Dibutyltin alkyl mercaptoacetates: Human health tier II assessment

12 December 2019

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
8-Oxa-3,5-dithia-4-stannatetradecanoic acid, 4,4-dibutyl-10-ethyl-7-oxo-, 2-ethylhexyl ester	10584-98-2
8-Oxa-3,5-dithia-4-stannaeicosanoic acid, 4,4-dibutyl-7-oxo-, dodecyl ester	20004-12-0
Acetic acid, 2,2'-[(dibutylstannylene)bis(thio)]bis-, diisooctyl ester	25168-24-5
8-Oxa-3,5-dithia-4-stannadocosanoic acid, 4,4-dibutyl-7-oxo-, tetradecyl ester	83833-21-0

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 in this group are structurally similar organostannic mercaptoacetates:

- dibutyltin bis(2-ethylhexylmercaptoacetate) (DBT(2-EHMA), CAS No. 10584-98-2);
- dibutyltin bis(isooctylmercaptoacetate) (DBT(IOMA), CAS No. 25168-24-5);
- dibutyltin bis(laurylmercaptoacetate) (DBT(LMA), CAS No. 20004-12-0); and
- dibutyltin bis(myristylmercaptoacetate) (DBT(MMA), CAS No. 83833-21-0).

DBT(2-EHMA) and DBT(IOMA) are isomers which differ only in the structure of the C8 alcohol of the mercaptoester ligand, and can be considered toxicologically equivalent (OECD, 2009).

The chemicals contain a dibutyl (Bu_2Sn-) group and two labile ligands (X). In general the toxicity of organotin compounds depends largely on the organotin moiety (R group), with the anionic ligand (X) mostly influencing physico chemical properties and local toxicity. The chemicals are grouped together for risk assessment due to their similar end uses and expected toxicity profiles.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified for the chemicals under previous mandatory/voluntary calls for information.

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 2017–18:

- glass and glass product manufacturing; and
- polymer product manufacturing.

International

Di-substituted organotin compounds are mainly used in the plastics industry as stabilisers in polyvinyl chloride (PVC). Dibutyltins are also used as catalysts in the production of polyurethane foams and in the room temperature vulcanisation of silicones (ATSDR, 2005; RPA, 2007).

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 Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the OECD High Production Volume chemical program (OECD HPV); and the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR).

The chemicals have reported uses in paint, lacquers and varnishes in the Substances and Preparations in the Nordic Countries (SPIN) database. However, it should be noted that SPIN does not distinguish between direct use of the chemical, or use of the materials that produced from the chemical reactions involving the chemical.

The chemicals have other reported domestic uses, including in:

- adhesives and sealants (concentrations unspecified);
- construction materials (including putties and fillers).

The chemicals have reported commercial uses, including:

- in the manufacture of motor vehicles;
- as electroplating agents;
- as corrosion inhibitors;
- as absorbents and adsorbents;
- as process regulators;
- in cleaning and washing agents; and
- as catalysts in condensation and esterification reactions (including curing of room-temperature-vulcanised (RTV) silcone elastomers)

The chemicals have reported site-limited use as stabilisers in the manufacture of polyvinyl chlorides (PVC) and chlorinated polyvinyl chloride (CPVC).

The chemicals are mainly manufactured as a mixture with their monobutyltin equivalents (i.e. monobutyltin tris(2-ethylhexyl mercaptoacetate) (MBT(2-EHMA), CAS No. 26864-37-9). The dibutyltin content will be dependent on the starting materials, with a range of 20 to 80 % (by weight) dibutyltin in the final mixture. Mixtures with greater than 50 % dibutyltin are considered to be dibutyltin substances, whereas mixtures with less than 50 % dibutyltin are considered to be monobutyltin substances. However for specialised PVC applications, the pure form of the dibutyltin is used (OECD, 2009).

Restrictions

Australian

The chemicals are covered by the group entry for 'TIN ORGANIC COMPOUNDS' in Schedule 7 of the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2019):

Schedule 7:

'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 per cent or less of the dialkyl, trialkyl or triphenyl tin component; or

d) in paint containing 1 per cent or less of such compounds calculated as tin in the nonvolatile 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, 2019).

Tin and its compounds are listed in Schedule 10 of the Model Work Health and Safety Regulations as restricted hazardous chemicals—the restricted use is 'abrasive blasting at a concentration of greater than 0.1% as tin' (Safe Work Australia, 2019).

International

Dibutyltin compounds—which includes the chemicals in this assessment—are listed on the following (European Parliament and Council, 2009; Galleria Chemica):

- Annex I to Regulation (EU) No 649/2012 of the European Parliament and of the Council concerning the export and import of hazardous chemicals—a severe restriction applies for the industrial chemical for public use (Galleria Chemica); and
- Annex XVII to the REACH Regulations—the chemicals cannot be used in mixtures and articles for supply to the general public where the concentration in the mixture or the article, or part thereof, is greater than the equivalent of 0.1 % by weight of tin. Organostannic compounds are also restricted for biocide and water treatment uses.

