Stannane, dichlorodimethyl-: Human health tier II assessment

26 October 2018

CAS Number: 753-73-1

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

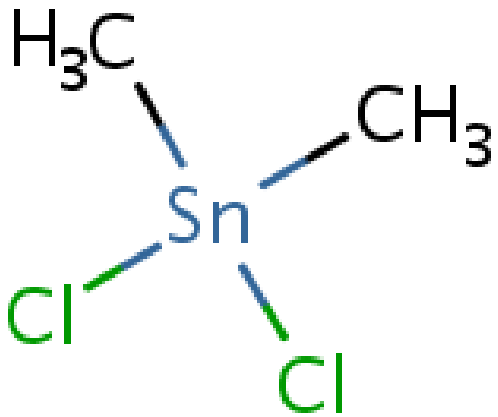
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	dimethyltin dichloride DMTC dichlorodimethyltin dimethyldichlorostannane
Structural Formula	
Molecular Formula	C2H6Cl2Sn
Molecular Weight (g/mol)	219.69
Appearance and Odour (where available)	Colourless crystalline solid
SMILES	C[Sn](C)(Cl)Cl

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified for the chemical.

The National Pollutant Inventory (NPI) holds data for all sources of organotin compounds in Australia.

The following site limited uses were identified for organotin compounds by the NPI in 2016–17:

• glass and glass product manufacturing; and

• polymer product manufacturing.

International

The following international uses have been identified through the Organisation for Economic Cooperation and Development (OECD) Screening information data set (SIDS) International Assessment Report (SIAR) (OECD, 2006); World Health Organization (WHO) Concise International Chemical Assessment Document (CICAD) 73 (WHO, 2006); Classification, Labelling and Harmonisation (CLH)

report (CLH, 2012); Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH); and Galleria Chemica.

The chemical dimethyltin dichloride (DMTC) (CAS No. 753-73-1) has reported site limited uses as:

- an intermediate in the production of heat stabilisers in PVC;
- an intermediate in manufacturing other organotin compounds, or other chemical and mineral products (e.g. plasters, cement); and
- a coating on glass.

The chemical DMTC is always manufactured as a mixture with monomethyltin trichloride (MMTC; CAS No. 993-16-8), either as an aqueous solution or as a solid material, and may contain 10–90 % DMTC by weight.

Mixtures with greater than 50 % DMTC are considered to be dimethyltin substances, whereas mixtures with less than 50 % DMTC are considered to be monomethyltin substances (OECD, 2006).

Restrictions

Australian

Tin organic compounds are listed in the Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) in Schedule 7 (SUSMP, 2018). This entry covers the chemical in this assessment.

"TIN ORGANIC COMPOUNDS, being dialkyl, trialkyl and triphenyl tin compounds where the alkyl group is methyl, ethyl, propyl or butyl except:

a) when separately specified in this Schedule;

b) in plastics;

c) in semi-solid sealants, adhesives or elastomers containing 1 % or less of the dialkyl, trialkyl or triphenyl tin component; or

d) in paint containing 1 % or less of such compounds calculated as tin in the non-volatile content of the paint.

Schedule 7 chemicals are described as: 'Dangerous poisons – Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply.' (SUSMP, 2018)."

Tin and its compounds are listed in the Work Health and Safety Regulations (2016 revision) as restricted hazardous chemicals—the restricted use is 'abrasive blasting at a concentration of greater than 0.1 % as tin' (Galleria Chemica).

International

Tin compounds (organic) are listed on the following (Galleria Chemica):

• Council of Europe Resolution AP (92) 2 on control of aids to polymerisation for plastic materials and articles intended to come into contact with foodstuffs—Limits for finished articles; a limit of 0.05 mg/kg (as Sn) applies.

• Europe Directive 2009/48/EC of the European Parliament and of the Council on the safety of toys—Maximum Migration Limits; limits of 0.2, 0.9 and 12 mg/kg of organic tin applies in sticky toy material, dry or brittle or powder like material, and scraped-off toy material, respectively.

• Council of Europe Resolution ResAP(2008)1 on requirements and criteria for the safety of tattoos and permanent make-up—Table 3 Maximum allowed concentrations of impurities in products for tattoos and PMU; a limit of 50 ppm tin (Sn) applies.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

- Acute toxicity – Category 2; H330 (Fatal if inhaled);
- Acute toxicity – Category 3; H311 (Toxic in contact with skin);
- Acute toxicity – Category 3; H301 (Toxic if swallowed);
- Skin corrosion – Category 1B; H314 (Causes severe skin burns and eye damage);
- Reproductive toxicity – Category 2; H361d (Suspected of damaging the unborn child);
- Specific organ toxicity (repeated exposure) – Category 1; H372 (Causes damage to the nervous system and immune system through prolonged or repeated exposure).

Exposure Standards

Australian

Tin organic compounds (as Sn) have an exposure standard of 0.1 mg/m^3 time weighted average (TWA) and 0.2 mg/m^3 short-term exposure limit (STEL).

