Dioctyltin alkyl mercaptoacetates: Human health tier II assessment

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
8-Oxa-3,5-dithia-4-stannatetradecanoic acid, 10-ethyl-4,4-dioctyl-7-oxo-, 2-ethylhexyl ester	15571-58-1
Acetic acid, 2,2'-[(dioctylstannylene)bis(thio)]bis-, diisooctyl ester	26401-97-8
8-Oxa-3,5-dithia-4-stannaeicosanoic acid, 4,4-dioctyl-7-oxo-, dodecyl ester	73246-85-2
8-Oxa-3,5-dithia-4-stannadocosanoic acid, 4,4-dioctyl-7-oxo-, tetradecyl ester	79330-84-0

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

Chemicals in this group are organostannic mercaptoacetates—dioctyltin bis(2-ethylhexylmercaptoacetate) (DOT(2-EHMA); CAS No. 15571-58-1), dioctyltin bis(isooctylmercaptoacetate) (DOT(IOMA); CAS No. 26401-97-8), dioctyltin bis(dodecylmercaptoacetate (CAS No. 73246-85-2) and dioctyltin bis(tetradecylmercaptoacetate) (CAS No. 79330-84-0).

These chemicals contain a dioctyl (Oct_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. These 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.

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

The following site limited uses were identified as sources of organotin compounds by the NPI in 2017–18:

- 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) dossier; Galleria Chemica; Classification, Labelling and Harmonisation (CLH) documents; and the Organisation for Economic Co-operation and Development (OECD) Screening information data set International Assessment Report (SIAR) (OECD, 2009a; OECD, 2009b; OECD 2009c);

DOT(2-EHMA) and DOT(IOMA) have a reported site-limited use as stabilisers in plastic.

DOT(IOMA) was reported to be used historically; DOT(2-EHMA) is now reported to be the more dominant product (OECD, 2009b).

DOT(2-EHMA) and DOT(IOMA) are commonly manufactured as mixtures with their corresponding monooctyltin (MOT) counterparts. Mixtures with greater than 50 % DOT are considered to be dioctyltin substances, whereas mixtures with less than 50 % DOT are considered to be monooctyltin substances (OECD, 2009a).

No specific use information were identified for CAS Nos 79330-84-0 and 73246-85-2. Uses are expected to be similar to the other chemicals in this group.

No evidence of the presence of these chemicals in consumer products was found in available North American databases, indicating that the chemicals are not likely to be widely available for domestic or cosmetic uses.

Restrictions

Australian

Tin and its compounds are listed in Schedule 10 of the 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

CAS No 15571-58-1 is recommended to be included in Annex XIV of the REACH Regulation (ECHA, 2019).

Dioctyltin compounds—which includes the chemicals in this assessment—are listed on the following (Galleria Chemica):

- Annex XVII to REACH Regulations—dioctyltin compounds shall not be used after 1 January 2012 in several articles for supply to, or use by, the general public, where concentration in 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 (European Parliament and Council, 2006)
- Part 1 of 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
- Council of Europe Resolution AP (92) 2 on the control of aids to polymerisation for plastic materials and articles intended to come into contact with foodstuffs—Limits for finished articles; a limit of 0.02 mg/kg (as Sn) applies for di-n-octyltin.

Tin compounds—which includes the chemicals in this assessment—are listed on the:

- 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 material, and scraped-off toy material, respectively (Galleria Chemica).

- 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 chemical, DOT(2-EHMA) 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):

- Reproductive Toxicity - Category 1B; H360D (May damage unborn child).

The other chemicals are not listed on the HCIS.

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 Bulgaria, Canada (Alberta, British Columbia, Ontario, Quebec, Saskatchewan, Yukon), Chile, Denmark, Egypt, Estonia, France, Greece, Malaysia, Mexico, 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^3 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^3 STEL 'to minimize acute symptoms such as eye and upper respiratory tract irritation, headache, and nausea.' (ACGIH, 2011).