Tin organic compounds—which includes the chemicals in this assessment—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 to tin compounds organic (Galleria Chemica); and
- 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 liquid or sticky toy material, dry or brittle or powder-like or pliable toy material, and scraped-off toy material, respectfully.

- Council of Europe Resolution ResAP(2008)1 on requirements and criteria for the safety of tattoos and permanent make-up (PMU)—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 chemicals are not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

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) (Safe Work Australia).

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 mg/m^3 STEL in different countries such as Abu Dhabi, Bulgaria, Canada (Alberta, British Columbia, Ontario, Quebec, Saskatchewan, Yukon), Chile, China (Hong Kong), Denmark, Egypt, Estonia, France, Greece, Malaysia, Mexico, New Zealand, Norway, Philippines, Singapore, South Africa, Spain, Sweden, Taiwan, the United Kingdom and the United States of America (California, Hawaii, Minnesota, Tennessee, Vermont).

The American Conference of Government Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) of 0.1 mg/m TWA for Tin, organic compounds, as Sn 'to minimize the potential for adverse effects on immune function and the central nervous system.' and 0.2 mg/m STEL 'to minimize acute symptoms such as eye and upper respiratory tract irritation, headache, and nausea.' (ACGIH, 2011).

Health Hazard Information

Data on DBT(2-EHMA) and DBT(IOMA) have been included in this report where available. Data indicate that the chemicals are hydrolysed to release mercaptoacetate moieties when placed in a simulated mammalian gastric environment (refer **Toxicokinetics** section). Two of the mercaptoacetate hydrolysis products 2-ethylhexyl mercaptoacetate (EHMA, CAS No. 7659-86-1) and isooctyl mercaptoacetate (IOMA, CAS No. 25103-09-7 are isomers and have similar physiochemical and toxicological properties (NICNASd). Although no toxicological data were identified for dodecylmercaptoacetate (DDMA, CAS No. 3746-39-2) and tetradecylmercaptoacetate (TDMA, CAS No. 57414-16-1), they are expected to be toxicologically similar to the other mercaptoacetates.

Although there is limited evidence that the chemicals are hydrolysed to dibutyltin dichloride (DBTC—CAS No. 683-18-1), in general the toxicity of organotin compounds depends largely on the organotin moiety (R group), with the anionic ligand (X) mostly influencing physicochemical properties and local toxicity.

Therefore when data for the chemicals being assessed are not available, health hazard information for EHMA, IOMA and for dibutyltin compounds including DBTC, dibutyltin dilaurate (DBTL—CAS No. 77-58-7) and dibutyltin diacetate (DBTA—CAS No. 1067-33-0), has been included in this report for read across for systemic toxicity endpoints. The Tier II Human Health assessment reports these chemicals (NICNASa; NICNASb; NICNASc; NICNASd) are available at **https://www.nicnas.gov.au**. These reports should be read in conjunction with this Tier II Human Health assessment.

Toxicokinetics

Sulfur or carboxylate based ligands in organotin compounds are easily displaced at low pH conditions (OECD, 2006; REACH).

In a study under simulated gastric conditions, 37 °C for four hours at pH 1.2 and 4, with analyses conducted using gas chromatography, DBT(2-EHMA) was reported to be rapidly and completely hydrolysed to DBTC at pH 1.2 over 1 hour (REACH). Other simulated gastric hydrolysis studies with analyses conducted using gas chromatography indicate that DBT(2-EHMA) and other dibutyltin compounds are rapidly hydrolysed to DBTC within <0.5 to 3.5 hours under physiological conditions (OECD, 2006). However, there is some uncertainty in the characterisation of the tin species using gas chromatography (KEMI, 2018).

Under another simulated gastric conditions, 0.1 M HCl at 37 °C for 4 hours at pH 1.2, DBT(2-EHMA) hydrolysed to its monochloroester metabolite (68 % within 4 hours). Metabolites were analysed with ^{119}Sn NMR spectroscopy. As no DBTC was found, it was concluded that a monochloro mercaptoacetate is the only metabolite of the chemical (REACHa).

In a dermal absoprtion study on DBT(2-EHMA) (18 % w/w tin) using human and rat epidermis, the proportion of DBT(2-EHMA) absorbed through the epidermis was reported to be 0.0004 % and 0.0001 % in occluded and non-occluded applications respectively, while in the rat 0.261 % and 0.189 % of DBT(2-EHMA) was absorbed over 24 hours. When the epidermis was washed, only 1 % and 10 % of DBT(2-EHMA), remained associated with the epidermis of humans and rats. Therefore, the chemical was not reported to be systematically available by the dermal route (REACH). The high molecular weight and low volatility of the dibutyltin alkyl mercaptoacetates are expected to minimise dermal and inhalation exposure

The tin and mercaptoacetate metabolites will be distributed, metabolised and excreted separately. Dibutyltin is reported to accumulate in the liver. Dealkylation of organotin compounds occurs in the liver by cytochrome P-450 dependent mono-oxygenase. The rate of metabolism is dependent on the number and size of alkyl groups in the organotin compound, with fewer and shorter alkyl chains being dealkylated more rapidly. In rats, dibutyltin is rapidly metabolised to monobutyltin and inorganic tin, which accumulate in the brain and can easily diffuse into cerebrospinal fluid and across the blood-brain barrier (Friberg et al., 1986).

