Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Compounds of dioctyltin

Evaluation statement

30 June 2022

Table of contents

Contents

AICIS evaluation statement

Subject of the evaluation

Compounds of dioctyltin

Chemicals in this evaluation

Name	CAS registry number
6H-1,3,2-Oxathiastannin-6-one, dihydro-2,2-dioctyl-	3033-29-2
5,7,12-Trioxa-6-stannaoctadeca-2,9-dienoic acid, 14-ethyl-6,6-dioctyl-4,8,11-trioxo-, 2-ethylhexyl ester	10039-33-5
1,3,2-Oxathiastannolan-5-one, 2,2-dioctyl-	15535-79-2
2-Butenoic acid, 4,4'-[(dioctylstannylene)bis(oxy)]bis[4-oxo-, (Z,Z)-	15571-60-5
1,3,2-Dioxastannepin-4,7-dione, 2,2-dioctyl-	16091-18-2
Stannane, bis(dodecylthio)dioctyl-	22205-30-7
2,7,9-Trioxa-8-stannatrideca-4,11-dien-13-oic acid, 8,8-dioctyl-3,6,10-trioxo-, methyl ester, (Z,Z)-	60494-19-1
3,8,10-Trioxa-9-stannatetradeca-5,12-dien-14-oic acid, 9,9-dioctyl-4,7,11-trioxo-, ethyl ester	68109-88-6
2-Butenoic acid, 4,4'-[(dioctylstannylene)bis(oxy)]bis[4-oxo-, diisononyl ester, (Z,Z)-	91422-01-4
Silicic acid (H4SiO4), tetraethyl ester, reaction products with bis(acetyloxy)dioctylstannane	93925-43-0

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

The chemicals are a group of dioctyltin compounds listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses of these chemicals.

These chemicals have been assessed as a group because the toxicity of organotin compounds depends largely on the organotin moiety, and these chemicals are structurally similar. Based on a review of the available information, dioctyltin compounds have been reported to cause developmental and immune system toxicity. These human health effects are likely to be the main drivers of any risk management recommendations for this group of chemicals.

Although data for local effects are presented for chemicals where available, this evaluation will not provide conclusions on these endpoints where data are not available.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of these chemicals in Australia. Data on emissions and sources of emissions for organotin compounds in Australia indicate site limited use in polymer product manufacturing.

Based on international information for 7 of the chemicals in this group, the chemicals are used as stabilisers and process regulators in the manufacture of plastic and other products used in a wide range of commercial applications.

Four of the chemicals have reported commercial use including in adhesives, sealants, paints and coatings. Although these product types may also be used in domestic applications, available data did not indicate widespread use in consumer products. One chemical (CAS No. 93925-43-0) had identified use in consumer product adhesives at concentrations of <1%.

Public consultation provided data that identified commercially active, most likely active, and inactive chemicals for all chemicals in this group (see **Supporting Information – Introduction and use: International** section).

Human health

Summary of health hazards

There is limited toxicological information for 8 of the chemicals in this group. The main driver of systemic toxicity associated with dioctyltin compounds is expected to be the dioctyltin moiety. Therefore, available data for other dioctyltin compounds, including dioctyltin dichloride, dioctyltin alkyl mercaptoacetates, dioctyltin oxide, and dioctyltin dicarboxylates are used to draw conclusions regarding the systemic effects of the chemicals in this group. These dioctyltin compounds were assessed previously and the reports should be read in conjunction with this evaluation statement (NICNAS 2018a; NICNAS 2018b; NICNAS 2018c; NICNAS 2019).

Based on read across information, the critical health effects for risk characterisation include:

- developmental toxicity
- immunotoxicity.

Based on read across data, the chemicals are expected to cause serious systemic health effects following repeated exposure. Consistent effects on the thymus following repeated exposure at low doses including decreased thymus weights and associated lymphoid depletion were observed in studies with dioctyltin dichloride, dioctyltin alkyl mercaptoacetates and dioctyltin oxide.

