MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

November 17, 2015

To: File for Thallium and Compounds (as Thallium), (CAS # 7440-28-0)

From: Mike Depa, Toxics Unit, Air Quality Division

Subject: Initial Threshold Screening Level

The acute Initial Threshold Screening Level (ITSL) for thallium compounds is 0.2 µg/m³ with an 8-hour averaging time. The chronic ITSL for thallium compounds is 0.1 µg/m³ with annual averaging time.

A literature review was performed in order to determine if relevant toxicity data was available for thallium. Thallium exists in three valence states: 0, +1 and +3 (Tl^0, Tl^{+1}, Tl^{+3}, respectively; also referred to as elemental thallium, thallium(I) and thallium(III), respectively). See Table 1 for information on some thallium compounds.

Table 1. Thallium and Compounds

Thallium and Compounds and Molecular Formula	Chemical Abstract Service (CAS) Number	Molecular Weight (g/mole)
Elemental thallium Tl	7440-28-0	204.38
Thallium(I) acetate $TlC_2H_3O_2$	563-68-8	263.43
Thallium(I) carbonate Tl_2CO_3	6533-73-9	468.78
Thallium(I) nitrate $TlNO_3$	10102-45-1	266.39
Thallous(I) oxide Tl_2O	1314-12-1	424.77
Thallium(I) sulfate Tl_2SO_4	7416-18-6	504.82
Thallium(I) sulfide, Tl_2S	1314-97-2	440.83
Thallic(III) oxide Tl_2O_3	1314-32-5	256.76
Thallium(III) trinitrate TlN_3O_9	13746-98-0	390.40

The literature sources reviewed included: Registry of Toxic Effects of Chemical Substances (RTECS), National Toxicology Program (NTP) Management Status Report-online, Integrated Risk Information System (IRIS)-online, National Library of Medicine (NLM)-online, Agency for Toxic Substances and Disease Registry (ATSDR) and American Conference of Governmental Industrial Hygienists (ACGIH) Guide.

ACGIH (2010) provided a detailed review of thallium compounds and their toxicity, including human poisoning and occupational exposure and related health effects. A Threshold Limit Value (TLV) of 0.02 mg/m³ (as thallium) was adopted by ACGIH in 2010 to prevent peripheral neuropathy and gastro-intestinal effects in exposed workers. ACGIH noted an occupational epidemiology study by Marcus (1985) where no effects

were observed in workers exposed to ambient factory levels of 0.022 mg/m³ thallium fume and dust. ACGIH (2010) also noted that in a 105 week oral feed study in rats by Downs et al. (1960). In that feed study, both soluble and insoluble forms produced alopecia at roughly the same dose level: 1.2 and 1.8 mg/kg/day, respectively (Downs et al., 1960). This indicates both soluble and insoluble forms of thallium are absorbed and result in the same critical toxicological endpoint when dosing occurs via the oral route. It was deemed appropriate to assume that similar absorption of insoluble and soluble forms of thallium would occur via the inhalation route; therefore, the ACGIH TLV was used to derive an ITSL for all forms of thallium. Pursuant to Rule 232(1)(c) the ITSL was calculated as follows:

ITSL = OEL/100

Where the OEL is an occupational exposure limit, such as the ACGIH TLV.

ITSL = (0.02 mg/m³)/100
ITSL = 0.0002 mg/m³ x 1000µg/mg
ITSL = 0.2 µg/m³

This acute ITSL is for all forms of thallium. Pursuant to Rule 232(2)(a) the averaging time is 8-hours.

U.S. EPA (2009) evaluated the available toxicity data for thallium and its compounds, including both soluble and insoluble. EPA (2009) calculated a candidate RfD for soluble thallium compounds of 3E-6 mg/kg/day:

> The 90-day oral toxicity study of thallium (I) sulfate in Sprague-Dawley rats (MRI, 1988) was identified as a potential principal study. PODs[1] for two alternative endpoints from the MRI study (1988) were selected for dose-response analysis: (1) hair follicle atrophy in female rats with alopecia and (2) clinical observations including those related to animal coat (rough coat, piloerection, shedding, and alopecia), eyes (including lacrimation, exophthalmos, and miosis), and behavior. Based on hair follicle atrophy in female rats, the high dose (0.2 mg/kg-day Tl) was identified as a lowest-observed-adverse-effect-level (LOAEL); the mid dose (0.04 mg/kg-day Tl) was considered a NOAEL[2] and was used as a candidate POD. Benchmark dose (BMD) modeling methods were used to analyze clinical observation data (U.S. EPA, 2000). Based on incidence of alopecia in female rats as representative of clinical observation data, the average 95% lower bound on the dose corresponding to a 10% excess risk (BMDL10) was 0.01 mg/kg-day Tl and was also considered a candidate POD.