Dibutyltin chloride has been found to be distributed to all tissues. The chemical has an expected half-life in the body of 3–5 days (NICNASc). Mercaptoacetates are expected to be initially hydrolysed in several tissues by carboxylesterases to mercaptoacetatic acid and the corresponding alcohols (NICNASb).

Acute Toxicity

Oral

Based on the available data, the chemicals in this group are expected to have moderate acute oral toxicity — warranting hazard classification (see **Recommendations** section).

The following oral LD50 values were reported for DBT(2-EHMA) (OECD, 2009; REACH):

- 4439 mg/kg bw in male and female Tif:Raif (SPF) 65:35 % DBT(2-EHMA): MBT(2-EHMA) mixture (according to OECD TG 401);
- 615 mg/kg bw in male and female Tif:Raif (SPF) 65:35 % DBT(2-EHMA): MBT(2-EHMA) mixture (according to OECD TG 401);
- 396 mg/kg bw in male and female Tif:Raif (SPF) rats using a 61.8:25.3:12.9 % DBT(2-EHMA): MBT(2-EHMA): epoxidised soybean oil mixture (similar to OECD Test Guideline (TG) 401), where observed sub-lethal effects included apathy, dyspnoea and diarrhoea;
- 758 mg/kg bw in male and female Tif:Raif (SPF) rats using a 65:35 % DBT(2-EHMA): MBT(2-EHMA) mixture (according to the non-guideline: 'standard acute method');
- 510 mg/kg bw in male rats (according to the non-guideline: 'standard acute method');
- 500–550 mg/kg bw in a limited, non-guideline study on rats;

- 1037 mg/kg bw in a limited, non-guideline study on rats;

In an acute oral toxicity study (according to OECD TG 401) with a 67:33 % DBT(IOMA): MBT(IOMA) mixture, rats were orally administered the mixture at doses of 250, 500, 1000, 2000, and 5000 mg/kg bw. Animals exhibited dyspnoea (laboured breathing), ruffled fur, curved body position, exophthalmos (bulging of the eyes), sedation, and salivation within one hour of dosing. Pathological changes observed included oedematous, mottled or haemorrhagic lungs, gastrointestinal dilations, fluid in the thoracic cavity, mottled thymus, haemorrhagic thymus, and dilation of the heart. Based on mortalities at the two highest doses, an LD50 value of 3088 mg/kg bw was reported (OECD, 2009).

In an acute oral toxicity study (according to OECD TG 401) with an identical DBT(IOMA): MBT(IOMA) mixture, rats were administered the mixture orally at doses of 250, 500, 1000, 2000, and 5000 mg/kg bw. The same clinical effects were reported, although with ventral body position. The same pathological effects were reported, although included dilation of the urinary bladder, and stenosis of the duodenum. An LD50 of 2505 mg/kg bw was reported (OECD, 2009).

In limited non-guideline acute oral toxicity studies on DBT(IOMA) (concentration not specified) with rats, the following LD50 values were reported: 647–1024 mg/kg bw, 510–1037 mg/kg bw, and 1780 mg/kg bw (OECD, 2009).

An acute oral LD50 of 500 mg/kg bw has been reported for DBT(IOMA) (Tin Research Institute, 1973).

Dermal

Based on the available data for DBT(2-EHMA), the chemicals in this group are expected to have moderate acute dermal toxicity — warranting hazard classification (see **Recommendations** section).

In an acute dermal toxicity study (equivalent to OECD TG 402) in Tif:Raif (SPF) rats with a mixture of 72:14:12 % DBT(2-EHMA): MBT(2-EHMA): epoxidised soybean oil, an LD50 of 777 mg/kg bw for the mixture was reported. The mixture was applied dermally to the animals (n=5/sex) at doses of 250, 500, 1000 and 2000 mg/kg bw. Mortalities were reported at the two highest doses, and clinical signs observed included sedation, dyspnoea, ruffled fur, diarrhoea, affected body position, tremor, necrosis and erythema. No pathological changes were reported (OECD, 2009; REACH).

In an acute dermal toxicity study (according to OECD TG 402), rats were treated dermally with a mixture of 61.8:25.3:12.9 % DBT(2-EHMA): MBT(2-EHMA): epoxidised soybean oil at doses of 250, 500, 1000 and 2000 mg/kg bw. At the highest dose, severe irritation was observed in animals, and very slight to well defined erythema at the 1000 mg/kg bw dose. Dermal swelling was observed in all animals at the highest two doses, as well as moderate to marked necrosis. All animals treated at 2000 mg/kg were euthanised for ethical reasons on day 8, due to severe signs of irritation. An LD50 of >1000 mg/kg bw was reported (OECD, 2009).