Based on read across data, the chemicals are expected to cause specific adverse effects on development following exposure. Consistent effects on developmental toxicity including increased post-implantation loss, increased incidence of resorption, decreased number of live pups, increased pup mortality and decreased foetal bodyweight were observed in studies with dioctyltin dichloride, dioctyltin alkyl mercaptoacetates and dioctyltin oxide. An increased incidence of foetal malformations was observed in studies with dioctyltin dichloride and

dioctyltin alkyl mercaptoacetates. A dose response relationship of increased incidence of incomplete ossification of cervical arches was observed in a recent prenatal developmental study with dioctyltin dilaurate (unpublished data, 2022).

Based on the available in vitro data for 4 of the chemicals and read across data from dioctyltin dichloride, dioctyltin alkyl mercaptoacetates and dioctyltin oxide, the chemicals are not expected to be genotoxic.

Based on data for 8 of the chemicals and read across data from dioctyltin dichloride, dioctyltin alkyl mercaptoacetates, dioctyltin oxide, and dioctyltin dicarboxylates, the chemicals may have low to moderate acute oral and low dermal toxicity. There are no data on inhalation toxicity.

Limited data for some of the chemicals in this group indicate that they are, at most, slightly irritating to skin or eyes apart from one chemical (CAS No. 68109-88-6) which is irritating to eyes and reported to cause skin necrosis after 24 hours of occluded exposure. There are no data on skin sensitisation for any of these chemicals. Dioctyltin alkyl mercaptoacetates are skin sensitisers. However, read across for this group of chemicals is not appropriate for local effects.

Hazard classification relevant for worker health and safety

These chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for hazard classes relevant for work health and safety. This evaluation does not consider classification of physical and environmental hazards. These recommended classifications are based on read across principles (see **Supporting Information – Grouping Rationale** section). If empirical data become available for any member of the group indicating that a lower (or higher) classification is appropriate for a specific chemical, this data may be used to amend the default classification for that chemical.

All chemicals in this group are recommended for classification for repeated dose toxicity and developmental toxicity.

The acute oral toxicity classification applies only to CAS No. 15535-79-2.

The eye irritation classification applies only to CAS No. 68109-88-6.

Health hazards	Hazard category	Hazard statement
Acute oral toxicity	Acute Tox. 4	H302: Harmful if swallowed
Serious eye damage/eye irritation	Eye Irrit. 2A	H319: Causes serious eye irritation.
Repeated dose	STOT Rep. Exp. 1	H372: Causes damage to the immune system through prolonged or repeated exposure
Reproductive and developmental	Repr. 2	H361d: Suspected of damaging the unborn child

Summary of health risk

Public

There may be exposure of the general public to these chemicals if they are present in domestic products, specifically do-it-yourself (DIY) sealants and adhesives, paints and coatings, and other building and construction materials. Based on the available data, use of the chemicals in consumer products is not expected to be widespread and any use is at low concentrations, expected to be <1%. In addition, exposure to DIY products is incidental and normal precautions to avoid prolonged contact are expected.

These chemicals are not listed in the Poisons Standard (TGA). The listing in Schedule 7 of the SUSMP for other dialkyltins does not apply at concentrations less than 1%. Based on the available use information, there are no identified risks to the public that require further risk management. However, if information becomes available indicating the chemicals have more widespread consumer use, further risk management may be required.

Based on the available use information, the public may also be exposed to the chemicals at very low concentrations in articles through their use in the manufacture of plastics and potential use of these in food contact applications.

Internationally, a tolerable daily intake (TDI) of (0.1 µg/kg bw as Sn) for organotin compounds in foodstuffs, based on systemic effects, has been established for this group (EC 2009).

To reduce the identified risk of organotin compounds transferred from food packaging to foodstuffs, the overall exposure should be lower than the TDI. The dominant contribution to human intake of organotin compounds (mainly tributyltin) is via consumption of fish. Exposure to other organotin compounds, including these chemicals, is expected to be generally low both from food contact and handling plastic articles.

