Thallium and water-soluble thallium compounds

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of thallium and water-soluble thallium compounds by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University, Wageningen, the Netherlands).

The evaluation of the toxicity has among others been based on a review by the World Health Organization/International Programme on Chemical Safety (WHO/IPCS) (WHO96). Data considered to be critical were evaluated by reviewing the original publications. In addition, literature was retrieved from the databases Medline, Toxline, and Chemical Abstracts covering the periods 1993 until February 1998, 1987 until October 1997, and 1992 until December 1997, respectively. The literature search was concentrated on those thallium compounds which are very soluble and soluble in water, according to the Handbook of Chemistry and Physics (Lid96), and the following key words were used: thallium, 563-68-8, 992-98-3, 1314-12-1, 7440-28-0, 7789-27-7, 10102-45-1, 12026-06-1, 13453-32-2, 13453-34-4, 13453-40-2, 13701-90-1, and 13826-63-6. The final search was carried out in February 1998.

In December 1998, the President of the Health Council released a draft of the document for public review. The committee received no comments.

Additional literature searches in May 1999 and May 2002 did not result in information changing the committee's conclusions.

2 Identity

name	molecular formula	synonyms	CAS number
thallium	Tl	Ramor	7440-28-0
thallium(I) acetate	$TlC_2H_3O_2$	acetic acid, thallium(I) salt; thallous acetate	563-68-8
thallium(I) cyanide	TlCN	thallous cyanide	13453-34-4
thallium(I) fluoride	TlF	thallous fluoride	7789-27-7
thallium(I) formate	$TlCHO_2$	formic acid, thallium(1+) salt	992-98-3
thallium(I) hydroxide	TlOH	thallous hydroxide	12026-06-1
thallium(I) nitrate	$TlNO_3$	nitric acid, thallium(1+) salt; thallous nitrate	10102-45-1
thallium(I) nitrite	$TlNO_2$	nitrous acid, thallium(1+) salt	13826-63-6
thallium(I) oxide	Tl_2O	thallous oxide	1314-12-1
thallium(I) perchlorate	$TlClO_4$	perchloric acid, thallium(1+) salt	13453-40-2
thallium(III) bromide tetrahydrate	$TlBr_3.4H_2O$		13701-90-1
thallium(III) chloride	$TlCl_3$		13453-32-2
thallium(III) chloride tetrahydrate	$TlCl_3.4H_2O$		13453-32-2

[a] The presence of an asterisk following a CAS number indicates that the registration is for a substance that CAS does not treat in its regular CA index processing as a unique chemical entity.

Thallium (Tl) is a heavy metal, with a natural abundance of approximately 0.7 ppm (Bud96).

Forty-seven isotopic forms of thallium, with atomic masses ranging from 179 to 210 are recognised. The half-life of the unstable isotopes ranges from 0.06 sec to 3.78 years. Natural thallium is a mixture of two isotopes: ^{203}Tl and ^{205}Tl (Lid96).

In contrast to the small world production of about 10-15 tonnes thallium per year, the amount of thallium in waste material is estimated to be about 600 tonnes per year (Kem91).

3 Physical and chemical properties

name	physical form	mol weight	solubility in water	melting point	boiling point
Tl	soft blue-whitish metal	204.38	insoluble	304ºC	1473ºC
$TlCHO_2$	hygroscopic colourless needles	249.4	very soluble	101ºC	-
TlOH	yellow needles	221.39	very soluble	139ºC, decomposes	-
$TlNO_2$	cubic crystals	250.39	very soluble	-	-
$TlCl_3$	monoclinic crystals	310.74	very soluble	155ºC	-
$TlC_2H_3O_2$	hygroscopic white crystals	263.43	soluble	131ºC	-
TlCN	white hexagonal plates	230.4	soluble	-	-
TlF	white orthorhombic crystals	223.38	soluble	326ºC	826ºC
$TlNO_3$	white crystals	266.39	soluble	206ºC	450ºC, decomposes
Tl_2O	black hygroscopic rhombohedral crystals	424.77	soluble	579ºC	ca. 1080ºC
$TlClO_4$	colourless orthorhombic crystals	303.83	soluble	-	-
$TlBr_3.4H_2O$	yellow orthorhombic crystals	516.16	soluble	-	-
$TlCl3._4H_2O$	orthorhombic crystals	382.8	soluble	-	-