Inhalation

Based on the available data for DBT(2-EHMA), the chemicals in this group are expected to have moderate acute inhalation toxicity — warranting hazard classification (see **Recommendations** section).

In an acute inhalation toxicity study (equivalent to OECD TG 403), Tif:RAIF rats (n=10/sex/dose) were exposed to an aerosolised mixture of 84:16 % DBT(2-EHMA): MBT(2-EHMA) at doses of 247, 561, and 1068 mg/m^3 over four hours**.** A median lethal concentration (LC50) of 941 mg/m^3 was reported. At the the intermediate dose, 1 male died, and at highest dose, 7 females and 6 males died. Areas of discolouration in the lungs were reported in males and females exposed at the highest dose, as well as small masses and lumps on the liver, discolouration of the bladder and enlargement of the adrenals (REACHa).

In an acute inhalation toxicity study (equivalent to OECD TG 403) using DBT(IOMA), rats (n=5/sex/dose) were exposed to the DBT(IOMA) in aerosol form at doses of 5, 10, 25, 50, and 100 mg/L over one hour. At the three highest doses, >50 % animals died, and all deaths occurred within 13 days after exposure. An LC50 of 22 mg/L was reported. Pathological signs in affected animals included blood in the lungs, enlarged thymus, adhesions in the chest cavity, and dark spleen. No clinical effects or further details were reported (OECD, 2009).

Corrosion / Irritation

Skin Irritation

Based on the available in vivo and in vitro data for DBT(2-EHMA) and DBT(IOMA), the chemicals in this group are expected to be corrosive to the skin— warranting hazard classification (see **Recommendations** section).

In a skin irritation/corrosion study according to OECD TG 404 in rabbits (n=3), a mixture of 80:20 % DBT(2-EHMA): MBT(2-EHMA) was applied dermally (0.5 mL) via semi-occlusive patch and animals observed over 72 hours. At 24 and 72 hours, moderate to severe erythema and moderate oedema was reported. At 48 hours, moderate to severe erythema and severe oedema were also reported. No further study results were reported. The substance was determined to be corrosive (causing burns to the skin) (OECD, 2009).

In a skin irritation/corrosion study according to OECD TG 404 on rabbits (n=3), a mixture of 67:33 % DBT(IOMA): butyltin tris(IOMA) was applied dermally (0.5 mL) via semi-occlusive patch and animals observed over 72 hours. At 24 hours, very slight to well-defined erythema and very slight to slight oedema was reported, and at 48 hours, well-defined erythema and slight to moderate oedema. Severe erythema and slight to severe oedema were reported after 7 days. Based on the results of the study, the mixture was reported to be corrosive (causing burns). No further study details were provided (OECD, 2009).

In in vitro studies of DBT(2-EHMA) using reconstructed human epidermis (RHE) (study in accordance to OECD TG 431), the following results were reported (REACH):

- non-corrosive at 3, 60, and 240 minutes, with relative tissue viabilities of 102.9 %, 108 % and 96.6 %, respectively (at 100 % concentration), where tissues remained blue (indicating viability); and

non-irritating 15 minutes post-exposure, with a relative mean viability of 97.3 % of treated tissues (at 100 % concentration), where tissues remained blue (indicating viability).

In a non-guideline skin irritation/corrosion study in rabbits (n=3/sex), a mixture of 72:28 % DBT(2-EHMA): butyltin tris(2-EHMA) was applied dermally (0.2 mL) via occlusive patch on abraded and intact skin sites (duration unknown) and animals were observed over 72 hours. At 24 and 74 hours, moderate to severe erythema and moderate oedema were reported. No further study details were provided. The mixture was determined to be corrosive (causes burns to the skin) (OECD, 2009).

In a non-guideline skin irritation study with a 95:5 % DBT(IOMA): MBT(IOMA) mixture, severe irritation after dermal application of the mixture to intact and abraded skin (duration unknown) of rabbits (n=6) was reported. Treatment-related effects included erythema and severe, irreversible necrosis. Mean erythema scores at 24 hours and 72 hours post-application were reported to be 3.3 and 4.0, for intact skin, and 3.6 and 4.0, for abraded skin. Mean oedema scores at 24 hours and 72 hours post-application were reported to be 3.2 and 3.0, for intact skin, and 3.3 and 3.0 for abraded skin. No further study details were provided. Based on a primary dermal irritation index (Pd(II)) of 6.85, the DBT(IOMA) mixture was reported to be highly irritating (OECD, 2009).

In a non-guideline skin irritation study with an 80:20 % DBT(2-EHMA): MBT(2-EHMA) mixture, well-defined erythema and slight to moderate oedema was reported in rabbits at intact and abraded skin sites (after an unknown exposure time) at 24 hours. At 72 hours, moderate to severe erythema and moderate oedema was observed. The mixture was reported to be moderately irritating. No further data was reported (OECD, 2009).

