Monomethyltin alkyl mercaptoacetates: Human health tier II assessment

29 June 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Acetic acid, 2,2',2''-[(methylstannylidyne)tris(thio)]tris-, triisooctyl ester	54849-38-6
8-Oxa-3,5-dithia-4-stannatetradecanoic acid, 10-ethyl-4-[[2-[(2-ethylhexyl)oxy]-2-oxoethyl]thio]-4-methyl-7-oxo-, 2-ethylhexyl ester	57583-34-3

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

Grouping Rationale

The chemicals monomethyltin tris(2-ethylhexylmercaptoacetate) (MMT(2-EHMA)— CAS No. 57583-34-3), monomethyltin tris(isooctylmercaptoacetate) (MMT(IOMA)—CAS No. 54849-38-6) are structurally similar and are expected to have similar physicochemical and toxicological properties (OECD, 2006a; OECD, 2006b).

The chemicals in this group are metabolised to monomethyltin trichloride (MMTC, CAS No. 993-16-8; NICNASa) and either 2-ethylhexyl mercaptoacetate (EHMA, CAS No. 7659-86-1) or isooctyl mercaptoacetate (IOMA, CAS No. 25103-09-7) when placed in a simulated mammalian gastric environment (OECD, 2006a). The two mercaptoacetates have similar physicochemical and toxicological properties (NICNASb).

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified for these chemicals.

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 European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development (OECD) Screening information data set (SIDS) International Assessment Report (SIAR) (OECD, 2006a; OECD, 2006b); World Health Organization (WHO) Concise International Chemical Assessment Document (CICAD) 73 (WHO, 2006); Classification, Labelling and Harmonisation (CLH) report (CLH, 2010); Galleria Chemica; and the Substances and Preparations in Nordic countries (SPIN) database.

MMT(2-EHMA) has reported commercial use in food contact applications.

MMT(2-EHMA) and MMT(IOMA) have reported site-limited use as stabilisers in the production of polyvinyl chloride materials. Small amounts are expected to be present in articles manufactured from those materials.

MMT(IOMA) was reported to be used historically; MMT(2-EHMA) is now reported to be the more dominant product (OECD, 2006b).

MMT(2-EHMA) and MMT(IOMA) are commonly manufactured as mixtures with their corresponding dimethyltin (DMT) counterparts. Mixtures with greater than 50 % MMT are considered to be monomethyltin substances, whereas mixtures with less than 50 % MMT are considered to be dimethyltin substances (OECD, 2006a).

Restrictions

Australian

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 are listed on the following (Galleria Chemica):

- Council of Europe Resolution AP (92) 2 on control of aids to polymerisation for plastics 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 Worker Health and Safety Controls

Hazard Classification

The chemical MMT(2-EHMA) is classified as hazardous, with the following hazard category and hazard statement for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

- Reproductive toxicity – category 2; H361d (Suspected of damaging the unborn child).

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

Only limited data are available for the chemicals. When data for the chemicals being assessed are not available, health hazard information for MMTC, EHMA and IOMA has also been included in this report, to cover other aspects of toxicity caused by both the tin and the mercaptoacetate moieties. Data for MMTC are considered relevant for systemic endpoints, since this will effectively be the only tin compound present under acidic conditions similar to the gastric environment (see **Toxicokinetics** section). EHMA or IOMA are also formed during metabolism (see **Toxicokinetics** section) (NICNASa; NICNASb).

For the specific toxicological data for MMTC, EHMA and IOMA, refer to the separate assessments (NICNASa; NICNASb).

The Tier II assessment report for MMTC is available at **https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=13327**. The Tier II assessment report for EHMA and IOMA is available at **https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1309**. These reports should be read in conjunction with this Tier II assessment.

Toxicokinetics

Studies have shown that organotin compounds with sulfur or carboxylate based ligands are easily displaced under mild physiological conditions (REACH).

Under gastric conditions the chemicals MMT(2-EHMA) and MMT(IOMA), rapidly convert (approximately 94 %) to MMTC and release the EHMA and IOMA ligands respectively within 0.5 hours.