International

The following exposure standards are identified for tin organic compounds (as Sn) (Galleria Chemica).

An exposure limit of 0.1 mg/m^3 TWA and 0.2–0.4 mg/m^3 STEL in different countries such as Bulgaria, Canada (Alberta, British Columbia, Ontario, Quebec, Saskatchewan, Yukon), Chile, Denmark, Egypt, Estonia, France, Greece, Hungary, Malaysia, Mexico, Norway, Philippines, Singapore, South Africa, Spain, Sweden, Taiwan, the United Kingdom and the United States of America (California, Hawaii,

Minnesota, Tennessee, Vermont, Washington).

Health Hazard Information

Toxicokinetics

The chemical is readily absorbed through rat epidermis, and to a lesser extent through human epidermis. There is also absorption through the gastrointestinal tract and placenta of pregnant rats, with high concentrations of organic tin distributed to the blood and brains of foetuses.

In a toxicokinetics study (similar to OECD Test Guideline (TG) 417), Sprague Dawley (SD) rats (n = 3/sex/dose) were administered either a single oral or intravenous dose (10 mg/kg bw) of DMTC. Plasma tin concentrations were higher in males than females, irrespective of the route of administration. However, absolute bioavailability (ratio of oral to intravenous area under the curve) was greater in females than males. Distribution of the chemical occurred over at least eight hours. At 12 hours after administration a drastic decrease in tin plasma concentration was noted indicating rapid removal of tin from the body, after which a more gradual decrease occurred, with a terminal plasma half life ranging between 60–268 hours. Analysis showed urinary kinetics was similar between the sexes with the main difference attributed to the route of administration—animals that were administered an oral dose excreted approximately 40 % of the administered tin in their urine, whereas those administered the intravenous dose excreted 100 % in their urine, with a terminal urinary half life ranging between 6–14 hours (REACH).

In a dermal absorption study (according to OECD TG 428), human and SD rat epidermis was exposed (open and occluded) to an 89:11 % mixture of DMTC:MMTC at 100 µg/cm^2 for 24 hours. In human epidermis, approximately 1.4 % of the applied tin was absorbed into receptor fluid under occlusive conditions, compared with 0.25 % of the total dose under open conditions. In rat epidermis, tin absorption into receptor fluid occurred at a much faster rate and was higher (10 %) under both occlusive and open conditions compared with human epidermis. Percutaneous absorption (the amount remaining in skin and considered potentially absorbable) was similar in human and rat epidermis—approximately 22 % under open conditions and 47 % under occluded conditions (REACH).

In an administration and distribution study, female SD rats (n = 12–13/group) were exposed to stannous chloride or DMTC at 0 or 40 mg tin/L via drinking water two weeks prior to breeding, through to the end of gestation. Dam body weights were similar between all groups throughout the study. Water intake was reduced in dams administered DMTC and it was estimated that rats administered stannous chloride had a 50 % higher total tin intake. Pups were euthanised at birth to determine how much DMTC was absorbed from the dam by transfer through the placenta to the blood and brains of the pups. Blood tin was higher in dams administered DMTC versus both stannous chloride and control. The pups born of dams treated with DMTC also had higher levels of tin in their blood and brains. Therefore, DMTC was readily absorbed orally and was transferred to offspring through the placenta, and partitioned to the blood and brain of the foetus (Noland et al., 1983).

In a cross-fostering study, SD pups exposed to DMTC through the DMTC-exposed dams (see previous paragraph) were weaned by control dams (DMTC-CON), or by another DMTC-exposed dam (DMTC-DMTC), while pups not exposed to DMTC through the dams were weaned by a DMTC-exposed dam (CON-DMTC) or another control dam (CON-CON). This process identifies the stage(s) of development that exposure to the chemical potentially affects. Pups exposed to DMTC during gestation (DMTC-CON and DMTC-DMTC) had the highest level of tin in their blood and brain compared with all other pups at birth. At post natal day (PND) 10 the level of tin in the blood and brain decreased by approximately 50 % in both prenatally exposed groups (DMTC-CON and DMTC-DMTC). Pups exposed to DMTC postnatally only (CON-DMTC) had significantly lower concentrations of DMTC in their blood and brain compared to both prenatally exposed groups at PND 10. On PND 21, CON-DMTC pups had higher blood and brain tin levels compared with DMTC-CON pups, but not DMTC-DMTC pups. The results indicate that DMTC is predominantly absorbed by the pups during the gestation period. Exposure during the lactation period

maintained a higher level of tin absorption overall in previously exposed pups (DMTC-DMTC), but pups that were only exposed postnatally (CON-DMTC) also absorbed tin to some extent. The differences were reported to be related to either relatively lower tin transfer to milk or reduced absorption in pups during lactation (Noland et al., 1983).