In a non-guideline skin irritation study with an 72:28% DBT(2-EHMA): MBT(2-EHMA) mixture, treatment-related effects including moderate to severe erythema and moderate oedema in the intact and abraded skin of rabbits (after an unknown exposure time) (n=3/sex) were reported. Based on a Pd(II) of 5.8, the mixture was reported to be moderately irritating. No further study results were reported (OECD, 2009).

Eye Irritation

Based on the available data for DBT(2-EHMA), the chemicals in this group are expected to be severely irritating to the eyes— warranting hazard classification (see **Recommendations** section).

In an eye irritation study (equivalent to OECD TG 405), a mixture of 65:35 % DBT(2-EHMA): MBT(2-EHMA) (0.1 mL) was applied to the eyes of New Zealand white rabbits (n=3/sex), without rinsing and with rinsing after 30 seconds. Average redness in unrinsed eyes was 2 at 24 hours, 48 hours, and 72 hours. Average chemosis in unrinsed eyes was 2 at 24 and 48 hours, and 2.3 at 72 hours. Average primary eye irritation (PEII) in unrinsed eyes was reported to be 8.7 and PEII was 6.1 for rinsed eyes after observation over 7 days. Rinsing of eyes reduced redness but not chemosis by day 7. As the mean scores for chemosis in the non-rinsed treated eye for 24, 48 and 72 hours were ≥ 2, the DBT(2-EHMA) mixture was reported to be irritating to the eyes (OECD, 2009; REACH).

In a non-guideline eye irritation study (Draize test), DBT(IOMA) (concentration not reported) was applied to the eyes of rabbits (0.1 mL). Slight to moderate conjunctivitis was reported, although the effects of irritation decreased over time. Slight erythema and oedema were reported to persist after 72 hours. The DBT(2-EHMA mixture was reported to be slightly irritating. No further study details were reported (OECD, 2009).

Sensitisation

Skin Sensitisation

Based on the available data for DBT(2-EHMA), the chemicals in this group are expected to be skin sensitisers — warranting hazard classification (see **Recommendations** section).

In a guinea pig maximisation test (GPMT) (study according to OECD TG 406), a mixture comprising DBT(2-EHMA): MBT(2-EHMA) at 80:20 % was tested in Pirbright White (Tif: DHP) guinea pigs (n=10/sex/dose). Intradermal induction used the mixture at 50 % concentration in saline. For topical induction, the mixture was applied at 30 % concentration in petrolatum. Challenge exposures used the mixture at 10 % and 3 % concentration in petrolatum. 55 % (11/20) of animals reacted to the DBT(2-EHMA) mixture at challenge at 10 % concentration, and the DBT(2-EHMA) mixture was reported to be moderately sensitising (a contact allergen) (OECD, 2009; REACH).

In a guinea pig maximisation test (GPMT) (study according to OECD TG 406), a mixture comprising DBT(IOMA): MBT(IOMA) at 67:33 % was tested in guinea pigs (n=10/sex). Intradermal induction used the mixture at 50 % in saline. For topical induction, the mixture was applied at 1 % in petrolatum. Challenge exposures used the mixture at 0.1 % in petrolatum. Sensitisation rates were reported at 40–95 % (OECD, 2009).

Repeated Dose Toxicity

Oral

Based on the available data on DBT(2-EHMA) and other dibutyltin compounds, the chemicals in this group are expected to cause adverse effects following repeated oral exposure — warranting hazard classification (see **Recommendations** section). In targeted studies, dibutyltins and dibutyltin dilaurate cause well established immunotoxicity. Hepatotoxicity and evidence of neurotoxicity have also been reported. The effects in the thymus reported in studies with DBT(2-EHMA) are consistent with adverse effects on the thymus reported for other dibutyltins following repeated oral exposure (EFSA, 2004; ATSDR, 2005; WHO, 2006; NICNASa; NICNASc).

In a combined repeat dose oral and reproductive/developmental toxicity study (according to OECD TG 414), DBT(2-EHMA) (as a mixture, >95 % dibutyltin) was administered to Sprague-Dawley (SD) rats by oral gavage over 14 days at doses of 2.5, 8.5 or 25 mg/kg bw/day. No mortality or clinical effects were reported. There was a treatment-related reduction in the size of the thymus, with moderate to high incidence of decreased cell population in the cortex at the highest dose. A no adverse effect level (NOAEL) of 8.5 kg was reported.

Limited data indicate that mercaptoacetates metabolites (2-EHMA and IOMA) did not cause damage to health from repeated oral exposure (NICNASb).

Dermal

No data are available for the chemicals in this group.

Inhalation

No data are available for the chemicals in this group.

Genotoxicity

Based on the in vitro data on DBT(2-EHMA) and DBT(IOMA), and available in vitro and in vivo data on dibutyltin compounds the chemicals in this group are expected to be genotoxic — warranting hazard classification (see **Recommendations** section).