The tin and mercaptoacetate esters will be distributed, metabolised and excreted separately (NICNASa; NICNASb).

Acute Toxicity

Oral

Based on the available data, the chemicals have moderate acute oral toxicity, warranting hazard classification (see **Recommendation** section). This is supported by the data for MMTC (NICNASa) and EHMA/IOMA (NICNASb).

The following oral LD50 values for MMT(2-EHMA) were reported (OECD, 2006a; REACH; RTECS):

- 880 mg/kg bw in Sprague Dawley (SD) rats using MMT(2-EHMA) (purity unspecified);
- 920 mg/kg bw in rats (strain unspecified) using MMT(2-EHMA) (purity unspecified); and
- 1100 mg/kg bw in rats (strain unspecified) using a mixture containing MMT(2-EHMA) (purity unspecified).

Observed sub-lethal effects included depression, piloerection, squinting, hunched posture, breathing difficulties and a lack of voluntary muscle coordination.

The following oral LD50 values for MMT(IOMA) were reported (OECD, 2006b):

- 829.5 mg/kg bw in SD rats using MMT(IOMA) (purity unspecified);
- 1231 mg/kg bw in male rats (strain unspecified) using MMT(IOMA) (purity unspecified);
- 1400 mg/kg bw in Tif RAI specific pathogen free rats (SPF) using MMT(IOMA) (purity unspecified); and
- 1840 mg/kg bw in SD rats using MMT(IOMA) (purity unspecified).

Observed sub-lethal effects included depression, piloerection, drooping upper eyelids, nasal discharge, rapid breathing and a lack of voluntary muscle coordination.

The metabolites MMTC, EHMA and IOMA were recommended for classification as hazardous for acute oral toxicity based on the available data (NICNASa; NICNASb).

Dermal

Based on the available data using a mixture of MMT(2-EHMA):DMT bis(EHMA) (purity unreported), the chemicals have moderate acute dermal toxicity, warranting hazard classification (see **Recommendation** section).

The reported dermal LD50 was 1000 mg/kg bw in female, and 2150 mg/kg bw in male, New Zealand White (NZW) rabbits (OECD, 2006a; REACH). The combined data would average to be within the classification range.

Observed sub-lethal effects include incoordination, tremors and hypersensitivity to external stimuli.

Inhalation

No data are available. The low volatility of the chemicals MMT(2-EHMA) and MMT(IOMA) (CLH, 2010; OECD, 2006a; REACH) is expected to minimise inhalation exposure.

Corrosion / Irritation

Skin Irritation

As severe local dermal toxicity was not observed in the acute toxicity studies (see **Acute toxicity: Dermal** section), the chemicals are not expected to cause dermal irritation.

Eye Irritation

No data are available.

Sensitisation

Skin Sensitisation

Based on the available data for MMT(2-EHMA), the chemicals are considered to be skin sensitisers, warranting hazard classification (see **Recommendation** section). The data for EHMA and IOMA support this classification (NICNASb).

In a local lymph node assay (OECD Test Guideline (TG) 429), female CBA/Ca mice (n = 6/dose) were treated topically with the chemical (25 µL, >88% purity) on the dorsum of both ears at concentrations of 0, 5, 25 or 50 % once daily for three consecutive days. Animals were observed for up to three days after exposure. Animals treated at 50 % had a decreased body weight gain compared to the control group. The EC3 value (the estimated concentration to produce a three-fold increase in lymphocyte proliferation) was calculated to be 8.40 %, based on stimulation index (SI) scores of 2.13, 7.5 and 9.05 at 5, 25 and 50 %, respectively (REACH).

The metabolites EHMA and IOMA were recommended for classification for sensitisation based on available data (NICNASb).

Repeated Dose Toxicity

Oral

No data are available for the chemicals. Based on the available data for MMTC (NICNASa), the chemicals are considered to cause serious health effects following repeated oral exposure, warranting hazard classification (see **Recommendation** section).