Workers

During product formulation and packaging, dermal 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 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. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical systemic long term health effects, these chemicals could pose a risk to workers. Control measures to minimise dermal exposure and inhalation exposure (if aerosolised) are needed to manage the risk to workers (see **Proposed means for managing any risks** section). Control measures implemented due to the repeated dose and developmental classifications are expected to be sufficient to protect workers from any potential local health effects.

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety.

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from exposure to these chemicals include, but are not limited to:

- using closed systems or isolating operations
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that
- the worker does not come into contact with these chemicals.

Measures required to eliminate or manage risk arising from storing, handling and using these hazardous chemicals depend on the physical form and how these chemicals are used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to these chemicals if valid techniques are available to monitor the effect on the worker's health
- conducting air monitoring to ensure control measures in place continue to work effectively.

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.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The conclusions of this evaluation are based on the information described in this evaluation statement.

Considering the proposed means of managing risks, the Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory and the proposed means of managing the risks identified during this evaluation are implemented.

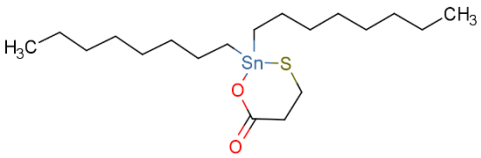
Note: Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.

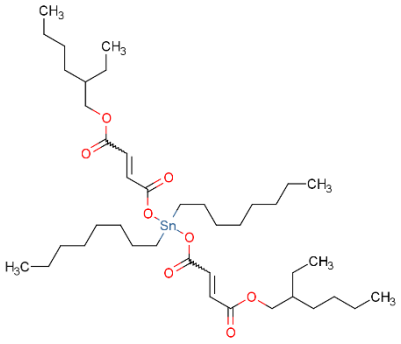
Supporting information

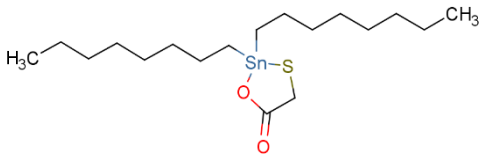
Grouping rationale

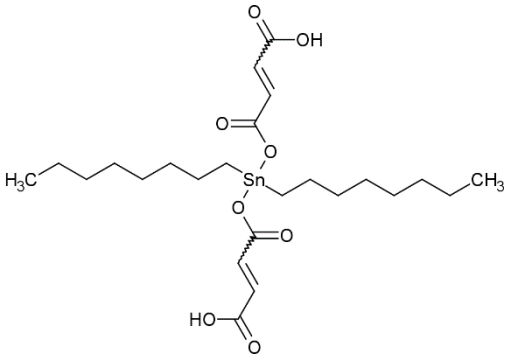
This group of chemicals consists of 10 dioctyl organotin compounds that are expected to release simpler dioctyltin compounds following metabolism. Di-substituted organotin compounds have the general formula R_2SnX_2. The toxicity of organotin compounds depends largely on the organotin moiety (R group), with the anionic ligand (X) mostly influencing physicochemical properties and local toxicity. Toxicological data are available for dioctyltin compounds with different X groups including tin compounds coordinated with oxygen, sulfur and halides. Although the levels at which effects are observed may vary for different dioctyltin compounds, similar effects and target organs were seen across the suite of studies, supporting the view that a similar mechanism of toxicity is operating. Because the systemic toxicological properties are sufficiently similar for these compounds, it is appropriate to read across from these chemicals to the chemicals in this evaluation for systemic effects.