Negative results were reported for DBT(2-EHMA) and DBT(IOMA) in several in vitro bacterial reverse mutation assays (in accordance with OECD TG 471) in *Salmonella typhimurium strai*ns TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2 uvrA strains, with or without metabolic activation with S9, at concentrations up to 500 µg/plate. This is consistent with results for DBTC, and DBTL (NICNASa; NICNASc).

There was a positive result for DBTC in an in vitro chromosome aberration test and in vivo mammalian erythrocyte micronucleus test (NICNASa).

There was a dose-dependent increase in DNA damage in an in vivo single cell gel electrophoresis assay focussing of cerebral cortical cells caused by applying DBTL (NICNASc).

Mercaptoacetates metabolites (2-EHMA and IOMA) were not considered to be genotoxic based on the available data (NICNASb).

Carcinogenicity

No data are available for the chemicals in this group. Another dibutyltin ester, dibutyltin diacetate, was considered not to be carcinogenic to male rats and male or female mice based on results of a 78 week study in rats. The loss of the tissues prevented a conclusion being made with regard to female rats (ATSDR, 2005).The limited data for the mercaptoacetates metabolites (2-EHMA and IOMA) do not indicate a concern for carcinogenicity (NICNASb).

Reproductive and Developmental Toxicity

Reproductive Toxicity

No data are available for the chemicals in this group. The analogue DBTC is classified as hazardous with the risk phrase ‘May damage fertility. May damage the unborn child—Cat. 1B (H360FD) in the HCIS (Safe Work Australia). Reported adverse observed effects included increased numbers of non-pregnant females, increased pre-implantation loss and increased early resorptions (NICNASa).

In the absence of data classification is recommended.

Developmental Toxicity

In a combined repeat dose oral and reproductive/developmental toxicity study (according to OECD TG 414), DBT(2-EHMA) (as a mixture, >95 % dibutyltin) was administered to Sprague-Dawley (SD) rats by oral gavage over gestation day 5–19 at doses of 2.5, 8.5 or 25 mg/kg bw/day. No adverse developmental effects were observed in foetuses, including incidences of external, soft tissue or skeletal abnormalities). No further details were reported. A NOAEL for developmental toxicity was reported to be 25 mg/kg bw/day (REACH).

In several studies with other dibutyltin compounds including DBTC, DBTL and DBTA teratogenic effects were observed at doses <10 mg/kg bw/day. The critical period for teratogenesis in rats was reported to be on gestation day 8.

In a reproductive and developmental toxicity screening test (OECD TG 421), 2-EHMA caused developmental effects when administered (gavage) up to 150 mg/kg bw/day. The NOAEL for developmental effects was 50 mg/kg bw/day, based on foetal and systemic (maternal) toxicity at 150 mg/kg bw/day. Although effects in the pups occurred at maternally toxic doses, a direct neonatal effect from the compound in maternal milk cannot be discounted (NICNASb).

The available study for DBT(2-EHMA) indicated that the chemicals do not cause the same developmental effects as other dibutyltin compounds. Effects at higher doses cannot be ruled out.

Other Health Effects

Neurotoxicity

Organotins have reported neurotoxic effects; however, most data available are for trialkylated tin compounds. Dibutyltin compounds have reduced neurotoxic effects compared to these chemicals, and neurotoxic effects are only prevalent at near lethal doses (EFSA, 2004; ATSDR, 2005).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (immunotoxicity, mutagenicity, reproductive and developmental toxicity), and systemic acute effects (acute toxicity from oral, dermal and inhalation exposure), and local effects (corrosion and skin sensitisation). Neurotoxic effects may occur at high doses.

Public Risk Characterisation

Although use of domestic products in Australia is not known, the chemicals are reported to be used in domestic products overseas. However, data indicate that use in products that could expose the public directly to these chemicals is not frequent or widespread. Provided that normal precautions are taken to avoid prolonged skin contact, the risk to the public posed by domestic products containing the chemicals is not considered unreasonable.

There may be exposure of the general public to these chemicals if the chemicals are present in domestic products, specifically do-it-yourself sealants and adhesives. The chemicals are currently listed on Schedule 7 of the SUSMP for preparations containing >1 %, and these preparations are therefore not available for domestic use. Based on the low concentration of these chemicals in these products (<1 %), the low dermal availability and the low volatility of these chemicals, the risk to public health is not considered to be unreasonable. Further risk management for these uses is not considered necessary for public safety.

The public could be exposed to these chemicals at low levels based on its use as a PVC stabiliser and catalyst for various products. Internationally, a group tolerable daily intake (TDI) of (0.1 µg/kg bw as Sn) for tributyltins, triphenyltins, dibutyltins and dioctyltins has been established (EFSA 2004, European Commission 2004). Based on an impact assessment report conducted in Europe (European Commission, 2009), the identified uses of these chemicals are not considered to significantly contribute to the overall TDI. Organotins have not been found in Australian drinking water (NWQMS, 2011). The use of these chemicals in baking and cooking silicone moulds and silicone coated baking paper has been phased out and; therefore, this is no longer considered a significant source of exposure. In addition, the dominant contribution to human intake of organotins is via consumption of fish. Exposure levels are expected to reduce over time due to the ban in the use of tributyltin of antifouling paints.