Health Hazard Information

The majority of data are available for DOT(2-EHMA) with some data for DOT(IOMA). The chemicals are commonly manufactured as a mixture with monooctyltin counterpart. Where purity has been specified in this report, the major impurity is the monooctyltin counterpart e.g. DOT(2-EHMA) (70 % purity) refers to a mixture containing 70:30 % of DOT(2-EHMA):octyltin tris(2-EHMA).

Data available 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) or 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 the other mercarptoacete metabolites, dodecylmercaptoacetate (CAS No. 3746-39-2) and tetradecylmercaptoacetate (TDMA, CAS No. 57414-16-1), they are expected to be toxicologically similar to the isomeric octyl mercaptoacetates. Although there is limited evidence that the chemicals are hydrolysed to

dioctyltin dichloride—DOTC (CAS No. 3542-36-7), the systemic toxicity of a range of dioctyltin compounds is similar (NICNASa; NICNASb; NICNASc).

Therefore when data for the chemicals being assessed are not available, health hazard information for EHMA, IOMA and dioctyltin compounds including DOTC, dioctyltin oxide—DOTO (CAS No. 870-08-6) and dioctyltin laurate—DOTL (CAS No. CAS No. 3648-18-8) has been included in this report for read across for systemic toxicity endpoints. The Human Health Tier II assessment reports for these chemicals (NICNASa; NICNASb; NICNASc; NICNASd) are available at **https://www.nicnas.gov.au**. These reports should be read in conjunction with this Human Health Tier II assessment.

Toxicokinetics

The chemicals contain a dioctyltin (Oct_2Sn-) group, and two labile ligands (X). In vitro toxicokinetic data are available for DOT (2-EHMA). No in vivo data are available. The toxicokinetics of the chemicals in the group are expected to be similar.

Based on a simulated gastric reaction study (pH 1–2, 37 °C) with DOT(2-EHMA), with analyses conducted using gas chromatography, it was concluded that the chemical was rapidly converted to DOTC (OECD, 2009c). However, there is some uncertainty in the characterisation of the tin species using this approach (CLH report, 2017).

Another hydrolysis study with DOT(2-EHMA) under simulated mammalian gastric conditions (pH 1.2, 37 °C), but using ^{119}Sn-NMR to identify reaction products indicated that instead of the loss of both mercaptoacetate ligands from the tin atom to form DOTC, one ligand remained attached forming a mono-chloroester of the chemical. At pH 4, 7 and 9 the chemical was considered hydrolytically stable (CLH report, 2017; KEMI, 2018; REACHa).

The high molecular weights of the chemicals reduce their potential for absorption via the dermal route. In an in vitro dermal absorption study using DOT(2-EHMA), occluded and unoccluded human and rat epidermis were treated with a 17 µg tin/cm^2 dose of the chemical for 24 hours. After the exposure period, the mean amount of tin absorbed through the human epidermis was 0.010 µg/cm^2 (unoccluded) and 0.011 µg/cm^2 (occluded), and 0.642 µg/cm^2 (unoccluded) and 0.547 µg/cm^2 (occluded) through the rat epidermis. Based on low recovery rates being reported the reliability of this study is limited (CLH report, 2017).

The tin and mercaptoacetate metabolites will be distributed, metabolised and excreted separately. Mercaptoacetates are expected to be initially hydrolysed in several tissues by carboxylesterases to mercaptoacetic acid and the corresponding alcohols (NICNASd).

Acute Toxicity

Oral

Based on the available data, the chemicals are considered to have low to moderate acute oral toxicity. Data are not sufficient to support classification of these chemicals.

The following oral median lethal dose (LD50) values for DOT(2-EHMA) were reported (OECD, 2009a; CLH report 2011; REACHa):

In a guideline study (OECD Test Guideline (TG) 401), Tif:RAIf (SPF) rats received doses of 1000 mg/kg bw and 2000 mg/kg bw of the chemical (90 % purity in carboxymethyl cellulose and polysorbate-80 vehicle). Animals in both dose groups exhibited clinical signs of toxicity (slight to moderate piloerection, dyspnea, hunched posture, and reduced locomotor activity). No substance-related gross organ changes were observed at necropsy. No mortality occurred at 1000 mg/kg bw. At 2000 mg/kg bw 1/5 and 4/5 females died. The LD50 was 2000 mg/kg bw.

