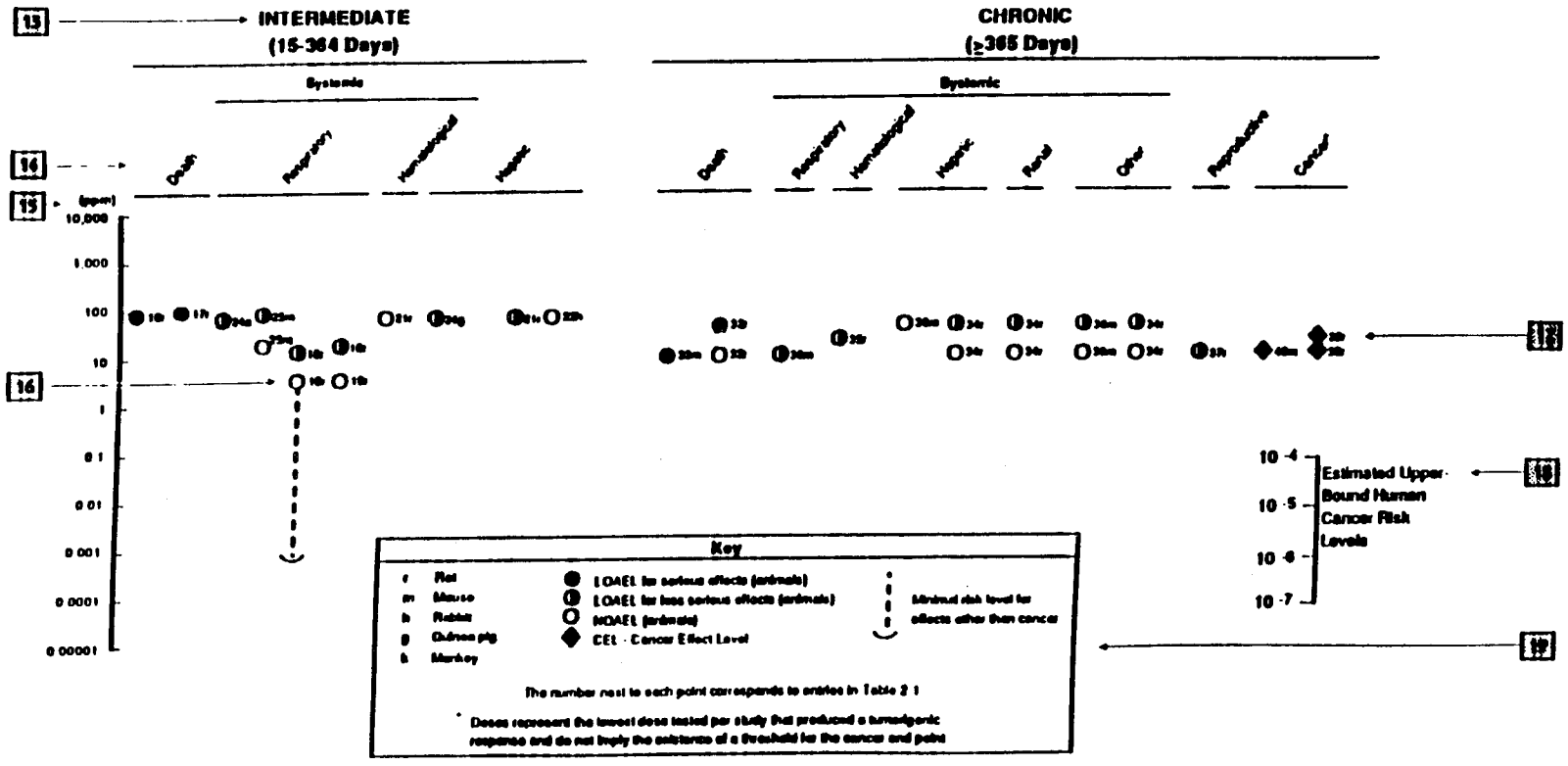

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around
   hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potiency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute - intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

APPENDIX A

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic informationknown about the substance. Other sections such as 2.6, “Interactions with Other Chemicals” and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MEL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f_1	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
Koc	octanol-soil partition coefficient
Kow	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration low
LC_{50}	lethal concentration 50 percent kill
LD_{Lo}	lethal dose low
LD_{50}	lethal dose 50 percent kill
LOAEL	lowest-observed-adverse-effect level

APPENDIX B

LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average

APPENDIX B

U.S.	United States
UF	uncertainty factor
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for thallium. The panel consisted of the following members: Dr. Curtis Klaassen, Associate Director, Environmental Health Science Division, Dept. of Pharmacology and Toxicology, University of Kansas; Dr. David Brown, Director, Toxicology Programs, Northeastern University; Dr. Kenneth Reuhl, Associate Professor, Department of Pharmacology and Toxicology, Rutgers University College of Pharmacology. These experts collectively have knowledge of thallium's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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