In a tracer study, pregnant SD dams were orally exposed to ^{14}C-DMTC (0.8 mL/100 g bw) on gestation day (GD) 19 and were subsequently euthanised at 5 min, 15 min, 30 min, 1 hr, 2 hr, 6 hr and 24 hrs after dosing. Brain and blood samples were collected from the dams and foetuses. The highest level of ^{14}C-DMTC in the blood of the dams occurred after 1 hour, while in pups it occurred after 6 hours. The level of ^{14}C-DMTC in the brain of both dams and pups continued to rise up to the 24 hour endpoint. At the 6 hour mark the proportion of ^{14}C in foetal blood was 16 % of the dam blood level, while ^{14}C levels in the foetal brain were 167 % that of the dam brain (Noland et al., 1983).

Acute Toxicity

Oral

The chemical is classified as hazardous with hazard category 'Acute toxicity - Category 3' and hazard statement 'Toxic if swallowed' (H301) in the HCIS. The available data support this classification.

The following oral median lethal dose (LD50) values were reported (OECD, 2006; WHO, 2006; CLH, 2012; RAC, 2012; REACH):

- 74 mg/kg bw in male Wistar rats using DMTC (purity unspecified);
- 141 mg/kg bw in male albino rats using DMTC (purity unspecified);
- 175 mg/kg bw in male and female SD rats using DMTC (>98 %) in corn oil;
- 205 mg/kg bw in male and female SD rats using a 85:15 % mixture of DMTC:MMTC; and
- 409 mg/kg bw in male and female rats (species unspecified) using a 85:15 % mixture of DMTC:MMTC.

Observed sub-lethal effects included breathing difficulties, dehydration, drooling, hunched posture, lethargy, rough haircoat, decreased food consumption and decreased defaecation.

Dermal

The chemical is classified as hazardous with hazard category 'Acute toxicity - Category 3' and hazard statement 'Toxic in contact with skin' (H311) in the HCIS. The available data support this classification.

A dermal LD50 value of 404 mg/kg bw was reported for male and female New Zealand White (NZW) rabbits using a 85:15 % mixture of DMTC:MMTC (OECD, 2006; CLH, 2012; RAC, 2012; REACH).

A dermal LD50 of >2000 mg/kg bw was reported in a non-GLP compliant limit study in male and female NZW rabbits using a 90:10 % mixture of DMTC:MMTC (OECD, 2006; CLH, 2012; RAC, 2012; REACH).

Observed sub-lethal effects included skin irritation at the site of administration, dehydration, lethargy, diarrhoea, reddened iris, wobbly gait, spasms, gauntness, raised area on the abdominal region, partial paralysis of hind limbs, decreased food consumption and decreased defecation.

Inhalation

The chemical is classified as hazardous with hazard category 'Acute toxicity - Category 2' and hazard statement 'Fatal if inhaled' (H330) in the HCIS. Although the available data are inconsistent, the study most similar to OECD TG 403 recorded a median lethal concentration (LC50) value of 0.115 mg/L/4 hr. No amendment to the classification is recommended.

The following inhalation LC50 values were reported (OECD, 2006; WHO, 2006; CLH, 2012; RAC, 2012; REACH):

- 0.115 mg/L/4 hrs in male and female Tif:RAI rats (n = 10/sex/dose) exposed (nose only) to the chemical (purity unspecified) as an aerosol (particle size from <1 µm to >7 µm, generally a higher proportion in the larger size range with increasing doses);
- 1.6 mg/L/1 hr (equivalent to 0.4 mg/L/4 hrs) in male and female Tif:RAI rats exposed (nose only) to the chemical (purity unspecified) as an aerosol (with predominantly (70 %) >7 µm particle size);
- 125 mg/L/1 hr (equivalent to 31.25 mg/L/4 hrs) in male and female rats (species unspecified) exposed to the chemical (purity unspecified) as an aerosol (3–10 µm particle size); and
- 195 mg/L/4 hrs in male Wistar rats exposed (nose only) to the chemical (purity unspecified) as an aerosol (particle size unspecified).

In other inhalation toxicity studies (similar to OECD TG 403), using a 1 hr exposure duration in male rats only, there were no mortalities. Four hour LC50 values were estimated to be >1.44 mg/L/4 hr for rats exposed to the chemical as an aerosol, and >4.2 mg/L/4 hr or >14.2 mg/L/4 hr for rats exposed to the chemical as a vapour (OECD, 2006; CLH, 2012; RAC, 2012; REACH).

Observed sub-lethal effects include breathing difficulties, shaking and ruffled fur. Lung haemorrhage was reported in the animals that died.

Corrosion / Irritation

Corrosivity

The chemical is classified as hazardous with hazard category 'Skin corrosion - Category 1B' and hazard statement 'Causes severe skin burns and eye damage' (H314) in the HCIS. The available data support this classification. Classification for respiratory corrosion is also warranted (see **Recommendation** section).