EPA (2009) calculated their candidate RfD as follows:

> A total uncertainty factor of 3,000 (10 for interspecies extrapolation, 10 for intraspecies extrapolation, 3 for extrapolation from a subchronic to chronic study, and 10 for database deficiencies) was applied to the PODs to yield candidate RfD values for thallium in the

[1] POD = point of departure
[2] No-observed-adverse-effect-level

> form of soluble thallium salts of 1×10^{-5} mg/kg-day Tl (for hair follicle atrophy) or 3×10^{-6} mg/kg-day Tl (for clinical observations).

Since there was no chemical specific reason for an uncertainty factor (UF) of 10 for database deficiencies, it was removed by this reviewer for purposes of ITSL derivation. A total UF of 300 (10 for interspecies extrapolation, 10 for intraspecies extrapolation, and 3 for extrapolation from a subchronic to chronic study) was used to recalculate an RfD for thallium, as follows:

> RfD = BMDL10/(UF1 x UF2 x UF3)
> RfD = 0.01 mg/kg-day Tl/(10 x 10 x 3)
> RfD = $3.3x10^{-5}$ mg/kg/day; or $3x10^{-5}$ mg/kg/day (using 1 significant figure)

It should be noted that EPA did not finalize their candidate RfD for the following reasons:

> The available toxicity database for thallium contains studies that are generally of poor quality. The MRI (1988) study that was selected as a candidate principal study suffers from certain critical limitations (e.g., high background incidence of alopecia, lack of histopathological examination of skin tissue in low- and mid-dose groups, and inadequate examination of objective measures of neurotoxicity), and there are particular difficulties in the selection of appropriate endpoints. Therefore, even though an RfD would generally be derived with a combined uncertainty factor of 3000, an RfD for soluble thallium salts is not derived in this specific case.

However, given that the nature of Michigan Department of Environmental Quality Air Quality Division screening levels are used as a screening assessment, the RfD of $3x10^{-5}$ mg/kg/day was deemed adequate to use to derive an ITSL for thallium. Using Rule 232(1)(b), the chronic ITSL was calculated as follows:

> ITSL = RfD x 70kg/$20m^3$
> ITSL = $3x10^{-5}$ mg/kg/day x 70kg/$20m^3$
> ITSL = $1x10^{-4}$ mg/m^3 x 1000µg/mg
> ITSL = 0.1 µg/m^3

The chronic ITSL is to be applied to all forms of thallium. This is based on the same reasoning as described above: that soluble and insoluble forms of thallium are reasonably presumed to have the same critical effect at very similar dose levels, as observed in a feed study by Downs et al. (1960). The current file review also concludes that the averaging time for the chronic RfD derived ITSL may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the averaging time is set to annual for the chronic ITSL of 0.1 µg/m^3.

References:

ACGIH (2010). American Conference of Governmental Industrial Hygienists (ACGIH) Guide. Documentation of Threshold Limit Values and Biological Exposure Indices. Cincinnati OH.

Downs, WL; Scott, JK; Steadman, LT; et al. (1960) Acute and sub-acute toxicity studies of thallium compounds. Industrial Hygiene J 21:399–406.

Marcus RL. (1985). Investigation of a working population exposed to thallium. J Soc Occup Med 35:4-9.

MRI (Midwest Research Institute). (1988) Toxicity of thallium (I) sulfate (CAS No. 7446-18-6) in Sprague-Dawley rats. Vol. 2. Subchronic (90-day) study [revised final report]. Prepared by Dynamac Corporation, Rockville, MD, for the Office of Solid Waste, Washington, DC; Project No. 8702-L(18); Work Assignment No. 111148-008. [An external peer review was conducted by EPA in November 2006 to evaluate the accuracy of experimental procedures, results, and interpretation and discussion of the findings presented. A report of this peer review is available through the EPA's IRIS Hotline, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (e-mail address) and at http://www.epa.gov/iris.]

U.S. EPA. (2000) Benchmark dose technical guidance document [external review draft]. Risk Assessment Forum, Washington, DC; EPA/630/R-00/001. Available online at http://cfpub.epa.gov/ncea/cfm/nceapublication.cfm?ActType=PublicationTopics&detype=DOCUMENT&subject=BENCHMARK+DOSE&subjtype=TITLE&excCol=Archive

U.S. EPA. (2009) Toxicological Review of Thallium and Compounds (CAS No 7440-28-0). In support of summary information on the Integrated Risk Information System (IRIS). September 2009. EPA/635/R-08/001F. www.epa.gov/iris.