If data become available indicating specific uses in Australia that could significantly contribute to the overall TDI for organotins, further assessment may be required.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation 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 these 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.

Given the critical systemic long-term, acute and local health effects, these chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation 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 amendments to the hazard classifications in the HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Assessment of these chemicals is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

If data become available indicating specific uses in Australia that could significantly contribute to the overall TDI for organotins, further assessment may be required.

Regulatory Control

Public Health

Products containing these chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2019).

Work Health and Safety

These 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 Not Applicable	Harmful if inhaled - Cat. 4 (H332) Harmful in contact with skin - Cat. 4 (H312)
Irritation / Corrosivity	Not Applicable	Causes severe skin burns and eye damage - Cat. 1B (H314)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1B (H317)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Repeat Dose Toxicity	Not Applicable	Causes damage to the immune system through prolonged or repeated exposure - Cat. 1 (H372)
Genotoxicity	Not Applicable	Suspected of causing genetic defects - Cat. 2 (H341)
Reproductive and Developmental Toxicity	Not Applicable	Suspected of damaging fertility - Cat. 2 (H361f)

[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 chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular and inhalation 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 the chemicals has not been undertaken as part of this assessment.

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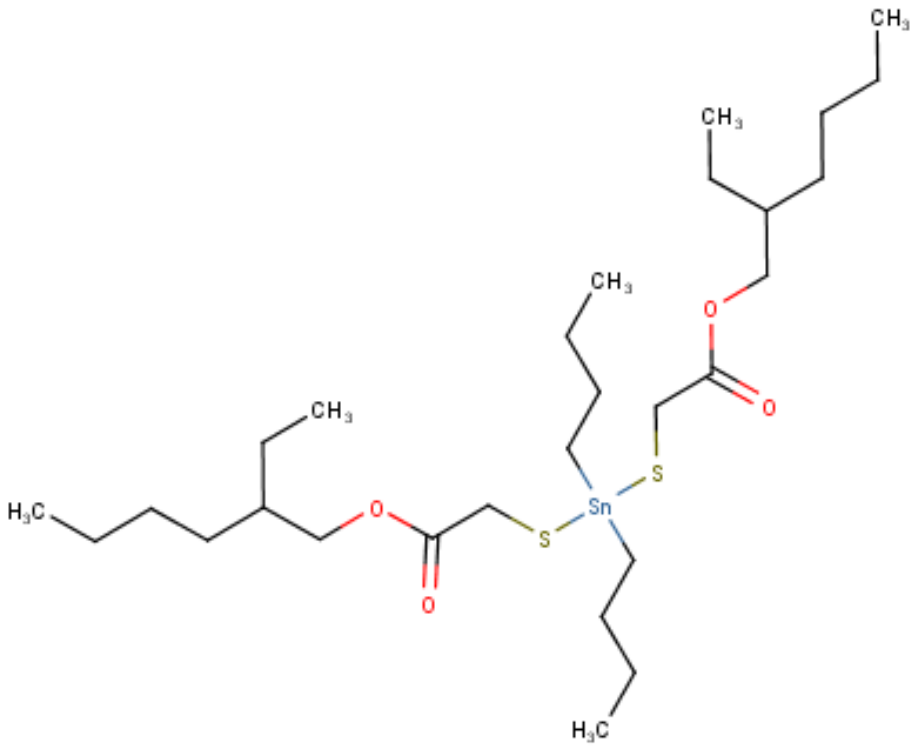
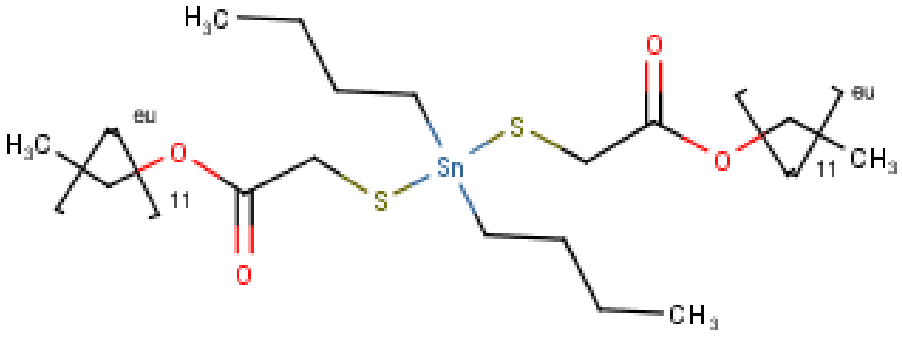
Last Update 12 December 2019

Chemical Identities

Chemical Name in the Inventory and Synonyms	**8-Oxa-3,5-dithia-4-stannatetradecanoic acid, 4,4-dibutyl-10-ethyl-7-oxo-, 2-ethylhexyl ester** dibutyltin bis(2-ethylhexylmercaptoacetate) (DBT(2-EHMA)) dibutyltin bis(2-ethylhexyl thioglycolate) (DBT(EHTG))

