

## Review Article

# A narrative review of thallium toxicity; preventive measures

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## ABSTRACT

Thallium (Tl) toxicity is an important clinical disease and its effects on the human body are devastating. Tl poisoning is an important health issue in many countries in the world. Thallium is a toxic heavy metal that exists in nature. Tl toxicity may occur in food and drinking water, occupational exposure, environment (air, industrial combustion of coal, water, and plants), arable soils and vegetables, aquatic and terrestrial animals, prenatal thallium exposure, illicit drugs, cigarette smokers. Adding lead to the opium is a recently health hazard that has been observed among opioid poisoned patients. The clinical manifestation of Tl poisoning has a wide spectrum but painful ascending peripheral neuropathy, gastrointestinal, and dermatologic manifestations are major characteristics in Tl toxicity. The toxicity of thallium based compounds is mainly caused by the similarity between Tl ions and potassium ions, which results in the disorder of potassium associated metabolic processes due to thallium interference. The aim of this review is to assess identify eliminate, sources or control sources, and environmental exposures and hazards to prevent thallium toxicity.

**Keywords:** Thallium, Poisoning, Toxicity

## INTRODUCTION

Contamination with heavy metals, including Thallium (Tl), zinc(Zn), copper(Cu), nickel(Ni), lead(Pb), chromium (Cr) and cadmium (Cd) are associated with a major environmental issue and threat to human health[1, 2]. Tl is a typical rare element widely dispersed in the natural environment; also, a heavy metal that has the qualities of a perfect criminal poison. It is used in electronic, chemical, aerospace, pharmaceutical and optical industry as well as in superconducting materials and high-energy physics. Its salts are tasteless, odorless, dissolve completely in liquids, are rapidly absorbed, and defy detection on routine toxicological screens[1, 3, 4]. Tl is considered as toxic for animal and human organisms, microorganisms and plants[1, 3]. In the study by Mulkey and Oehme[5], shown Tl status in normal human and animals are <1 ppb in blood and urine, and <10 ppb in tissues. Also, it is extremely toxic, far exceeding the toxicity of As and Hg, with a lethal dose of only 8-10 mg/kg for human adults[6, 7]. The therapeutic use of these salts has been abandoned, but the hazards of an accidental ingestion of thallium-containing rodenticides, or its use in suicidal or homicidal ingestion, occur occasionally[8]. Furthermore, evidence studies demonstrated that the concentrations of Tl were increasing from 1999 to 2019 among worldwide[9, 10]. Within the United States, 6 percent to 15% has been reported for acute

thallium toxicity[11]. The toxicity of thallium to human body is characterized by gastrointestinal (e.g., vomiting, diarrhea), hair loss, and effects on the nervous system, lungs, heart, liver, kidneys and finally death[12]. Thallium toxicity is one of the most complex and serious toxic patterns known to man. The symptomatology is usually nonspecific due to the multi-organ involvement. The first symptoms of thallium toxicity include fever, gastrointestinal symptoms, and neurological signs (e.g., delirium, convulsions, and coma). Signs may appear rapidly, but during acute poisoning, they are replaced by a gradual development and expression of mild gastrointestinal disturbances, encephalopathy, polyneuritis, skin eruptions, tachycardia, stomatitis, atrophic changes of the skin, Mee's lines, and skin hyperesthesia. Development of psychotic symptoms with dementia and hallucinations has also been reported in advanced stages of intoxication. In human body beings, the most characteristic symptom of thallium poisoning is alopecia, which usually appears 20 days after intoxication[6, 11, 12]. Human exposure to Tl is mainly linked to the consumption of contaminated food or drinking water, occupational exposure, prenatal thallium exposure, illicit drugs, cigarette smokers. Thallium rapidly enters the bloodstream and is transported across the whole organism, which leads to accumulation in bones, kidneys and the nervous

system[1, 3, 12]. The several papers about adverse and hazards effects of Tl on human worldwide and meanwhile the prevalence, incidence and sources of its contamination is clear. But this is the first comprehensive review about Tl toxicity. The fact is that information on Tl contamination is dispersed and incomplete. In this review, all papers published about sources and hazards of Tl exposure during the past two decades have been gathered and criticized to reach a conclusion about exact risk of Tl in a large country with highest rate of import and export.