Following repeated oral exposure, MMTC was reported to decrease the size of the thymus and there was evidence of neurotoxicity (NICNASa). Limited data indicate that IOMA and EHMA did not cause serious damage to health from repeated oral exposure (NICNASb).

Genotoxicity

No data are available. The chemicals MMTC, IOMA and EHMA were not considered to be genotoxic based on the available data (NICNASa; NICNASb).

Carcinogenicity

No data are available for the chemicals. The limited data available for the metabolites do not indicate a concern for carcinogenicity (NICNASa; NICNASb).

Reproductive and Developmental Toxicity

Based on the available data for MMTC (NICNASa) and EHMA (NICNASb), the chemicals are considered to have the potential to cause developmental effects following repeated oral exposure, warranting hazard classification (see **Recommendation** section).

MMTC and EHMA are classified as hazardous with the hazard category 'Reproductive Toxicity Category 2' and hazard statement 'Suspected of damaging the unborn child' (H361d) in HCIS (Safe Work Australia).

While the available data for MMTC were inconsistent, increased post implantation loss and some developmental neurotoxicity was observed (NICNASa).

EHMA was reported to cause developmental effects at maternally toxic levels, however direct neonatal effects resulting from exposure to maternal milk could not be discounted (NICNASb).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (repeated dose toxicity and developmental toxicity) following oral exposure and local effects (skin sensitisation). The chemicals can also cause harmful effects following acute oral and dermal exposure.

Public Risk Characterisation

The public could be exposed to the chemicals at low levels based on their use as PVC stabilisers and use in food contact applications. At these levels the acute and local effects are not expected. Internationally, a group tolerable daily intake (TDI) of (0.1 µg/kg bw as Sn) for organotins in foodstuff based on systemic effects has been established (European Commission, 2009). To reduce the identified risk of organotins transferred from food packaging to foodstuffs, the overall exposure should be lower than the TDI. The dominant contribution to human intake of organotins (mainly tributyltin) is via consumption of fish. Exposure to other organotins, including these chemicals is expected to be generally low both from food contact and handling PVC articles. Hence, the public risk from these chemicals is not considered to be unreasonable. If data becomes available indicating specific uses in Australia that could significantly contribute to the overall TDI for organotins, further assessment of these chemicals may be required.

Occupational Risk Characterisation

During product formulation, ocular and dermal 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 chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed. Good hygiene practices to minimise oral exposure are expected to be in place.

Given the critical systemic long-term and acute health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise oral and dermal exposure are implemented. The chemicals 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.

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

NICNAS Recommendation

Assessment of these chemicals are considered to be sufficient, provided that the recommended amendments to the classification are 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

Work Health and Safety

The chemicals are 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]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1B (H317)
Repeat Dose Toxicity	Not Applicable	May cause damage to the nervous system and immune system through prolonged or repeated exposure - Cat. 2 (H373)
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 industry

Control measures

Control measures to minimise the risk from oral and dermal exposure to the chemicals 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 chemicals are 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 chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemicals, 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 chemicals.

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 chemicals 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 these chemicals has not been undertaken as part of this assessment.

References

Classification, Labelling and Harmonisation (CLH) Report 2010. Monomethyltin tris(2-ethylhexylmercaptoacetate) (MMT(EHMA)) (CAS No. 57583-34-3). Dossier submitted by France, Accessed May 2018 at: https://echa.europa.eu/documents/10162/13626/clh_report_ehma_en.pdf

European Commission 2009. COMMISSION STAFF WORKING DOCUMENT Impact Assessment Report Proposal for a COMMISSION DECISION amending Council Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations (Organostannic compounds). Accessed May 2018 at http://ec.europa.eu/growth/sectors/chemicals/reach/studies/index_en.htm

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Safe Work Australia. Hazardous Chemicals Information System (HCIS). Accessed May 2018 at http://hcis.safeworkaustralia.gov.au/HazardousChemical