In another guideline study (OECD TG 401) received the chemical (58 % purity in polyethylene glycol 400) at doses of 1000 mg/kg bw/day, 2500 mg/kg bw/day and 5000 mg/kg bw/day. Clinical signs of toxicity included sedation, dyspnea, ruffled fur and curved body position. The LD50 was 2775 mg/kg bw/day.

The reported LD50 values in rats and mice from several non-guideline studies were 1400–3050 mg/kg bw/day.

The following oral LD50 values for DOT(IOMA) in rats and mice from several non-guideline studies were 1120–3512 mg/kg bw/day (OECD, 2009b; REACHb). Observed sublethal effects included lethargy, body weakness, ruffled fur, breathing difficulties, diarrhoea, bulging of the eye/s and bloody noses. In studies where mortality was observed there was evidence of an irritant or corrosive effect of the test material on the gastrointestinal mucosa. The gastric reaction is dependent upon dissolution of the test substance (OECD, 2009a). As some of these studies used the chemical in the absence of a vehicle or used large dosage volumes, they did not conform to test guidelines. It is assumed that the presence of a vehicle would reduce the effects on gastrointestinal mucosa.

Dioctyltin dodecylmercaptoacetate has an oral LD50 of 3700 mg/kg bw/day in male rats (WHO, 1980).

Dermal

Based on the available data, the chemicals are considered to have low acute dermal toxicity.

The following dermal LD50 value for DOT(2-EHMA) was reported (OECD, 2009a; REACH):

- >2000 mg/kg bw in male and female SPF rats.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemicals are considered to be at least slight skin irritants. The severity of effects observed in guideline studies do not warrant classification.

In an in vivo skin irritation study (according to OECD Test Guideline (TG) 404), New Zealand White (NZW) rabbits (n=4 males, 2 females) were treated with 0.5 mL of DOT(2-EHMA) via semi-occlusive patch on shaved skin for 4 hours. After patch removal the animals were monitored for up to 12 days. Erythema was observed in 6 of the rabbits over 24, 48 and 72 hours with a mean score of 2.1/4, while oedema was observed in 4 of the rabbits with a mean score of 0.33/4. All observed irritation was fully reversed within 11 days (CLH report 2011; REACHa).

In an in vivo skin irritation study (according to OECD TG 404), NZW rabbits (n=3, sex unspecified) were treated with 0.5 mL of DOT (2-EHMA) (90 % purity) via semi-occlusive patch on shaved skin for 4 hours. After patch removal the animals were monitored for up to 10 days. A mean erythema score of 1.78/4, and mean oedema score of 1.33/4 was obtained over the duration of the study. During the third day of the observation period, slight flaking of the skin was noted for 2 animals, and by day 7 all the animals had slight flaking; however, these effects disappeared within 10 days of removing the patch (OECD, 2009a; CLH report, 2011; REACHa).

In an in vivo skin irritation study, NZW rabbits (n=6, sex unspecified) were exposed to 0.5 mL of DOT(IOMA) via a patch on abraded and intact skin for 24 hours. After patch removal the animals were observed for up to 72 hours. At 24 hours the average erythema score was 1.5 (abraded) and 1 (intact). After 72 hours the average erythema score was 3.5 (abraded) and 2.3 (intact) (OECD, 2009b; REACHb).

In an in vivo skin irritation study, NZW rabbits (n=3 males) were treated with 0.5 mL of DOT(2-EHMA) via semi-occlusive patch onto abraded and intact skin for 24 hours. After removal of the patch, the animals were monitored for up to 72 hours. On the abraded skin, very slight erythema (6/6), and oedema (3/6) were observed in the animals 24 hours after patch removal. After 72 hours this progressed to very slight erythema (1/6), defined/severe erythema (5/6), and very slight to slight oedema (5/6) in the animals. On intact skin, very slight erythema (5/6) and oedema (1/6) were observed after 24 hours. After 72 hours this progressed to slight erythema (2/6) to defined/severe erythema (3/6) and very slight oedema (5/6) (OECD, 2009b).