## METHODS

We looked up the terms thallium, Tl, poisoning, toxicity, exposure, source and Iran in all bibliographical databases such as Google Scholar, Pub Med, Scopus. This review includes relevant articles published between 1980 and 2019.

### Occupational exposure with thallium

Exposure to high concentration of Tl can result in harmful health effects. An evidence on workers exposed on the job over many years demonstrated nervous system impacts, including numbness of fingers and toes, from breathing Tl. No evidence was found regarding the absorption of Tl salts via inhalation. There are a few case reports in which occupational exposure has been linked to toxicity, but it could not be determined if exposure occurred via inhalation, oral and dermal. The use of Tl salts in the past as depilatory agents, treatment for ringworm of the scalp, and treatment for night sweats linked to tuberculosis suggests dermal absorption[3, 13-16]. Occupational exposure with Tl limit is 0.1 mg/m to the skin per 8 hours a day. Concentrations of 15mg/m are demonstrated immediately dangerous to public health. Tl is readily absorbed through the skin as well as during inhalation. Due to Tl being tasteless, odorless, and water soluble, criminal and accidental intoxication have been shown[17]. The evidence study examined 128 men who were exposed to Tl in three cement manufacturing plants in the Franconia region of Germany. Health impacts were determined through medical physical and a histories examination for signs. Information on the scope of the physical evaluation was not provided. Analyses of roasted pyrites and electro-filter dust confirmed the presence of Tl in various production areas. The median levels of Tl in the urine in exposed workers were 0.8 µg/g. Medical physical and histories examinations did not shown Tl toxicity. The health status of exposed workers, however, was not compared with an unexposed reference population, and a single measurement of urinary Tl did not provide a measure of past exposures[18]. In the study by Mamoru Hirata[19], from the present results of neurological, neurophysiological examination, and analysis of the Tl contents of hair, which the subjects probably suffered from chronic Tl toxicity due to occupational exposure to Tl containing

dust. Also, reported medical records occupationally exposed to Tl at a magnesium seawater battery factory. Exposure was determined by measuring Tl in urine cases. Exposed workers did not have an enhanced in incidence of benign neoplasms or any other clinical diagnoses when compared with unexposed workers. That looked at populations surrounding a cement factory that released Tl only attempted to compare Tl exposure with congenital malformations or surveyed signs. Finally, the available epidemiology literature is considered limited and inconclusive[20, 21].

### Thallium in the environment (air, industrial combustion of coal, water, plants)

Tl is a typical rare element widely dispersed in environment. Thallium is used in chemical, pharmaceutical, electronic, aerospace and optical industry, and high-energy physics[1, 4, 22]. It is estimated that approx. 5000 t of Tl is released to the environment due to industrial activity[23]. World Health Organization reported Tl considered major hazardous wastes. Also, Tl listed as one of the technology critical elements, bearing consequential potential human health threats[22, 24]. Emissions, which associated with enhanced status of Tl in the environment, might natural or linked to anthropogenic activity[1]. In environmental Tl is bound with soil, which considerably limits its transport, although dissolved Tl are susceptible to flushing and might introduced to the aquatic environment[1]. Also, resources of Tl in coal amount to 630,000 t. The production of Tl reached 12 t; however as of the beginning of 2005, it remains at a relatively stable level of 10 t per annum[25]. In other hand, Tl is emitted to the atmosphere in the form of dust, vapors or liquids during industrial processing[1]. United States Environmental Protection Agency has shown the maximum permissible concentration at 2µg/L in drinking water, with the goal of lowering it to 0.5µg/L, in order to minimize health risks arising from thallium[26]. Also, the average Tl content in three main rivers in Poland, the levels of Tl in the analyzed samples was two to three times higher. This suggests that thallium is released from river sediments[27, 28]. The natural content of thallium in plants is usually at approx. 0.05 mg kg<sup>-1</sup>[29], and in case of grasses the concentration ranged from 0.02 to 0.6 mg kg<sup>-1</sup>. Therefore, further in-depth relevant studies are critical to provide theoretical foundations for industrial applications at the commercial status. The perspective of more frequent Tl contamination in the environment under accelerated industrialization, researches based on lab scale implementation of all the aforementioned treatment technologies should be evaluated at the pilot and industrial scale, to ensure the sustainable water security and human health[22].