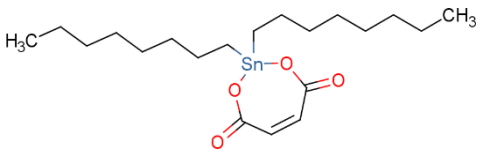
Chemical identity

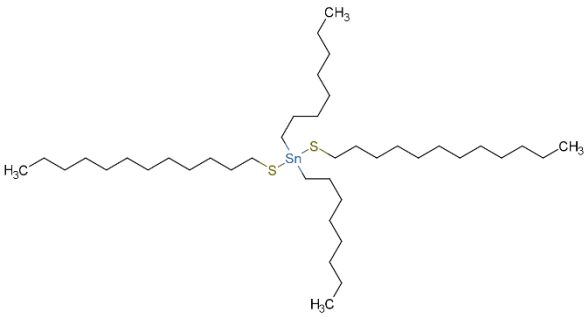
Chemical name	6H-1,3,2-Oxathiastannin-6-one, dihydro-2,2-dioctyl-
CAS No.	3033-29-2
Synonyms	dioctyltin 3-mercaptopropionate-O,S
Structural formula	
Molecular formula	$C_{19}H_{38}O_2SSn$
Molecular weight (g/mol)	449.3
SMILES	O=C1O[Sn](SCC1)(CCCCCCCC)CCCCCCCC
Chemical description	Organometallic compound

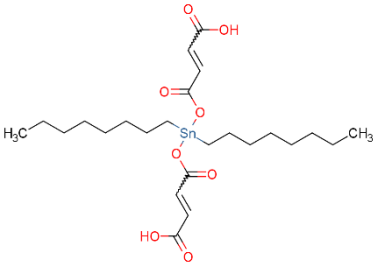
Chemical name	5,7,12-Trioxa-6-stannaoctadeca-2,9-dienoic acid, 14-ethyl-6,6-dioctyl-4,8,11-trioxo-, 2-ethylhexyl ester
CAS No.	10039-33-5
Synonyms	di-n-octyltin bis[2-ethylhexyl maleate]
Structural formula	
Molecular formula	$C_{40}H_{72}O_8Sn$
Molecular weight (g/mol)	799.7
SMILES	O=C(OCC(CC)CCCC)C=CC(=O)O[Sn](OC(=O)C=CC(=O)OCC(CC)CCCC)(CCCCCCCC)CCCCCCCC
Chemical description	Organometallic compound

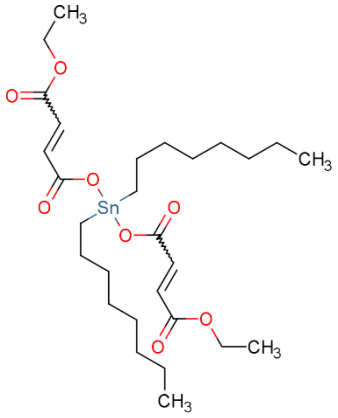
Chemical name	1,3,2-Oxathiastannolan-5-one, 2,2-dioctyl-
CAS No.	15535-79-2
Synonyms	dioctyltin O,S-thioglycollate
Structural formula	
Molecular formula	$C_{18}H_{36}O_2SSn$
Molecular weight (g/mol)	435.3
SMILES	O=C1O[Sn](SC1)(CCCCCCCC)CCCCCCCC
Chemical description	Organometallic compound

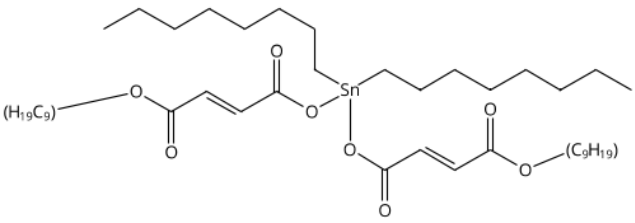
Chemical name	2-Butenoic acid, 4,4'-[(dioctylstannylene)bis(oxy)]bis[4-oxo-, (Z,Z)-
CAS No.	15571-60-5
Synonyms	-
Structural formula	
Molecular formula	$C_{24}H_{40}O_8Sn$
Molecular weight (g/mol)	575.3
SMILES	O=C(O)C=CC(=O)O[Sn](OC(=O)C=CC(=O)O)(CCCCCCCC)CCCCCCCC
Chemical description	Organometallic compound