Eye Irritation

Based on the available data, the chemicals are slightly irritating to the eyes.

In an in vivo eye irritation study (according to OECD TG 405), 0.1 mL of DOT(2-EHMA) was instilled into the right eye of NZW rabbits (n=6). Eyes were held closed for 1 second, released, and then observed for 4 days. All animals showed conjunctival irritation (mean score conjunctivae redness 0.5 and chemosis 0.22). All signs of conjunctival irritation reversed by day 4. No corneal or iridial irritation was observed over the duration of the study (OECD, 2009a; CLH report, 2011; REACHa).

In an in vivo eye irritation study (according to the Draize Test), 0.1 mL of DOT(IOMA) was instilled into one eye of NZW rabbits (n=6), which were monitored for up to 72 hours without rinsing. At 24 hours the average irritation score was 2 as 4/6 animals had red eyes, and 1/6 had ocular discharge. At 48 hours the average irritation score was 0.3 as 1/6 animals had red eyes and no animals had ocular discharge. At 72 hours after exposure there was no redness or discharge resulting in an average irritation score of 0 (OECD, 2009b; REACHb).

Sensitisation

Skin Sensitisation

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

In a guinea pig maximisation test (according to OECD TG 406), Pirbright White guinea pigs (n=10/sex/dose) were induced intradermally with 5 % DOT(2-EHMA) (70 % purity) in peanut oil. Topical induction used DOT(2-EHMA) at concentrations of 20, 50 and 80 % in petrolatum. The animals were then challenged epicutaneously with 50 % DOT(2-EHMA) in petrolatum, and then rechallenged occlusively with 20 % DOT(2-EHMA) in petrolatum. At 24 and 48 hours after the first challenge, 85 and 100 % of the induced animals had skin reactions (erythema) respectively. At 24 and 48 hours after the second challenge, 85 and 75 % of the induced animals had skin reactions (erythema) respectively (OECD, 2009a; CLH report, 2011). The conduct of the study was not clear from the reports, while multiple topical induction concentrations were mentioned, only a single challenge result set was reported.

In a guinea pig maximisation test (according to OECD TG 406), Pirbright White guinea pigs (n=10/sex/dose) were induced intradermally with 5 % DOT(2-EHMA) (90 % purity) in peanut oil. Topical induction used DOT(2-EHMA) at concentrations of 20, 50 and 80 % in petrolatum. The animals were then challenged occlusively with 30 % DOT(2-EHMA) in petrolatum, and then rechallenged occlusively with 10 % DOT(2-EHMA) in petrolatum. At 24 and 48 hours after the first challenge, 90 and 100 % of the induced animals had skin reactions (erythema) respectively. At 24 and 48 hours after the second challenge, 85 and 80 % of the induced animals had skin reactions (erythema) respectively (OECD, 2009a; CLH report 2011). The conduct of the study was not clear from the reports, while multiple topical induction concentrations were mentioned, only a single challenge result set was reported.

Repeated Dose Toxicity

Oral

Based on the available data for DOT(2-EHMA) and DOT(IOMA), these chemicals are considered to cause serious health effects following repeated oral exposure, warranting hazard classification (see **Recommendation** section). The effects on the thymus (reduced size and depletion of lymphocytes) are consistent with those observed for other dioctyltin compunds (NICNASa; NICNASb). Limited data indicate that the metabolites IOMA and EHMA do not cause serious damage to health from repeated oral exposure (NICNASd).