Data from Lid96

The only vapour pressure found was for thallium: 0.13 kPa at 825ºC. All other compounds are expected to have a low vapour pressure. Therefore, conversion factors for the concentration in air are not applicable; the concentration can only be expressed in mg/m^3.

Further, no data on flash point, explosion limits, or log $P_{octanol/water}$ values were found.

Thallium oxidises in air to form a superficial layer of Tl_2O. It forms alloys with other metals and readily amalgamates with mercury (ACG91). Thallium is flammable; it should therefore be kept under water. It reacts violently with peracetic acid and halogens, with a risk of fire and explosion (Che98).

Solutions of thallous fluoride and thallous hydroxide are strongly alkaline. On exposure to air thallous oxide gradually oxidises to thallic oxide, becoming insoluble in water (Bud96).

4 Uses

Thallium is used in the semiconductor industry and is alloyed with mercury in some switches. In addition, it is used in mineralogical solutions, optical systems, photoelectric cells, and low-range glass thermometers (ACG91).

^{201}Thallium is widely used in myocardial imaging (Bel94).

Thallous cyanide is used in organic synthesis; thallous fluoride in the preparation of fluoro esters; thallous nitrate as a reagent in analytical chemistry, especially for the determination of iodine in the presence of Br and Cl. Thallous oxide is used in the manufacturing of glass with a high coefficient of refraction for optical purposes (thallium flint glass) and for artificial gems (Bud96).

5 Biotransformation and kinetics

Human data

Thallium is rapidly absorbed (up to 80-100%) by the mucous membranes, after ingestion, inhalation, or contact with intact skin. A rapid distribution from blood to tissue follows absorption. Because of the similar ionic radii of thallium (I) and potassium, thallium can substitute for potassium in a variety of potassium-dependent transport processes such as the ‘active transport’ and, consequently, accumulate intracellularly. In humans, thallium is found to accumulate in kidneys, muscles, certain brain areas, and testicles (Kem91).

Examination of a population living in Germany near a cement plant with thallium emission and of workers of that plant has been done over the period 1979-1981. The frequency distributions of thallium content in blood, urine, and hair samples of 1980/81 showed a shift to higher values compared with those of unaffected areas. Nevertheless, the range of all results is distinctly different from the thallium concentrations in body fluids and hair found in acute thallium intoxications. Moreover, no individual result reached the urinary thallium level of 300 µg/L, suggested as the threshold value for factory workers (Kem91). Analysis of liver and kidney tissue obtained from autopsied dead individuals (54 males, 16 females; 18-76-year old) from the North Bohemia territory of the Czech Republic showed median levels of thallium of 0.5 µg/kg wet tissue weight (geometric mean: 1 µg/kg; range: 0.5-110 and 0.5-5.5 µg/kg for liver and kidney, respectively) (Ben00).

In working environments, exposure via inhalation and skin contact has also been reported. For inhabitants of an emission region of a coal-fired power plant, a daily thallium intake by ingestion and inhalation of 0.15-0.18 µg/kg body weight has been calculated (Kem91). From the UK 1994 Total Diet Study, a total dietary intake of thallium of 2 µg/day has been estimated (Ysa99).

Increased levels of thallium have been observed in the lungs of coal miners, but no data are available concerning the absorption of thallium salts after inhalation exposure. Generally, it is assumed that about 35% of respirable dusts is deposited in the lung and that up to 100% of the deposited thallium is absorbed (WHO96).