Skin

In an in vivo dermal irritation study (according to OECD TG 404), NZW rabbits (n = 3/sex) were exposed (semi occlusive) to 0.5 mL of a 85:15 % mixture of DMTC:MMTC on shaved intact skin for 4 hours and monitored for 72 hours after patch removal. There were no deaths. After 1 hour there was necrosis and blanching with severe oedema (fluid build up) at the site of application. After 72 hours the dermal irritation had progressed into eschar (scabbing) on 3 of the animals. Non-reversible erythema (average score of 4/4) and non-reversible oedema (average score of 3.94/4) were noted in all animals averaged across the 24, 48 and 72 hr time points (OECD, 2006; CLH, 2012; REACH).

In a second dermal irritation study (according to the 'Hazardous Substances Regulations' under the U.S. Hazardous Substances Labelling Act Sect. 191.11), NZW rabbits (n = 3) were exposed to 0.5 g of the chemical (moistened with a 50 % solution of polyethylene glycol (PEG) in water) on shaved and abraded sites occlusively for 24 hours. After 24 hours, the skin at the test site was necrotic with fissures occurring into the subcutaneous tissue in all the animals. The animals were subsequently euthanised (OECD, 2006; REACH).

In a third dermal irritation study (similar to OECD TG 404), NZW rabbits (n = 6 males) were exposed (occluded) to 0.5 g of the chemical on shaved and abraded sites for 24 hours and monitored for 72 hours after patch removal. Non-reversible erythema (average score of 3/3 for 24 and 72 hour time points) was noted in all animals on both intact and abraded skin. There was also eschar formation in all animals, at all sites, at the 24 and 72 hour time points. After 24 hours, oedema was noted (average score of 1/1) but was fully reversible after 72 hours (OECD, 2006; CLH, 2012; REACH).

In a fourth dermal irritation study (similar to OECD TG 404), Russian rabbits (n = 3/sex) were exposed to 0.5 g of the chemical (dissolved in a 50 % solution of PEG in water) on shaved and abraded sites occlusively for 24 hours. Shaking, spasms and unbalanced movement were noted at 24 hours, and a hunched posture at 48 hours. An average (24 and 72 hours) primary dermal irritation index score of 0.8 was reported (REACH).

Eye

In an ocular irritation study (similar to OECD TG 405), NZW rabbits (n = 9 males) were administered 100 mg of the chemical in their right eye for either 2 or 4 seconds before being washed out with warm water, or not washed out. The average scores over the 24, 48 and 72 hour time points were maximum for iris, conjunctivae, corneal opacity and chemosis effects (2, 3, 4 and 4 respectfully). The scores obtained were consistent across all the animal groups. The eyes of the animals were severely corroded by the chemical and the damage was irreversible (OECD, 2006; REACH).

In a second ocular irritation study (similar to OECD TG 405), NZW rabbits (n = 3/sex) were administered 0.1 g of DMTC in their left eye which was held shut for 1 second before being washed out after 30 seconds. Signs of pain were reported at the time of chemical administration, and by 6 hours all animals appeared lethargic. After 1 hour, partial corneal destruction was observed in some animals—the iris was only partially visible in one animal, and not visible in three animals. Conjunctival swelling and eventual conjunctival necrosis was reported in all the animals, and five of the animals suffered from a loss of touch sensation to their cornea. No scores were available as the animals were euthanised at 24 hours (OECD, 2006; REACH).

In an ocular irritation study (similar to OECD TG 405), Russian rabbits (n = 3/sex) were administered 0.1 g of DMTC in their left eye which was held open for 30 seconds before being washed out with 10 mL of water. During the seven day observation period 4 of the animals died, while all the remaining animals had irreversible damage to their eyes. After 7 days, the mean irritation index scores obtained were 80/80 for the cornea, 10/10 for the iris, and 12.5/20 for the conjunctivae (REACH).

Respiratory

Considering the irreversible necrotic effects reported following dermal and ocular exposure (including mucous membranes, see above), and the acute inhalation toxicity (see **Acute toxicity: Inhalation** section) with breathing difficulties at sub-lethal concentrations and lung haemorrhage at lethal concentrations, respiratory corrosive effects are likely.

Sensitisation

Skin Sensitisation

Only limited data are available.

In a guinea pig optimisation test, albino guinea pigs (n = 10) were exposed to the chemical at 0.1 % (formulated with polyethylene glycol) via 10 intradermal injections (the first as 0.5 mL, and the remaining 9 as 0.1 mL) administered on alternate days. The animals were challenged two weeks after the last induction with a single 0.05 mL intradermal injection of 0.1 % DMTC. Erythema scores between 0.5–1 (out of a maximum possible score of 4) were reported in 9 of the test animals at induction, with the last animal having a score of 2. Skin thickness near the injection sites increased between 0 and 1 mm in all animals. Reactions following the challenge were similar to those during the induction period. It was reported that there was no evidence of delayed-type skin sensitisation (OECD, 2006; REACH).