In a 90-day repeated dose toxicity study (according to OECD TG 408), Wistar rats (n=15/sex/dose) were administered the chemical DOT(2-EHMA) (97 % purity) in the diet at 10, 25, 50, 100, 250, 500 and 1000 ppm. Mortalities were observed in the three highest dose groups (≥250 ppm) with the greatest amount of mortalities occuring in the highest dose group. The average food intake and body weights were reduced at doses ≥250 ppm. Decreases in the relative thymus weights occurred at doses ≥25 ppm. This was

accompanied by treatment related histopathological changes (lymphoid depletion) at doses ≥100 ppm. Other organ weight changes included slight increases in the relative kidney weights at doses ≥100 ppm, significant increases in the relative brain (male and females), gonads (males) and heart (females) weights at 500 ppm and the relative spleen weight slightly increased in some of the dose groups. Treatment related histological lesions were observed in the kidneys and livers of animals in the ≥250 ppm dose groups. Treatment related effects in clinical chemistry (including increased serum alkaline phosphatase (SAP) and glutamic-pyruvic transaminase levels), haematology (including decreases in haemoglobin, lymphocytes, leukocytes and total white blood cell count) and urinalysis (decrease in the specific gravity) were reported The no observed adverse effect level (NOAEL) was determined to be 10 ppm (0.5 mg/kg bw/day) based on the lowest observed adverse effect level (LOAEL) at 25 ppm (1.3 mg/kg bw/day) resulting in thymus effects (CLH report, 2011; OECD, 2009a; REACHa).

In a 90-day repeat dose toxicity study (according to OECD TG 408), SD rats (n=20/sex/dose) were administered DOT(2-EHMA) (70 % purity) in the diet at 0, 25, 50 and 100 ppm (approximately 0, 1.6, 3.3 and 6.6 mg/kg bw/day) for 13 weeks. No mortality occurred during the study period. No changes in food consumption was noted. No treatment related clinical, haematological and urinalysis changes were noted. Significant decreases in thymus weight were observed in the 50 and 100 ppm groups. Histopathological findings were not reported. The NOAEL for this study was determined to be 25 ppm (1.6 mg/kg bw/day) (OECD, 2009a).

In the corresponding 30-day repeat dose toxicity study (no guideline followed), SD rats (n=20/sex/dose) were administered DOT (2-EHMA) (70 % purity) in the diet at 0, 25, 50 and 100 ppm (approximately 0, 1.6, 3.3 and 6.6 mg/kg bw/day) for 4 weeks. No mortality occurred during the study period. No change in food consumption was noted. No treatment related clinical, haematological and urinalysis changes were noted. Significant decreases in thymus weight were observed in the 50 and 100 ppm groups. The NOAEL for this study was determined to be 25 ppm (1.6 mg/kg bw/day) (OECD, 2009a).

In a 90-day repeat dose toxicity study (according to OECD TG 408), SD rats (n=15/sex/dose) were administered DOT(IOMA) in the diet at 0, 20, 50 and 150 ppm for 13 weeks. No mortality occurred during the study period. No changes in food consumption or body weight were noted. No changes in organ weight was noted. No treatment related clinical or haematological changes were noted. One animal in the 150 ppm dose group, and 2 in the 20 ppm group had urine stains. One animal in the 50 ppm group was observed to have swelling around its neck at week 13. Effects on the thymus were not investigated in this study. The NOAEL for this study was determined to be 150 ppm (OECD, 2009b; REACHb).

In a 30-day repeat dose toxicity study (no guideline followed), Long Evans rats (n=10 males/dose) were administered DOT(IOMA) in the diet at 0, 25, 75 and 225 ppm for 4 weeks. No mortality occurred during the study period. Animals in the high dose group initially refused to eat, but after a few days accepted their new diets. No body weight changes were observed. Brain to body weight ratios at 75 and 225 ppm, kidney to body weight ratios at 225 ppm and liver to body ratios at 75 ppm were significantly higher than controls. Effects on the thymus were not investigated in this study. The NOAEL for this study was determined to be 25 ppm (OECD, 2009b; REACHb).

Effects in the thymus were also observed in reproductive and developmental toxicity studies (see **Reproductive and Developmental Toxicity** section).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available data, the chemicals are not considered to be genotoxic.