Quantitative data on penetration through the skin, expressed as mg Tl/cm^2 of skin per hour, were not found (Bel94, Hos93, Kem91, WHO96).

The toxicokinetics of thallium in humans are described by a 3-compartment model. The first phase, which lasts about 4 hours, represents intravascular distribution. The second phase lasts 4-48 hours during which thallium is distributed into the central nervous system. In general, the distribution phase is completed within about 24 hours. The elimination phase starts about 24 hours after ingestion and its duration depends on the therapeutic intervention used (Ano93).

Thallium can pass the placenta and be excreted in breast milk (Hof00, WHO96).

The myocardial clearance of ^{201}Tl, after intravenous injection into 15 volunteers, while exercising, was 13% per hour. There are no further data (Lee94).

The excretion of thallium in humans differs from that in laboratory animals, since the rate of excretion is generally much lower in humans (rate constant: 0.023-0.069 per day) than in laboratory animals (average rate constant: 0.18 per day) (WHO96).

Half-life times for elimination in man have been reported to range between 1.7 and 30 days, depending on the time since, and chronicity of, ingestion (Ano93) and 9 and 11 days, based on urinary thallium contents after accidental or suicidal ingestion (Kem91).

Another major difference between humans and animals is the relative contribution of the different routes of excretion. In humans, renal excretion seems to be much more important than in animals. In one study, urinary excretion of thallium was ±73%, whereas the gastrointestinal excretion was 3.7%. Excretion through hair and skin, and sweat has been estimated to be 19.5% and 3.7%, respectively (WHO96). However, others report that faecal

excretion is more important than urinary excretion (Ano93, Bel94, Kem91). It probably depends on the status of the patient, the dose taken up, the quantity of potassium present, and the time of measurement.

Faeces, urine, and hair samples may serve as indicator specimens in chronic exposure to small amounts of thallium. Concentrations of up to 2 µg Tl/L in whole blood and up to 5 µg/L urine may be considered as normal (Kem91).

Others, however, propose different reference values: 0.5 µg Tl/L blood, 0.5 µg Tl/L plasma for non-occupationally exposed individuals, based on the concentration of thallium found in blood of healthy donors in the UK (n=ca. 2620) (Ham94). When the concentration data of thallium found in the blood of 123 healthy inhabitants of Central Italy are taken, a reference interval is proposed of 0.014-0.19 µg Tl/L blood (Sab94). For urine, these numbers are: 0.5 µg Tl/L (Ham94), and 0.019-0.17 µg Tl/L (Sab94).

Animal data

Using different routes of administration of a thallous nitrate solution (oral, subcutaneous, intramuscular), thallium was rapidly and almost completely absorbed in rats. No effect of the route of administration on distribution was observed (WHO96). After intravenous injection, an initial increase in the thallium concentration of the blood is followed by a steep decrease within 5 to 15 minutes. A similar trend is observed after oral administration of thallium to rats (WHO96). Thallium is rapidly distributed to all organs and passes the placenta. Because of its rapid accumulation in cells, concentrations of thallium in whole blood do not reflect the levels in tissues. In acute poisoning of experimental animals or humans, initially high concentrations of thallium appear in the kidney, low concentrations in fat tissue and brain, and intermediate concentrations in the other organs; later, the thallium concentration of the brain also increases (WHO96). In rats, the main routes of elimination are gastrointestinal (about two thirds) and renal (about one third); in rabbits, the contribution of the 2 routes is about equal (WHO96).

6 Effects and mechanism of action

Human data

Thallium poisoning is accompanied with a range of symptoms in humans that are usually non-specific because of the multi-target organ toxicity involved. The

initial symptoms of thallium poisoning may include fever, gastrointestinal problems, delirium, convulsions, and coma. Symptoms may appear rapidly but more commonly, the acute toxicity subsides and is replaced by a gradual development of mild gastrointestinal disturbances, polyneuritis, encephalopathy, tachycardia, skin eruptions, stomatitis, atrophic changes of the skin, nail changes, and skin hyperaesthesia. Degenerative changes of the heart, liver, and kidney, subarachnoid haemorrhage, bone marrow depression, and increased radiopacity of the liver may also occur. Psychotic behaviour with hallucinations and dementia has been reported. Alopecia is the most characteristic sign of toxicity in humans (Bel94).