Sensitisation studies of dimethyltin mixtures are known to give variable outcomes. In two studies of dimethyltin compounds, one was determined to be sensitising while the other was not. A mixture of mono- and dimethyltins was determined not to result in a sensitisation reaction (WHO, 2006).

Repeated Dose Toxicity

Oral

The chemical is classified as hazardous with the hazard category 'Specific target organ toxicity (repeated exposure) Category 1' and hazard statement 'Causes damage to the nervous system and immune system through prolonged or repeated exposure' (H372) in the HCIS (Safe Work Australia). The available data (thymus effects) support this classification (see also **Other health effects: Neurotoxicity** section).

In a 90-day repeated dose toxicity study (similar to OECD TG 408), SD rats (n = 15/sex/dose) were administered a 90:10 % mixture of DMTC:MMTC in drinking water at 0, 25, 75 or 200 ppm (equivalent to 0, 1.6, 5.2 and 15.5 mg/kg bw/day in males; and 0, 2.2, 6.7 and 19.4 mg/kg bw/day in females) for 13 consecutive weeks. A satellite group was examined for neurotoxicity

(see **Other health effects: Neurotoxicity** section). Several animals (7 males and 21 females) in the high dose group were deceased or were euthanised due to poor health within the first 4 weeks. The remaining animals in the high dose group were euthanised by study day 36. One male in the 75 ppm group was found deceased on day 41 of the study. In all animals exposed at 200 ppm, and males at 75 ppm, significant decline in body weight and food consumption was noted. Significant decreases in food consumption were noted in females exposed to the chemical at 75 ppm and males exposed at 25 ppm. Water consumption was significantly lower across all treated groups when compared to the controls. No differences in haematology were noted between the treated groups and the controls. Significant differences in the clinical chemistry were noted in males from the high dose group only and included increases in blood urea nitrogen (BUN), creatinine, aspartate transaminase (AST), alkaline phosphatase (ALP) and phosphorus, as well as decreased potassium. Males exposed at 200 ppm also had an increased urinary pH in week 4. Significant decreases in the absolute and relative thymus weights were noted in males in the high dose group and in males in the 75 ppm group upon the completion of the study. Thymus lymphoid atrophy was reported in animals exposed at 75 ppm. Significant increases in the absolute and relative kidney weights in females in the 25 and 75 ppm groups were noted upon the completion of the study. Neurobehavioural changes were noted in animals in the 75 and 200 ppm dose groups (see **Other health effects: Neurotoxicity** section). The no observed adverse effect level (NOAEL) was determined to be less than 25 ppm (<1.6–2.2 mg/kg bw/day) (OECD, 2006; WHO, 2006; CLH, 2012; RAC, 2012; REACH).

In a second 90-day repeated dose toxicity study (OECD TG 408), Wistar rats (n = 10/sex/group) were administered a 67:33 % mixture of DMTC:MMTC in the diet at 0, 1, 6, 15 or 200 ppm (equivalent to approximately 0, 0.065, 0.4, 1 and 17 mg/kg bw/day) for 13 consecutive weeks. A satellite group was examined for neurotoxicity (see **Other health effects: Neurotoxicity** section). Three females in the high dose group were found deceased within the first 4 weeks of the study. The remaining animals in the high dose groups showed signs of neurotoxicity, including severe convulsions and tremors, and were subsequently euthanised. Decreased food intake corresponded to delayed growth in the animals in the high dose group. No changes to food consumption, body weight or toxicologically relevant effects were noted in the other dose groups. No treatment related changes were noted in the clinical chemistry, haematology, organ weights and urinalysis undertaken on animals exposed to concentrations up to 15 ppm; these measurements were not undertaken in the high dose group due to their early study termination. Histopathological changes in the thymus, kidneys and brain were noted in the high dose group. The changes in the thymus (increased incidence of corticomedullary bleeding and cortical lymphoid depletion) were proposed to be an indirect effect caused by stress due to the toxicity of the chemical, and not toxicologically relevant. The effects on the kidneys and brain were considered to be toxicologically relevant. The kidneys underwent tubular dilation in the cortical area, while neuronal death occurred in several areas of the brain and there was submeningeal swelling. The observed brain effects were more prominent in females. The NOAEL was determined to be 15 ppm (approximately 1 mg/kg bw/day), based on the kidney and brain effects noted in the high dose group (OECD, 2006; WHO, 2006; CLH, 2012; RAC, 2012; REACH).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

Accidental inhalation exposure to vapours from a mixture of dimethyltin dichloride and trimethyltin chloride by 6 workers (males and females) occurred while cleaning a cauldron in a chemical plant. The workers were exposed to the vapours for a maximum of 1.5 hours total over a 3 day period. After 12 days, one of the workers died and preceding signs of toxicity included high urinary tin excretion, hypoventilation and coma. Two of the surviving workers experienced long-term (>6 years) neurological disabilities, while the remaining workers suffered from memory loss for approximately 6 months (WHO, 2006; REACH).