Mainly negative results were reported using the chemical in vitro (OECD, 2009a; OECD, 2009b; CLH report 2011):

- Negative results were reported in an Ames test (OECD TG 471 and 472) in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, TA1537 and in *Saccharomyces cerevisiae* D4, exposed to DOT(IOMA) at 0.001–5.0 µL/plate, with and without metabolic activation;

- Negative results were reported in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* strains TA98, TA1535, TA1537, TA1538 and in *S. cerevisiae* D4, exposed to DOT(2-EHMA) (70 % purity) at 0.005–10 µL/plate, with and without metabolic activation;
- Negative results were reported in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 exposed to DOT(2-EHMA) at 15–1215 µg/0.1 mL, with and without metabolic activation;
- A positive result was reported in a bacterial reverse mutation assay (OECD TG 471) exposed to DOT(2-EHMA) (70 % purity) between 300–24300 µg/0.1 mL in *S. typhimurium* strains TA1537 (with activation at 300 and 2700 µg/0.1 mL) and TA100 (without activation at 2700 µg/0.1 mL). Negative results were reported in the other strains (TA98, TA1535, and TA1538).
- A positive result was reported in a bacterial reverse mutation assay (no guideline followed) in *S. typhimurium* strain TA100 exposed to DOT(2-EHMA) (70% purity) at between 0.005–10 µL/plate, without metabolic activation; and
- Negative results were reported in a mammalian cell gene mutation assay (OECD TG 476) in mouse lymphoma L5178Y cells exposed to DOT(2-EHMA) at 20 µg/mL and 0.36 µg/mL without activation for 4 and 24 hours respectfully, and up to 85 µg/mL with activation for 4 hours;

Negative results were obtained for the chemical in vivo (OECD, 2009b):

- Negative results were reported in a mouse micronucleus assay (similar to OECD TG 474) in male and female Carworth Farms (CF-1) mice exposed to DOT(IOMA) (80 % purity) at 2250, 4500 and 9000 mg/kg bw as 2 equal administrations (gavage) separated by a period of 24 hours;
- Negative results were reported in a mouse micronucleus assay (similar to OECD TG 474) in male and female CD-1 mice exposed to DOT(IOMA) (80 % purity) at 4500 mg/kg bw as 2 equal administrations separated by a period of 24 hours. Following the last dose the animals were monitored for 48 hours.

Carcinogenicity

No data are available for the chemical. Limited data available using mixtures containing dioctyltin compounds are insufficient to derive a conclusion on carcinogenicity.

In a 2-year study, rats were exposed to a mixture of mono- and dioctyltin chlorides (65:35 %) in diet at 0, 5, 15, 50 or 150 ppm (equivalent to 0, 0.25, 0.75, 2.5 and 7.5 mg/kg bw/day). A NOAEL of 15 ppm (0.75 mg/kg bw/day) was reported, based on significantly increased incidence of generalised malignant lymphomas in males exposed at ≥50 ppm (≥2.5 mg/kg bw/day), and significantly increased incidence of thymic lymphomas in females exposed at 150 ppm (7.5 mg/kg bw/day). In other long-term studies in rats or dogs exposed to mixtures containing mono- and dioctyltins, carcinogenicity was not reported (WHO, 2006). No further details are available.

Reproductive and Developmental Toxicity

The chemical DOT(2-EHMA) is classified as hazardous with hazard category 'Reproductive Toxicity - Category 1B' and hazard statement 'May damage unborn child' (H360D) in the HCIS (Safe Work Australia). Category 1B is used where data from animal studies provide clear evidence of a developmental effect. Although effects observed in studies (increased post-implantation loss, increase incidence of resorption, increased pup mortality, decreased foetal weight) are indicative of developmental effects, the evidence is not considered sufficient for Category 1B. The chemicals are recommended for classification in Category 2. This is consistent with the findings of proposed harmonised classification (CLH report, 2017) and the classifications for other dioctyltin compounds including DOTC (NICNASa; NICNASb; NICNASc).