Most cases of thallium toxicity occur after oral ingestion but severe toxicity has been reported after inhalation of contaminated dust from pyrite burners in zinc and lead smelting and in the manufacture of cadmium (Ano93).

Thallium intoxication is considered one of the most frequent causes of intentional or accidental human poisoning.

The lowest oral dose of thallium found to induce toxicity in humans was 5.7 mg/kg bw. It induced effects on the peripheral nervous system, eyes, and skin (Lew92). The lowest lethal dose in a human being was 4.4 mg/kg bw (route of exposure not given) (Lew92). The lowest lethal oral dose of thallous acetate was 12 mg/kg bw (9.3 mg Tl/kg bw) (Lew92). Others concluded that a dose of 1.0 g/bw of soluble thallium salts (14-15 mg Tl/kg bw) could considered to be the lowest dose causing mortality (Bel94).

Studies of long-term exposure to thallium resulting in chronic poisoning have been summarised, without any information about doses. Depending on the level of exposure, a relatively long latent period (several weeks) may be followed by just a few symptoms. Peripheral sensorial disturbances, mental aberrations, loss of weight, and sleeplessness seem to be the most common symptoms (WHO96).

Limited data are available on the effects of thallium on human reproduction. Menstrual cycle, libido, and male potency may be adversely affected. Effects on sperm are known to occur following chronic intoxication. However, apart from a relatively low weight and alopecia of newborn babies, fetal development was not affected in about 20 cases of thallium intoxication during pregnancy. There are no quantitative data (WHO96). In a recent review on the outcome of pregnancy in thallium-poisoned women, 25 cases were identified, 7 of which were not included because they did not describe maternal of fetal outcome. In 5 out of the remaining 18 cases, thallium exposure was in the first trimester, in 5 in the second, and in 8 in the third trimester. Maternal toxicity consisted of the

classical signs and symptoms of thallium poisoning while fetal effects ranged from severe toxicity with residual sequelae to outwardly normal development. Some newborns appeared normal despite severe maternal toxicity. The only consistent effect identified was a trend toward prematurity and low birth weight in children exposed to early gestation. A case of maternal thallium poisoning during the first trimester of pregnancy resulting in fetal demise initiated this review (Hof00).

Occupational exposure of 51 (former) Soviet Union workers to more than 0.01 mg Tl/m^3, for 16 to 17 years, caused disorders of the vascular system, as well as neurological symptoms. However, there were no detailed data available, the author only summarised the study without reference to the original data (Ohn85). On the other hand, in another study, there were no statistically significant differences in cardiovascular or gastrointestinal effects in a cohort of 86 exposed workers compared with 79 unexposed controls in a factory of magnesium seawater batteries. Exposure to thallium was in the form of fume from alloying in the furnaces, skin contact in the strip-rolling of the thallium-magnesium alloy, and as a dust generated in the scrap-brushing of the alloy (Mar85).

In a group of persons, living near a thallium atmospheric emission source, a clear dose-response relationship was found between urinary thallium concentration and the prevalence of several neurological symptoms. However, in a group of cement plant workers, no such relationship was found (WHO96).

Animal data

Data on acute, single dose toxicity of some water-soluble thallium compounds are presented in Table 1.

When rats were given daily dietary doses of 0.45 mg thallous acetate/kg bw (equals 0.34 mg Tl/kg) for up to 4 months, only alopecia was noted after 6 weeks. At 4 months, there was elevated mortality (ACG91, study from 1928).