Chemical name	1,3,2-Dioxastannepin-4,7-dione, 2,2-dioctyl-
CAS No.	16091-18-2
Synonyms	di-n-octyltin maleate
Structural formula	
Molecular formula	$C_{20}H_{36}O_4Sn$
Molecular weight (g/mol)	459.2
SMILES	O=C1O[Sn](OC(=O)C=C1)(CCCCCCCC)CCCCCCCC
Chemical description	Organometallic compound

Chemical name	Stannane, bis(dodecylthio)dioctyl-
CAS No.	22205-30-7
Synonyms	dioctyltin didodecylmercaptide
Structural formula	
Molecular formula	$C_{40}H_{84}S_2Sn$
Molecular weight (g/mol)	747.9
SMILES	S(CCCCCCCCCCCC)[Sn](SCCCCCCCCCCCC)(CCCCCCCC)CCCCCCCC
Chemical description	Organometallic compound

Chemical name	2,7,9-Trioxa-8-stannatrideca-4,11-dien-13-oic acid, 8,8-dioctyl-3,6,10-trioxo-, methyl ester, (Z,Z)-
CAS No.	60494-19-1
Synonyms	5,7,12-trioxa-6-stannatrideca-2,9-dienoic acid, 6,6-dioctyl-4,8,11-trioxo-, methyl ester, (Z,Z)-
Structural formula	
Molecular formula	$C_{26}H_{44}O_8Sn$
Molecular weight (g/mol)	603.3
SMILES	O=C(O)C=CC(=O)O[Sn](OC(=O)C=CC(=O)O)(CCCCCCCC)CCCCCCCC
Chemical description	Organometallic compound

Chemical name	3,8,10-Trioxa-9-stannatetradeca-5,12-dien-14-oic acid, 9,9-dioctyl-4,7,11-trioxo-, ethyl ester
CAS No.	68109-88-6
Synonyms	dioctylbis(3-carboxyacryloyloxy)stannane, diethyl ester
Structural formula	
Molecular formula	$C_{28}H_{48}O_8Sn$
Molecular weight (g/mol)	631.4
SMILES	O=C(OCC)C=CC(=O)O[Sn](OC(=O)C=CC(=O)OCC)(CCCCCCCC)CCCCCCCC
Chemical description	Organometallic compound

Chemical name	2-Butenoic acid, 4,4'-[(dioctylstannylene)bis(oxy)]bis[4-oxo-, diisononyl ester, (Z,Z)-
CAS No.	91422-01-4
Synonyms	-
Structural formula	
Molecular formula	$C_{42}H_{76}O_8Sn$
Molecular weight (g/mol)	827.8
SMILES	-
Chemical description	Organometallic compound

Chemical name	Silicic acid (H_4SiO_4), tetraethyl ester, reaction products with bis(acetyloxy)dioctylstannane
CAS No.	93925-43-0
Synonyms	-
Structural formula	No structure available.
Molecular formula	Unspecified
Molecular weight (g/mol)	Unspecified
SMILES	Unspecified
Chemical description	Organometallic compound and UVCB

Relevant physical and chemical properties

Limited data are available for the chemicals in this group. Regarding the chemicals with data (REACHa; REACHb; REACHc; REACHd; REACHe; REACHf; SciFinder):

- they are solids (CAS Nos. 3033-29-2; 15535-79-2) or colourless liquids (CAS Nos. 10039-33-5; 22205-30-7; 68109-88-6; 93925-43-0)
- melting points range from -70–200 ºC at 101.325 kPa
- the chemicals generally decompose when heated >250ºC
- vapour pressures are low (< 0 Torr), thus the chemicals are expected to have low volatility
- water solubility is low (<0.4 mg/L).

Introduction and use

Australia

No specific information is available regarding the introduction, import and use of these chemicals in Australia.