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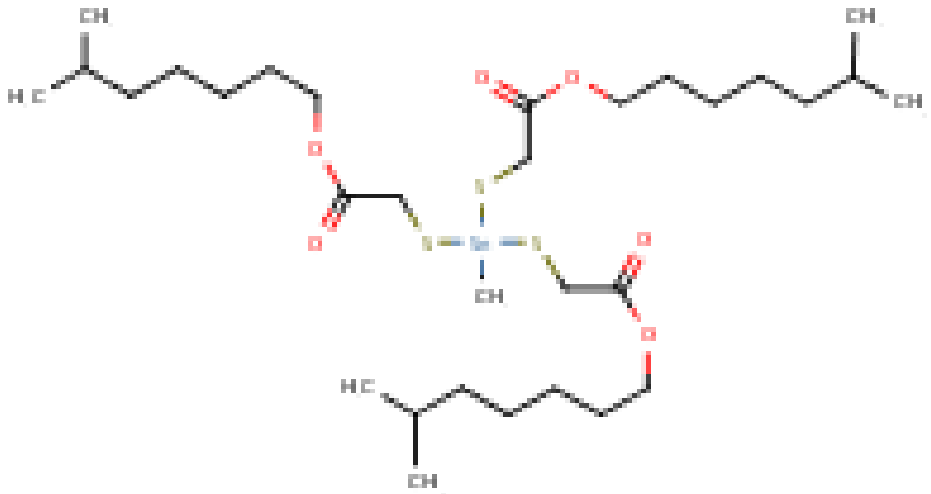
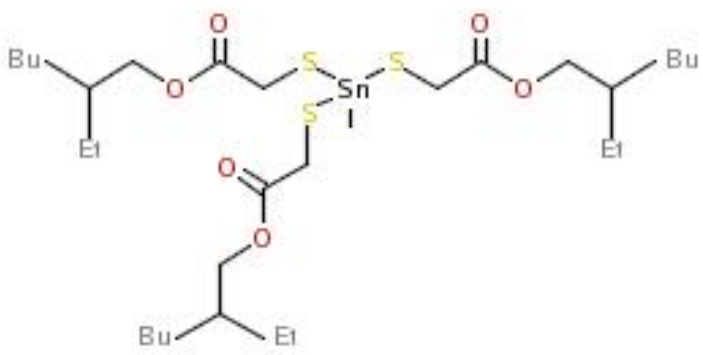
World Health Organization (WHO), Concise International Chemical Assessment Document 73 (CICAD), 2006. Mono and disubstituted methyltin, butyltin, and octyltin compounds. Accessed May 2018 at http://www.inchem.org/documents/cicads/cicads/cicad73.pdf
Last Update 29 June 2018

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Acetic acid, 2,2',2''-[(methylstannylidyne)tris(thio)]tris-, triisooctyl ester** stannane methyltris[(carboxymethyl)thio monomethyltin tris[isooctylmercaptoacetate] MMT(IOMA) monomethyltin tris[isooctyl thioglycolate] MMT(IOTG)
CAS Number	54849-38-6
Structural Formula	
Molecular Formula	C31H60O6S3Sn
Molecular Weight	743.70

Chemical Name in the Inventory and Synonyms	**8-Oxa-3,5-dithia-4-stannatetradecanoic acid, 10-ethyl-4-[[2-[(2-ethylhexyl)oxy]-2-oxoethyl]thio]-4-methyl-7-oxo-, 2-ethylhexyl ester** monomethyltin tris[2-ethylhexylmercaptoacetate] MMT(2-EHMA) 2-ethylhexyl 10-ethyl-4-[[2-[(2- ethylhexyl)oxy]-2-oxoethyl]thio]- 4-methyl-7-oxo-8-oxa-3,5-dithia- 4-stannatetradecanoate monomethyltin tris[2-ethylhexyl thioglycolate] MMT(EHTG)
CAS Number	57583-34-3
Structural Formula	
Molecular Formula	C31H60O6S3Sn
Molecular Weight	743.70

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