In a second case study, two chemists were intermittently exposed to a mixture of dimethyltin dichloride and trimethyltin chloride over 3 months. Clinical symptoms suffered by both workers included headaches, memory loss, insomnia, anorexia, pain in organs, disorientation, mental confusion and epileptic seizures. These symptoms disappeared after they were removed from the source of exposure (WHO, 2006; REACH).

It is noted that these case studies may be confounded by concurrent exposure to trimethyltin chloride, which is known to cause neuropathological effects in humans (WHO, 2006).

Genotoxicity

Based on the weight of evidence from available studies, the chemical is not considered to be genotoxic.

Mixed results were obtained using the chemical in the following in vitro genotoxicity studies (OECD, 2006; REACH):

- negative results in bacterial reverse mutation assays (OECD TG 471 and 472) in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and in *Escherichia coli* WP2 uvr A, exposed to a 72:28 % DMTC:MMTC mixture at 10–5000 µg/plate, with and without metabolic activation;
- positive results in a bacterial reverse mutation assay (modified Ames test, similar to OECD TG 471) in *S. typhimurium* TA100 strain, exposed to the chemical at 0.1–10 µg/tube without metabolic activation, but negative results under the same conditions for *S. typhimurium* TA98 strain;
- negative results in an SOS chromotest (DNA damage) in *E. coli* PQ37 exposed to the chemical at up to 100000 µg/tube without metabolic activation;
- positive results in a *Bacillus subtilis* rec-assay (DNA damage) using H17 Rec+ and M45 Rec- strains exposed to the chemical at up to 100000 µg/50 µL without metabolic activation;
- negative results in an in vitro mammalian cell gene mutation test (OECD TG 476) in Chinese hamster ovary (CHO) cells exposed to mixes of methyltin compounds (further details not available) at 0–200 µg/mL without metabolic activation and 0–150 µg/mL with metabolic activation;
- positive results, at cytotoxic levels (1 mM) only, in CHO-9 cells exposed to the chemical at 0.5 µM to 1.0 mM in a cytokinesis blocked micronucleus assay, nuclear division index assay, chromosome aberration assay and sister chromatid exchange; and
- negative results in an in vitro mammalian chromosomal aberration test (OECD TG 473) in human peripheral lymphocytes exposed to mixes of methyltin compounds (further details not available) at 0–32 µg/mL without metabolic activation, but positive results at doses ≥40 µg/mL when exposed at 0–160 µg/mL with metabolic activation.

Negative results were obtained using the chemical in the following in vivo genotoxicity studies (OECD, 2006; REACH):

- an unscheduled DNA synthesis (UDS) test (OECD TG 486) in hepatocytes from male Fischer 344 rats (n = 3/dose) orally administered a single dose of a mixture of methyltin chloride compounds at concentrations of 0, 50, 110 or 225 mg DMTC/kg bw either 2 or 16 hours before being euthanised; and
- a micronucleus assay in erythrocytes from Swiss Webster mice (n = 15/sex/dose) orally administered the chemical (>99 % DMTC) at 0, 100, 200 or 400 mg DMTC/kg bw and assessed at 24, 48 and 72 hours.

Carcinogenicity

No data are available for the chemical. Carcinogenicity was not observed in long-term studies using mixtures of mono- and dimethyltins (WHO, 2006). No further details are available.

Reproductive and Developmental Toxicity

The chemical is classified as hazardous with the hazard category 'Reproductive Toxicity Category 2' and hazard statement 'Suspected of damaging the unborn child' (H361d) in the HCIS (Safe Work Australia). The available data support this classification.

In a 20-day prenatal development toxicity study (similar to OECD TG 414), two studies were performed. In the first study pregnant female Wistar rats (n = 10/group) were administered DMTC (>99 %) at concentrations of 0, 5, 10, 15 or 20 mg/kg bw/day on GD 7–17. Two treatment-related mortalities were noted in dams administered 20 mg/kg bw/day, one each on GD 18

and 19. No pathological changes in the organs of the deceased animals were noted at necropsy, but the dams showed signs of toxicity (nasal and ocular staining, vaginal bleeding, tremors and convulsions) from four days prior to death. Significantly reduced maternal body weight was noted in animals in the two highest dose groups, and there was significantly reduced food intake in the highest dose group. In the surviving dams exposed at 20 mg/kg bw/day, signs of toxicity (nasal and ocular staining, vaginal bleeding, tremors and convulsions) were reported from GD 15 onwards. At necropsy, there was a dose-dependent decrease in maternal thymus weights, with significant reductions at ≥15 mg/kg bw/day. On GD 20, one dam in the 20 mg/kg bw/day group had no viable foetuses as they had undergone total resorption. There was a dose dependent decrease in the average body weight of foetuses (both sexes) with significant reductions noted at 15 and 20 mg/kg bw/day. An increase in external malformations (cleft palate) was noted in 21 of the living foetuses from 5 out of the 7 dams that were administered the chemical at 20 mg/kg bw/day on GD 20. There was a statistically significant increase in the number of foetuses from dams administered the chemical at 20 mg/kg bw/day that had visceral variations and dilation of the renal pelvis. No significant differences in the number of living foetuses, implants, corpora lutea or incidence of post implantation loss and sex ratio were noted. The NOAEL for maternal and foetal toxicity was reported to be 10 mg/kg bw/day (OECD, 2006; WHO, 2006; CLH, 2012; RAC, 2012; REACH).