Four groups of 5 male and 5 female rats were placed on a basal diet containing 0, 0.0005, 0.0015, and 0.005% thallous acetate, for 15 weeks. Two additional groups of rats were added to this study several weeks later; they received 0 and 0.003% thallous acetate in their diet. At 0.005%, all animals died within 14 days. At 0.003%, increased mortality was observed and growth depression after 30 days. The only major finding on gross autopsy was moderate to marked alopecia in the rats fed 0.0015% and higher. After 15

weeks, no histological changes were observed in any of the organs examined (heart, lung, liver, kidney, spleen, stomach, brain, testes, adrenals, bone marrow, femur, and spinal cord). There was no apparent difference between thallium administrated as the readily soluble thallous acetate and thallium administered as the relatively insoluble thallic oxide (Dow60). It can be concluded that feeding rats with 0.0005% thallous acetate for 15 weeks does not lead to any effects.

Carcinogenicity

The Commission of the European Communities could not classify thallium metal, thallic oxide, and thallium sulphate with respect to its (potential) carcinogenicity because of the absence of experimental animal, epidemiological, and mutagenicity and genotoxicity data. However, these compounds are extremely toxic and probably therefore, no need for further work was indicated by the Commission (Are93).

Table 1 Acute lethal toxicity data of some water-soluble thallium compounds (Lew92, WHO96).

species	thallium compound	route	results[a]
rabbit	$TlC_2H_3O_2$	oral	LD_{lo}: 24.5 mg/kg bw (19 mg Tl/kg bw)
dog		oral	LD_{lo}: 13 mg /kg bw (10 mg Tl/kg bw)
dog		oral	LD_{lo}: 25.8 mg/kg bw (20 mg Tl/kg bw)
guinea pig		oral	LD_{lo}: 15.5 mg/kg bw (12 mg Tl/kg bw)
rat		oral	LD_{50}: 41.3 mg/kg bw (32 mg Tl/kg bw)
mouse		oral	LD_{50}: 35 mg/kg bw (27 mg Tl/kg bw)
rabbit		intravenous	LD_{lo}: 26 mg/kg bw (20 mg Tl/kg bw)
rat	TlF	oral	LD_{lo}: 50 mg/kg bw (46 mg Tl/kg bw)
dog	$TlNO_3$	oral	LD_{lo}: 45 mg/kg bw (35 mg Tl/kg bw)
mouse		oral	LD_{50}: 33 mg/kg bw (25 mg Tl/kg bw)
dog		intravenous	LD_{lo}: 15 mg/kg bw (11.5 mg Tl/kg bw)
rabbit		intravenous	LD_{lo}: 14 mg/kg bw (10.7 mg Tl/kg bw)
rat, fed a low K+-diet		intravenous	LD_{50}: 16.3 mg/kg bw (12.5 mg Tl/kg bw)
rat, fed a high K+-diet		intravenous	LD_{50}: 18.9 mg/kg bw (14.5 mg Tl/kg bw)

[a] LD_{lo} : lowest lethal dose reported.

Mutagenicity and genotoxicity

Thallium was reported to induce chromosomal aberrations in CHO cells and human lymphocytes and to inhibit DNA formation in bone marrow cells of mice (only abstract available) (Cui88).

Thallous acetate was negative in 2 separate bacterial mutagenicity tests using *S. typhimurium* strains TA98, TA1535, TA1537, and TA1538 at concentrations of 0.0031-29.2 thallium/plate (no information on metabolic activation) and in strains TA98, TA100, TA1535, TA1537, and TA1538 with and without metabolic activation (concentrations no reported), respectively (WHO96). It enhanced virus-induced cell transformation in cultured hamster embryo cells (ACG91).

Thallous nitrate was positive in the rec assay in B. subtilis indicating that it may induce DNA damage but negative in subsequent bacterial mutation assays in *S. thyphimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and *E. coli* strain WP2 and B/r WP2 (only tested without metabolic activation) (Kan80).