CAS Number	10584-98-2
Structural Formula	
Molecular Formula	C28H56O4S2Sn
Molecular Weight	639.58

Chemical Name in the Inventory and Synonyms	**8-Oxa-3,5-dithia-4-stannaeicosanoic acid, 4,4-dibutyl-7-oxo-, dodecyl ester** dibutyltin bis(dodecylmercaptoacetate) (DBT(DDMA))
CAS Number	20004-12-0
Structural Formula	
Molecular Formula	C36H72O4S2Sn

Molecular Weight	751.803

Chemical Name in the Inventory and Synonyms	**Acetic acid, 2,2'-[(dibutylstannylene)bis(thio)]bis-, diisooctyl ester** dibutyltin bis(isooctylmercaptoacetate) (DBT(IOMA)) dibutyltin bis(isooctylthioglycolate) (DBT(IOTG))
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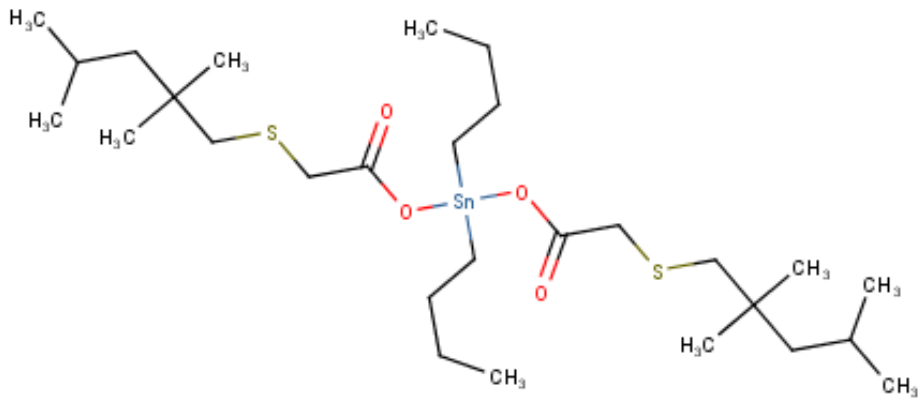
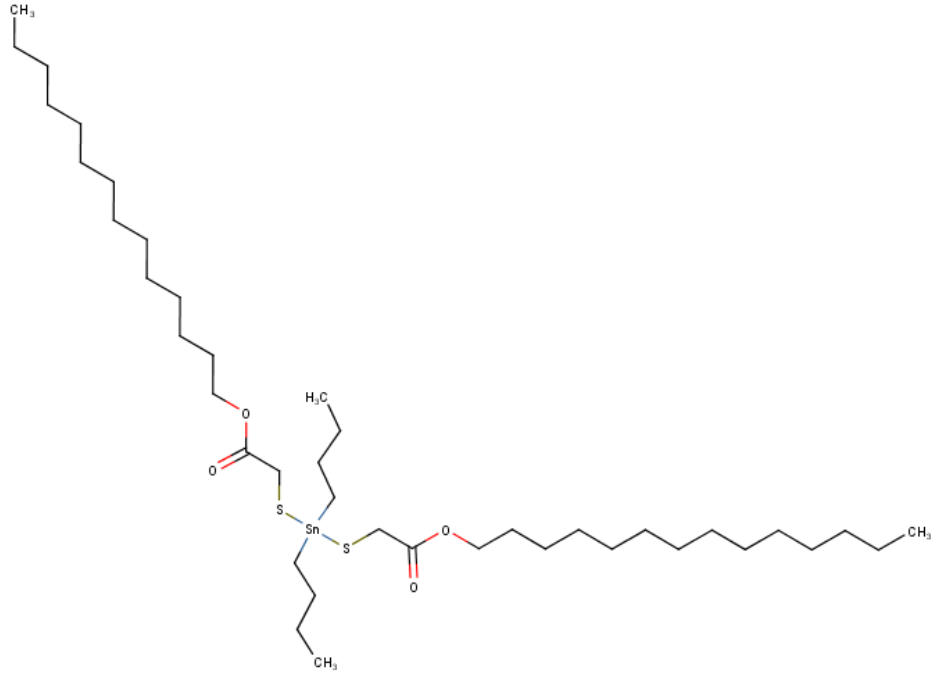
Structural Formula	
Molecular Formula	C28H56O4S2Sn
Molecular Weight	639.6

Chemical Name in the Inventory and Synonyms	**8-Oxa-3,5-dithia-4-stannadocosanoic acid, 4,4-dibutyl-7-oxo-, tetradecyl ester** dibutyltin bis(tetradecylmercaptoacetate) (DBT(TDMA))
CAS Number	83833-21-0
Structural Formula	

	
Molecular Formula	C40H80O4S2Sn
Molecular Weight	807.91 807.9

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