In the second part of the above study, pregnant female Wistar rats (n = 8–11/dose/administration period) were administered DMTC (>99 %) at concentrations of 0, 20 or 40 mg/kg bw/day for 2–3 consecutive days, during one of four periods of gestation (GD 7–9, 10–12, 13–15 or 16–17). All surviving animals were euthanised on GD 20. At the highest dose, significant reductions in maternal body weight gain were noted on GD 13, 16 and 17, and there was reduced food intake from GD 12. There was a significant decrease in maternal thymus weights in all rats administered 40 mg/kg bw/day and those administered 20 mg/kg bw/day on GD 10–12. One of the rats administered 20 mg/kg bw/day showed a total resorption of foetuses, while a dose dependent decrease in the average body weight of the living foetuses was noted. A significant increase in the number of cervical ribs was noted in foetuses from groups administered the chemical at 40 mg/kg bw/day on GD 7–9 and 13–15. There were also significant increases in the number of foetuses with splitting of the first cervical vertebral arch and kinked ureter in the group administered the chemical at 40 mg/kg bw/day on GD 7–9 and 16–17 (OECD, 2006; WHO, 2006; CLH, 2012; RAC, 2012; REACH).

In a developmental neurotoxicity study (similar to OPPTS 870.6300), female SD rats (n = 30/dose) were exposed to DMTC at 0, 3, 15 or 74 ppm (approximately equivalent to 0.28–0.52, 1.16–2.55 and 4.38–12.2 mg/kg bw/day) via drinking water for two weeks before mating, and through gestation and lactation up to postnatal day (PND) 21 (see **Other health effects: Neurotoxicity** section). Maternal effects during the exposure period included significant decrease in water consumption across all groups, while in the high dose group there was a significantly lower body weight gain. There were fewer males born in the treated dams, but this was not statistically significant. Pup weights were similar across all groups. There was no significant difference in the number of pups that died compared with control. The average male pup weight was not significantly changed due to DMTC exposure when compared with controls. There were no external abnormalities noted in any pups (CLH, 2012; RAC, 2012; REACH).

In a second developmental neurotoxicity study (similar to OPPTS 870.6300) pregnant SD rats (n = 21–22/group) were administered DMTC at 0, 3, 15 or 74 ppm (approximately equivalent to 0.33–0.57, 1.53–2.67 and 7.26–11.9 mg/kg bw/day) from GD 6 through to lactation (see **Other health effects: Neurotoxicity** section). Maternal effects observed from the beginning of exposure to the end of gestation included a significantly lower fluid intake in the 15 and 74 ppm groups. In the second week of exposure a decrease in food consumption was noted in animals in the 3 ppm group, while significantly lower body weight in the high dose group was noted during the lactation period. No dose related effects on pup birth rate was noted. Significantly decreased body weight in males in the high dose group was noted during lactation while significant body weight decreases occurred in females on PND 17 and 21. There were no external abnormalities noted in any pups (CLH, 2012; RAC, 2012; REACH).

Other Health Effects

Neurotoxicity

The chemical is classified as hazardous with the hazard category 'Specific target organ toxicity (repeated exposure) Category 1' and hazard statement 'Causes damage to the nervous system and immune system through prolonged or repeated exposure' (H372) in the HCIS (Safe Work Australia). The available neurotoxicity study data support this classification (see also **Repeated dose toxicity: Oral** section).

In a 90-day repeated dose toxicity study (similar to OECD TG 408), SD rats (n = 15/sex/dose) were administered a 90:10 % mixture of DMTC:MMTC in drinking water at 0, 25, 75 or 200 ppm (equivalent to 0, 1.6, 5.2 and 15.5 mg/kg bw/day in males; and 0, 2.2, 6.7 and 19.4 mg/kg bw/day in females) for 13 consecutive weeks (see **Repeated dose toxicity: Oral** section). Animals administered the chemical at 200 ppm showed behavioural effects such as tremors, convulsions, increased aggression and touch hypersensitivity. Animals exposed at 75 ppm also had tremors and were hypersensitive to touch. Functional observational battery (FOB) test outcomes in the fourth week showed that females in the high dose group had significantly lower body temperature, lower hindlimb grip strength and reduced rearing. Three females also exhibited tremors and seizures, while one other female exhibited signs of uncoordination. One male had tremors, jaw convulsions, and an unsteady gait, while another male had a hunched posture. Females administered the chemical at 75 ppm showed reduced motor activity. The brain weight of males exposed at 75 ppm was significantly increased at the end of the study. Necropsy of the animals identified neuronal necrosis, ventricular dilation, and white matter vacuolisation in the brain and spinal cord of all treated groups. At 200 ppm, there was also axonal degeneration of spinal cord tissue (OECD, 2006; WHO, 2006; CLH, 2012; RAC, 2012; REACH).