### **Arable soils and vegetables as a source of thallium exposure**

Soil contamination by industrial activities is one of the universal issues worldwide. Large amounts of hazardous wastes containing toxic metal by mining or metallurgical activities have penetrated into the soils and ecosystem via various pathways due to inadequate waste management or inefficient pollution control[30-32]. Thus, heavy metal often exist in agricultural soils and elevate their uptake by crops, which threatens food security and endangers the health of local inhabitants and even the wide public[33-35]. The potentially devastating impacts of excessive toxic metal on food security are now widely. However, limited concerns have been drawn to Tl polluted farmland and its side effects[31]. The high toxicity of Tl is primarily because it can replace K in the metabolic profiles of plants. Tl can bind with phosphate and sulfhydryl ligands of proteins, wherein inactivation of these components increased its toxicity[36]. In the study by Liu[31], demonstrated that most of the agricultural soils exhibit contaminated concentration of Tl, with Tl contents mostly exceeding the maximum permissible status for agricultural land use. Sequential extraction procedure indicates that even Tl is predominantly retained in the residual fraction; significant levels of Tl are still present in the geochemically mobile fractions. Besides, metals like Cu, Cd, Mn, and Co are mostly distributed in the labile fractions. Almost all metal in edible parts of the vegetables exceed their corresponding maximum permissible status for consumption. In overall, the deficient Tl threshold contents in soil and food should be taken seriously. Tl threshold content in other countries, most samples of farmlands and cultivated vegetables are moderately high in total Tl. Even the pyrite mining areas far away from the upstream are suffering contamination from Tl. Further reported on larger scale should be carried out to depict a comprehensive Tl contamination map, identifying more specific sites and the population exposed by high potential Tl pollution risks[31].

### **Aquatic and terrestrial animals as a source of thallium exposure**

Levels of Tl in animal muscle tissue amount to fish (0.74–110.5 ng), rabbit (0.84 ng), pig (1.7 ng), and cattle (0.74 ng)[37-39]. Tl levels measured in phytoplankton and macrophytes span a large range of values and depend on the type of organism, the exposure duration, the aqueous levels of Tl, the status of K, and ambient pH[40-42]. Reported regarding sea fish belonging to the salmon family from central Pacific Ocean revealed that the level of Tl in their body reached 0.2–12 nmol g<sup>-1</sup>[43, 44]. Tl levels in muscle tissue of northern pike originating from lakes subjected to uranium milling wastewater discharge were four to five times higher compared to concentrations of thallium in tissues of fish originating

from non-contaminated lakes in the same area[45, 46]. Tl accumulation was examined in the liver and kidney of five species of dabbling ducks and three species of diving ducks[47]. The difference in Tl levels can be due to differences in Tl status in their prey since dabbling Tl ducks feeding in shallow areas whereas diving ducks collect food [44].

### **Prenatal thallium exposure**

It is estimated that approximately 5000 tons of Tl per year are released into the environment because of industrial activity[1]. Of particular interest are possible adverse outcomes linked to prenatal exposure to Tl, because fetuses are known to be more susceptible to some chemical exposures than adults[48]. Prenatal exposure to heavy metals (e.g., lead, cadmium, and arsenic) has been linked to reduced birth weight[49-51]. Prenatal Tl exposure can cause side effects on the developing fetus. Evidence studies showed that Tl toxicity during pregnancy might result in fetal death, congenital malformations, or reduced birth weight[52]. According to the World Health Organization (WHO), Low birth weight, which is defined as a birth weight of, is a main cause of mortality and morbidity in the neonatal period[53]. However, the implication of Tl exposure during pregnancy on infants after birth is still unknown. In the pilot study that shown a negative association between thallium status and birth weight in 81 Chinese mother–infant pairs[54]. Also, in the case–control study of prenatal Tl exposure, results suggest that prenatal exposure to high levels of Tl may be linked to an enhanced risk of low birth weight[55]. In addition, evidence study demonstrated that the children born in an industrial area with thallium contamination had higher status of urinary thallium, and had about a 6-fold higher risk of congenital abnormalities compared with the unexposed children[56]. In other hand, in cohort study shown that prenatal thallium exposures might have a sex specific effect on child anthropometric measurements in the first 2 years of life. Umbilical cord serum thallium status tended to be reduced child's stature and weight in young girls[57]. Thallium crosses the placenta freely and might impact mitochondrial function in placenta and fetal tissue, which is critical for fetal and growth. Also, some evidence reported that thallium triggers oxidative stress in the cell through enhancing lipid oxidation and inhibits enzymes with active sites containing cysteine residues. Enhanced oxidative stress might an important role in restricting fetal growth; therefore, thallium induced oxidative stress may also impair fetal growth[52, 58-60]. It has several influences in early interventions of public health, although further studies on epidemiology and mechanism studies are recommended.