Reproduction toxicity

Oral administration of doses of thallous acetate or of the slightly soluble thallous chloride of 3 or 6 mg/kg bw/day to NMRI mice on gestation days 6-15 had no observable effects on skeleton or organs at gestation day 18. The high dose caused a weight reduction in the embryos. Doses of thallous acetate of 4.5 mg/kg bw given to rats according to a similar regimen were lethal to the dams while doses of 3 mg/kg bw induced malformations of ribs and vertebrae and a slight increase in mortality during the first 3 weeks after birth (WHO96).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for thallium and water-soluble compounds in the Netherlands is 0.1 mg/m^3, 8-hour TWA, with a skin notation.

Existing occupational exposure limits for thallium and water-soluble thallium compounds in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

A wealth of human data is available, especially on incidental poisoning. There are several 'lowest doses' reported, the lowest of them being 4.4 mg Tl/kg body weight, which was lethal to a human being.

Long-term occupational exposure data are contradictory. On the one hand, 0.01 mg/m^3 is said to cause vascular and neurological disorders (Ohn85), whereas others report that occupational exposure to 0.1 mg/m^3 is without effects (Mar85), and, therefore, these human data cannot be used for the risk assessment.

The best available long-term animal study is the 15-week feeding study with thallous acetate (Dow60). The critical effect is alopecia, observed in rats fed 0.0015% and higher. The lowest dose tested, 0.0005%, was a no observed adverse effect level (NOAEL). The authors estimated the total intake for a rat fed 0.0015% to be approximately 0.3 mg thallous acetate per day. According to the authors, this is equivalent to a dose ranging from 1 to 3 mg/kg bw/day, depending on the body weight of the rats. Therefore, rats fed 0.0005% thallous acetate received a dose of approximately 0.3-1 mg/kg bw/day that is equivalent to 0.23-0.78 mg Tl/kg bw/day. The committee takes the mid dose of 0.5 mg Tl/kg bw/day as a starting point for deriving a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, a factor of 4 for the allometric scaling from rat to man, based on caloric demand, and an overall factor of 27 covering inter- and intraspecies variation and differences between experimental conditions and the exposure pattern of the worker are applied resulting in an NAEL for humans of 0.0046 mg/kg bw/day. Assuming a 70-kg worker inhales 10 m^3 of air during an 8-hour working day and a retention of 100%, and applying the preferred value approach, a health-based occupational limit of 0.02 mg/m^3 is recommended for thallium and its water-soluble compounds.

The committee recommends a health-based occupational exposure limit of 0.02 mg/m^3 for elemental thallium and its water-soluble compounds, as an 8-hour time-weighted average (TWA). Since there are many reports indicating that thallium can pass the skin, the committee recommends a skin notation.

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Annex

Occupational exposure limits for thallium and water-soluble thallium compoundsa in various countries.

country -organisation	occupational exposure limit[a]		time-weighted average	type of exposure limit	note[b]	reference[c]
	ppm	mg/m^3				
the Netherlands						
-Ministry of Social Affairs and Employment	-	0.1	8 h	administrative	S	SZW02
Germany						
-AGS	-	0.1[d]	8 h			TRG00
	-	0.4[d]	15 min			
-DFG MAK-Kommission	-	-[e]				DFG02
Great-Britain						
-HSE	-	0.1	8 h	OES	S	HSE02
Sweden	-	-				Arb00b
Denmark	-	0.1	8 h		S	Arb00a
USA						
-ACGIH	-	0.1	8 h	TLV	S	ACG02b
-OSHA	-	0.1	8 h	PEL	S	ACG02a
-NIOSH	-	0.1	10 h	REL	S	ACG02a
European Union						
-SCOEL	-	-				CEC00

[a] As thallium.

[b] S = skin notation, which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[c] Reference to the most recent official publication of occupational exposure limits.

[d] Inhalable fraction.

[e] Listed among compounds for which studies of the effects in man or experimental animals have yielded insufficient information for the establishment of MAK values.