In a two generation reproduction toxicity study (according to OECD TG 416), SD rats (n=25/sex/dose) were administered DOT(IOMA) (79 % purity) at concentrations of 20, 60 and 200 ppm in the diet (approximately 1.5, 4.4 and 15 mg/kg bw/day for P generation and 1.6, 4.7 and 16 mg/kg bw/day for the F1 generation). The P generation males were administered the chemical 10 weeks prior to mating, throughout mating (approximately 3 weeks), and post mating until sacrifice. The P generation females were administered the chemical 10 weeks prior to mating, throughout mating, gestation and lactation. No substance related mortality or adverse clinical signs were noted in the P generation groups. In the 60 ppm dose group a slight decrease in the relative thymus weights in males was observed, while in the high dose group, significant decreases in thymus weight were observed in both males and females with a

significant increase in the incidence of thymic involution in males. In the high dose group a decrease in food consumption in females was noted. In the high dose group there was a slight increase in the incidence of pup mortality. Male and female pups born to the high dose group dams were found to have significantly decreased body weights at lactation days 14 and 21. In the high dose group a slight decrease in the viability index, and a significant decrease in the lactation index were reported. A delay in vaginal opening was observed in females in the high dose group.

The subsequent F1 males were administered the chemical for 14 weeks starting from lactation, through to mating, post mating until being euthanised. The F1 females were administered the chemical for 14 weeks from lactation through to mating. Effects in the thymus were observed at doses ≥60 ppm. In the high dose group there were significant decreases in the relative thymus weight in both males and females with a significant increase in the incidence of thymic involution in males. In the high dose group there was a significant decrease in the body weight of males, a significant reduction in food consumption in females on lactation days 14–21, a slight reduction in the viability index, a significant reduction in the lactation index, and significant reductions in male and female pup body weight on lactation days 4, 7, 14 and 21. Also observed within the high dose group was a significant increase in the number of stillbirths (26) compared to the controls (5) (12 of these were in a single litter), an increase in the incidence of pup mortality from lactation days 4–21 and a delay in morphological changes for F2 generation such as ear and eye opening, and pinna unfolding compared to controls. No teratogenic effects were observed.

The chemical did not cause an adverse effect on mating, fertility, pregnancy rates, gestation, litter size or neonatal body weight. Adverse effects on the body weights and viability of the F1 and F2 generation from day 4 onwards was observed. This may not be a reproductive effect as the effects but a result of a direct toxic effect of dioctyltin species give that the pups may be receiving two sources of exposure (maternal milk and diet). The NOAEL for P and F1 generation animals was determined to be 20 ppm (1.5–1.6 mg/kg bw/day) based on the thymus effects on the animals in the 60 ppm group (CLH report, 2017).

In a prenatal developmental toxicity study (according to OECD TG 414), Swiss mice (n=25 pregnant females/dose) were administered DOT(2-EHMA) at concentrations of 0, 15, 30 or 60 mg/kg bw/day, on gestation days (GD) 5–17. No treatment related deaths of the dams was noted during the study. The maternal body weight gain of the dams in the high dose group was significantly lower than that of the controls. The thymus weight in the dams in the mid- and high dose groups was significantly reduced when compared to the controls. No treatment related effects were noted in mean gravid uterus weight, number of corpora lutea, number of implantations in all the groups, and number of early or late resorptions. There was a statistically significant positive trend on percentage of post implantation loss (0.9 ± 2.8 at low, 1.5 ± 4.9 at mid, and 2.6 ± 5.6 at high dose, respectively). The NOAEL for maternal toxicity was 15 mg/kg bw/day. A NOAEL for developmental toxicity was not established (CLH report, 2017).