### illicit drugs

There is a high prevalence of narcotic drugs in Iran because Iran is situated in the neighborhood of Afghanistan (the largest opium-producing country) and is one of the main routes for drug trafficking to Europe. In this regard, the report released by the World Health Organization suggests that the mean prevalence of opioids use in the general population was 0.6 to 0.8 percent throughout the world in 2013, while that was nearly three times larger in Iran in 2010, i.e. 2.275 percent[61]. The prevalence of opioids use is rising in Iran and the following statistics have been reported for Iran according to the latest survey in 2011: 3.02 percent for at least one time use of opioids, 1.56 percent for opioids dependence in the past 12 months, and prevalence of using any type of illicit drugs and opioids more than 5 times in the lifetime for males respectively were 6.4 and 2.8 percent, which for females was 0.54 and 0.29 percent that is approximately 10 to 12 times more in males[62]. In Iran, opium is the most prevalent opioid (82%), followed by opium ashes (28%), methadone for non-medical usages (16.6%), heroin and heroin / cracked (16%), morphine (2.6%). Apart from opioids, the common substances that are illegally used in Iran include alcohol with a prevalence of two percent within the past 12 months in 2012[63], cannabis with a prevalence of one percent, and methamphetamine with a prevalence of 0.5 percent in 2011[62]. However, the main focus has been placed upon the treatment of opioids dependence in Iran, and there exists about 5000 Outpatient Buprenorphine and methadone maintenance treatment (MMT) programs, that put a population of about 500 thousand people under treatment[64, 65]. Recently, thallium has been identified as an infamous adulterant added by street druggists to opioids, heroin and cocaine, leading to intoxication at varying levels[66-69]. To date, drug adulteration such as lead, Tl and steroid concurrent toxicities have not been investigated in admitted opioid overdose cases with history of drug use[70]. Substance use is a major public health hazard across the globe. In Iran, where people believe that opioid consumption may prevent hypertension, cardiovascular diseases, and diabetes, is a problem looming larger than ever[71, 72]. In previous articles, we shown clinical findings of opioid and heroin poisoned patients with Tl exposure as an adulterant[66, 69, 73, 74]. In settings that drug abuse overdose are common, and thallium has been demonstrated as an adulterant across a country such as Iran, testing symptomatic opioid overdose for Tl should be emphasized. The applied benefit of this study might extend to rehabilitation centres, where physicians can use available assays to detect thallium.

### Cigarette smokers

Cigarette use is the largest preventable cause of disability, disease, death and numbers of smokers have been increasing steadily all over the world. Each year, an estimated 443,000 people die prematurely from smoking or exposure to passive smoke and another 8.6 million live with a serious illness caused by smoking[75]. On the other hand, the WHO estimates that smoking (cigarette and smoke) is currently responsible for death of 6 million people worldwide and many of premature deaths [76], and a third of all cancer deaths are associated with smoking[77, 78]. Tobacco smoke contains more than 4,000 different toxic substances, cigarette-specific nitrosamines, heavy metals (e.g., cadmium, thallium and lead), and polyaromatic hydrocarbons in heart disease, renal and respiratory problems in long term[77-84]. Thallium and lead are heavy metals, which can pose significant negative effects on human health. Toxicity has been the subject of many reported and is well documented[85]. Thallium might induce numerous adverse health effects. Long-term exposure to Tl results in chronic intoxication, which may manifest mainly as OCPD and renal tubular disease. Also, maybe effects on the reproductive, skeletal and cardiovascular systems[86]. Any levels of thallium are abnormal[87]. Exposure to Tl compounds can link to high poisoning and teratogenicity properties[88-90]. Also, various drug abuses, especially heroin and opium can create thallium poisoning symptoms including neurologic, gastrointestinal, and skin symptoms[66, 67, 69]. Agency Toxic Substances and Disease Registry in a report on toxicological profile of thallium has shown that smoking is one of thallium sources and its suspects that amount of thallium in smokers body is twice of nonsmokers[91]. Ghaderi et al. [92], have documented that the mean value for urinary Tl in the smokers was significantly higher than in the control group (2.39 µg/L). Also, there was a significant relationship between smoking duration and urinary thallium levels. In thy study, a subgroup of smokers addicted to opium and opium residues, the mean level of thallium (37.5 µg/L) was significantly higher than in the other smokers (4.93 µg/L). This can lead to various disturbances and can result in excessive damage due to oxidative stress induced by free radical formation[85]. Both thallium exposure and passive smoker's exposure are more prevalent, which further supports the need for public education about the dangers of thallium exposure and smoking. Further studies are needed to confirm our findings.