In a second 90-day repeated dose toxicity study (OECD TG 408), Wistar rats (n = 6/sex/group) were administered a 67:33 % mixture of DMTC:MMTC in the diet at 0, 1, 6, 15 or 200 ppm (equivalent to approximately 0, 0.065, 0.4, 1 and 17 mg/kg bw/day) for 13 consecutive weeks (see **Repeated dose toxicity: Oral** section) and studied for neuropathological outcomes. Animals in the 200 ppm dose group exhibited hunched posture, signs of involuntary eye closure (blepharospasm), tremors and convulsions. Necropsy of the animals in the 200 ppm dose group showed the presence of neuronal death in various areas of the cerebellum, and a slight increase in the presence of swollen axons within the spinal cord. Other areas of the brain with lesions included the amygdala; the entorhinal, perirhinal and pirifor cortices; and the region around the olfactory nuclei. No other dose group exhibited any of these neuropathological symptoms or neuropathological effects (OECD, 2006; WHO, 2006; CLH, 2012; RAC, 2012; REACH).

In a developmental neurotoxicity study (similar to OPPTS 870.6300), female SD rats (n = 30/dose) were exposed to DMTC at 0, 3, 15 or 74 ppm (approximately equivalent to 0.28–0.52, 1.16–2.55 and 4.38–12.2 mg/kg bw/day) via drinking water for two weeks before mating, and through gestation and lactation up to postnatal day (PND) 21. One male offspring from each litter was tested in each of the different neurobehavioural tests. There were no significant treatment related differences between the groups in a runway learning test and subsequent extinction trials, in a motor activity test and in the Morris water maze test (observes the memory, spatial learning and cognitive function). In males exposed at the highest dose, neuropathological examination revealed mild vacuolation of the neuropil (a dense network of nerve fibres, branches and synapses) of the grey matter in the cerebral cortex in 60 % of offspring on PND 22 and in 20 % as adults. In the lower dose groups (3 and 15 ppm), 20 % of the tested adult animals had mild vacuolation of the neurophil. There were significant decreases in the brain weight of the males in the low and high dose groups. By PND 22, decreased apoptosis and mild vacuolation in cerebellar and cortical brain occurred in some offspring across the dose groups (CLH, 2012; RAC, 2012; REACH).

In the second experiment from the above developmental neurotoxicity study, pregnant SD rats (n = 21–22/group) were administered DMTC at 0, 3, 15 or 74 ppm (approximately equivalent to 0.33–0.57, 1.53–2.67 and 7.26–11.9 mg/kg bw/day) from GD 6 through to lactation. In runway testing, the number of male offspring that failed to learn to negotiate the runway increased in a dose dependent manner, and learning was significantly reduced in rats at 15 and 74 ppm. In motor activity testing, there were no differences in motor activity between groups and between the sexes and spontaneous alternation testing (tests spatial learning and memory) showed no significant differences in the number of arm visits or alternations. In the Morris water maze test, it was noted that there was no difference in the swim speed or latency to find the visible platform across the dose groups. No significant treatment related changes in brain weight were identified in adult mice (male and female). One male offspring from the 74 ppm group had a central chromotolysis with a single neuron in the midbrain (CLH, 2012; RAC, 2012; REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (developmental toxicity, neurotoxicity and thymus effects) and local effects (corrosion). The chemical may also cause systemic acute effects (acute toxicity from oral, dermal and inhalation exposure).

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Hence, the public risk from this chemical is not considered to be unreasonable.

The chemical is currently listed in Schedule 7 of the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2018), precluding its use in consumer products in Australia.

Occupational Risk Characterisation

During product formulation, oral, dermal, inhalation and ocular exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term, acute and local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, inhalation and ocular exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls. There is uncertainty regarding the risks to workers from repeated inhalation exposures. However, the control measures expected to be in place to protect workers from the risks of the known health effects (acute toxicity and corrosivity) should be adequate to minimise the risks of repeated inhalation exposure.

The data available support an amendment to the hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation. The chemical is not available to the public (SUSMP, 2018).

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Toxic if swallowed - Cat. 3 (H301)* Toxic in contact with skin - Cat. 3 (H311)* Fatal if inhaled - Cat. 2 (H330)*
Irritation / Corrosivity	Not Applicable	Corrosive to the respiratory tract (AUH071) Causes severe skin burns and eye damage - Cat. 1B (H314)*
Repeat Dose Toxicity	Not Applicable	Causes damage to the nervous system and immune system through prolonged or repeated exposure - Cat. 1 (H372)*
Reproductive and Developmental Toxicity	Not Applicable	Suspected of damaging the unborn child - Cat. 2 (H361d)*

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and

- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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