In a prenatal developmental toxicity study (according to OECD TG 414), New Zealand White (NZW) rabbits (n=24 pregnant females/dose) were administered DOT(2-EHMA) at concentrations of 0, 4, 20 or 80 mg/kg bw/day on GD 5–28. A statistically significant decreased thymus weight occurred in the high dose dams. No treatment related effects were noted in the number of corpora lutea, number of implantation sites, number of early or late resorptions, or percentage of post implantation loss across all the groups. A dose dependent reduction in foetal bodyweight was observed. A statistically significant reduction in the mean foetal crown-rump length was noted in the high dose group when compared to controls. The lowest observed adverse effect level (LOAEL) for maternal and developmental effects was 80 mg/kg bw/day (CLH report, 2017).

In a prenatal developmental toxicity study (conducted similarly to OECD TG 414), Han Wistar SPF rats were administered DOT(IOMA) (purity 80 %) at concentrations of 1, 5 or 25 mg/kg bw/day on GD 6–15. There was a slight (non-significant) decrease in corrected body weight and corrected body weight gain from day 6 to day 21 in the high dose (25 mg/kg/day) group. This reduction was attributed largely to one single dam. No embryofoetal effects were reliably attributed to treatment as the observed embryolethality was marginal (observed in only the same dam that had significant bodyweight loss). The NOAEL for maternal and developmental toxicity was reported as 5 mg/kg bw/day (CLH report, 2011; CLH report 2017).

In a prenatal developmental toxicity study (conducted similarly to OECD TG 414), mice (NMRI) were administered DOT(IOMA) (purity 80 %) at concentrations of 20, 30, 45, 67 or 100 mg/kg bw/day on GD 6–17. Statistically significant decreased thymus weights were seen at 45 and 100 mg/kg bw/day with a non-significant decrease at 67 mg/kg bw/day. Resorption rates were significantly increased at the highest two doses. A significant increased incidence of cleft palate and skeletal abnormalities was observed in foetuses of dams exposed at the highest two doses. Skeletal variations were also reported at the lower doses. The NOAEL for maternal toxicity was 30 mg/kg bw/day and the embryo-foetal NOAEL for malformations was 45 mg/kg bw/day. There were a number of deficiencies in the study including the absence of historical control data (CLH report, 2011; CLH report 2017).

In a prenatal developmental toxicity study (conducted similarly to OECD TG 414), NZW rabbits were administered DOT(IOMA) (purity 80 %) at concentrations of 1, 10 or 100 mg/kg bw/day on GD 6–18. Abortion was diagnosed in 4 out of 24 dams at the highest dose. Resorption rates were significantly increased at the highest dose. Embryotoxic effects were reported at the highest dose including minor visceral anomalies (severely dilated renal pelves and additional small vessels originating from the aortic arch), minor skeletal

head anomalies (incomplete ossified bones in the skull), and skeletal variations of the sternum and feet bones (not or incomplete ossified sternebrae and feet bones); and a significant reduction in foetal body weight. The NOEL for maternal and developmental toxicity was reported as 1 mg/kg bw/day (CLH report, 2011; CLH report 2017).

2-EHMA was reported to be toxic to development (NICNASd).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (reproductive toxicity and thymus effects) following repeated oral exposure and local effects (skin sensitisation).

Public Risk Characterisation

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

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). Based on an impact assessment report conducted in Europe (European Commission, 2009), these chemicals with their identified uses are not considered to significantly contribute to the overall TDI. Organotins have not been found in Australian drinking water (NWQMS, 2011). In addition, the dominant contribution to human intake of organotins (mainly tributyltin compounds) is via the consumption of fish. Hence, the public risk from the chemical 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 the chemical may be required.

Occupational Risk Characterisation

During product formulation, exposure may 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 and systemic acute health effects, these chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise exposure are implemented. These 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 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.

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.

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]
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1B (H317)
Repeat Dose Toxicity	Not Applicable	Causes damage to the immune system through prolonged or repeated exposure - Cat. 1 (H372)
Reproductive and Developmental Toxicity	Not Applicable	Suspected of damaging fertility or the unborn child - Cat. 2 (H361fd)

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

Advice for industry

Control measures

Control measures to minimise the risk from exposure to these 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 is used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- 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.

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