### Signs of thallium poisoning

Features of thallium toxicity depend on the route, dose of consuming, individual susceptibility, and onset of treatment[6]. Short-term exposure to Tl might induce hair loss, skin lesions, and damage to the CNS. The clinical features of short-term Tl

intoxication include gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea), and followed by severe painful dysesthesia and paresthesia in the distal limbs, erythematous rashes in the cheeks and perioral region, and hyperkeratosis and loss of hair in the sub acute stage. In the long-term, complete hair loss and severe poly-neuropathy have been shown. The severity of dermatological pictures is supposed to be associated with the severity of Tl intoxication. However, the correlation between the dermatological features and the Tl levels has been rarely studied. In addition, the cutaneous sensory nerve pathological features have rarely been demonstrated. The severe burning pain is associated with the damage in the small myelinated and unmyelinated nerve fibers. Free nerve endings in the epidermis of the skin are responsible for thermal and nociceptive stimuli. A skin biopsy specimen could be used to research small-fiber sensory neuropathy, and the sections stained with protein gene product 9.5 can demonstrate the epidermal nerves[8, 14, 68, 93-95]. In the evidence studies, Tl has had an affinity for sulfhydryl groups and has interfered with sulfhydryl-containing enzymes, which are highly rich in the skin tissue. Cysteine is a sulfhydryl-containing amino acid, and many cysteine residues can cause insolubility and resistance to the stretching of keratin bonds and account for the alopecia in short-term Tl toxicity. The series cutaneous nerve biopsy specimens revealed denervation of the epidermis and total loss of the epidermal nerves and fragmented nerves, compatible with sensory neuropathy with dysesthesia and paresthesia in short-term Tl intoxication. The evidence indicated persistent damage to the small sensory nerve fiber terminals even after 1 year[96-98]. In the study by Lu[93], shown persistent damage to the sensory nerve endings in the short-term Tl intoxication, also, the disappearance of the dermatological features and the appearance of Mees lines associated with the reduce of blood and urinary Tl levels.

### Pathophysiology

The clinical symptoms of acute thallium toxicity, consisting of the characteristic dermatological (e.g., alopecia, hyperkeratosis, and Mees' lines), neurological signs (e.g., dysesthesia, painful neuropathy, muscle weakness, cranial nerve palsies, ataxia, tremor, convulsion, coma, and death). Thallium intoxication may induce CNS and peripheral pathology. Neuro-pathological reported of the brain is limited and reveal edematous changes and vascular engorgement in the cerebral hemispheres, and chromatolytic changes in the motor cortex, globuspallidus, substantianigra, and brainstem nuclei[99-102]. In evidence reports, mental disorder and symptomatic epilepsy may present[102]. To our knowledge, neuroimaging studies have rarely been done[68]. Normal brain MRI scans have been demonstrated in subjects with

cognitive impairments and frequent aggressive outbursts after Tl toxicity[68, 103]. Also, although the underlying pathology is unknown, previous pathological evidence has demonstrated alterations in the cortical and corpus striatum neurons, with central chromatolysis, and edematous changes in the subcortical white matter[104, 105]. The cellular mechanisms of Tl poisoning include the substitution of potassium, and a high affinity for the sulfhydryl or thiol group of mitochondrial membranes[102]. Thus, Tl inhibits many enzyme reactions and protein production. However, the mechanisms of differential involvement in the corpus striatum and asymmetrical lesions. In evidence studies, the highest Tl levels were found in the corpus hypothalamus, thalamus, and striatum[105]. Also was noted that Tl accumulated more rapidly in the hypothalamus and corpus striatum than in other brain regions[106, 107]. However, further investigations are warranted.

### Nervous system

A several of reported have specifically the effect of Tl compounds administered to experimental animals and demonstrated effects on the liver, kidneys, heart, and nervous system[108]. At intervals from 3 months after exposure was initiated, nine animals were sacrificed and nervous system tissues were subject to perfusion fixation; one cat was exposed weekly for 26 weeks. Ataxia and hypotonia were observed in nearly all the cats[105]. The nervous system as a target organ of Tl is supported by observations from human case reports and animal studies. Relatively high doses of Tl cause neurological symptoms in humans including parenthesis, weakness, tremors, coma, and convulsions. Also, neurological symptoms includes parenthesis and weakness were reversible. Other effects, including mental problems, were more persistent. In addition, neurological signs have been linked to chronic exposure to Tl in humans. These signs (e.g., sleep disorders, tiredness, weakness, nervousness, headache, psychological alterations, and neurological and muscular problems).In the animal evidences, Tl exposure has been linked to lipid peroxidation, biochemical, and histopathology changes in the peripheral nerves and brain. The areas affected in the brain differ with the age of the treated animal; nevertheless, all measured endpoints indicate that high doses of Tl induce significant degradation of the nervous system. Results from in vitro studies further confirm these observations. Despite the fact that the nervous system is a known target of Tl poisoning, studies using standard measures of neurobehavioral toxicity have not been performed[99, 103, 105, 108, 109].

### Diagnosis

Diagnosis Tl is based on a characteristic clinical presentation and on laboratory confirmation of Tl in biological fluids. The triad of poly-neuropathy, gastroenteritis, and dermal is regarded as the classic

syndrome of Tl toxicity. Typical alopecia and Mees' lines in the nails appear after 2 weeks in Tl poisoning. Tl concentration is usually examined in urine, blood and hair. In the study by Ghaderi et al., found that qualitative is highly sensitive and specific when compared to quantitative in determining Tl levels in urine. Qualitative assays could be a good surrogate for quantitative tests. In addition, among the analytical techniques that can be used are spectrophotometry, mass spectrophotometry, atomic absorption spectrometry, voltametry, neutron activation analysis, X-ray fluorimetry, and inductively coupled plasma techniques[8, 73, 94, 110-113].

### Prevention and treatment

Monitoring probable intervention and the exposure for decreasing additional exposure to heavy metals including thallium, lead, aluminum, chromium, cadmium, and mercury) in the humans and environment can become a momentous step towards prevention. Also, national international co-operation is vital for framing appropriate tactics to prevent heavy metal poisoning[85]. In after thallium poisoning, the patient receives gastric lavage and is induced emesis in order to prevent further absorption of Tl into the body. Also, hemodialysis is recommended to prevent further Tl distribution through blood. To minimize the impacts on the liver, charcoal can be suggested. In addition, treatment with potassium chloride may promote renal excretion of thallium. Ferric hexacyan of errate has been the most common antidote for Tltoxicity. This compound is known as also known as iron blue, Prussian blue, Paris blue Chinese blue, Turnbull's blue, Brunswick blue and in addition to serving as industrial and art painting pigment, it is used to interrupt re-adsorption of Tl in the intestine and enhance its elimination from the body[15, 114-116]. In the case study by Yumoto[117], report a 23-year-old woman who was poisoned by a business colleague when she unknowingly drank tea containing the toxic substance several times. Also, in the study treatments include Prussian blue and hemodialysis, which are associated with good outcomes.

### CONCLUSION

Thallium poisoning might occur in occupational and environment (air, industrial combustion of coal, water, plants, food, and drinking water) exposure, arable soils and vegetables, aquatic and terrestrial animals, prenatal thallium exposure, illicit drugs, cigarette smokers. Thus, Identification of elimination, sources and control of sources, and monitoring environmental exposures and hazards can be used to prevent thallium toxicity.

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