The National Pollutant Inventory (NPI) provides information on emission sources of organotin compounds in Australia. The following site limited uses were identified by the NPI in 2019/2020:

- glass and glass product manufacturing
- in polymer product manufacturing.

Information provided through public comment state that dioctyltin compounds are not used in glass or glass product manufacturing (unpublished information, 2022).

International

Public consultation resulted in the provision of the following information for all chemicals in this group (unpublished information, 2022):

- Six chemicals (CAS Nos.3033-29-2, 10039-33-5; 16091-18-2, 22205-30-7, 68109-88-6; 93925-43-0;) were identified to be commercially active.
- One chemical, CAS No. 15535-79-2 was identified as unlikely to be in commerce. It is a by-product in the manufacture of dioctyltin bis(2-ethylhexylthioglycolate) (DOTE, CAS No. 15571-58-1), a stabiliser used in the manufacture of plastics.
- Three chemicals (CAS Nos. 15571-60-5; 60494-19-1; 91422-01-4) were identified to be commercially inactive.

International uses for 7 of the chemicals (CAS Nos. 3033-29-2, 10039-33-5, 15535-79-2, 16091-18-2, 22205-30-7, 68109-88-6, 93925-43-0) have been identified through the:

- European Union Registration, Evaluation and Authorisation of Chemicals (REACH)
- Substances in Preparations in Nordic countries (SPIN) database
- Canadian Inventory Update activities (2017)
- Galleria Chemica (Chemwatch)
- US Chemical Data Reporting under the Toxic Substances Control Act 2012/2016
- PubChem database.

Based on this information, the chemicals are reported to be primarily used in site limited applications as process regulators or aids, additives, plasticisers or heat stabilisers in the manufacture of plastic products (including soft and rigid PVC) and resins. Typical concentrations for use as heat stabilisers in PVC of 2% were reported for CAS Nos. 15535-79-2 and 68109-88-6 (ECHA). A maximum concentration of 31 but <30% by weight was reported for CAS No. 15535-79-2 for use as a processing aid in plastics manufacture (US EPA 2016).

The chemicals are also reported to be used as intermediates in the manufacture of chemicals and in the manufacture of rubber products, textiles, leather or fur, wood and wood products, pulp, paper and paper products, fabricated metal products, electrical, electronic and optical equipment, machinery and vehicles and furniture.

Some of the chemicals (CAS Nos. 15535-79-2; 16091-18-2; 93925-43-0; 22205-30-7) are reported to have the following commercial uses (Government of Canada 2017; REACHd; REACHf; SPIN; US EPA 2016):

- adhesives and sealants
- paints, coatings and surface treatment
- building and construction materials.

A maximum concentration of 1 but <30% by weight was reported for CAS No. 15535-79-2 for use in building and construction materials (US EPA 2016).

Some of these commercial uses may also be used in domestic applications. There were no identified products containing the chemicals in North American consumer product databases DeLima Associates). Consumer uses were not identified for CAS No. 16091-18-2 as part of the inventory update in Canada (Government of Canada 2017) and consumer uses were not identified for CAS No. 15535-79-2 reported under the US Chemical Data Reporting (CDR) under the Toxic Substances Control Act (US EPA 2012; US EPA 2016). Except for

CAS No. 93925-43-0, no consumer uses are registered under REACH and the SPIN database. A Safety Data Sheet (SDS) indicated potential use of CAS No. 93925-43-0 in consumer product adhesives at concentrations of <1%.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for these chemicals.

Public

No specific controls are currently available for these chemicals.

Workers

Tin and its compounds are listed in the Work Health and Safety Regulations (2021 revision) as restricted hazardous chemicals—the restricted use is 'abrasive blasting at a concentration of greater than 0.1% as tin' (SWA 2021).

These chemicals are not specifically listed as hazardous chemicals on the HCIS (SWA).

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) (SWA).

In 2020, Safe Work Australia reviewed and recommended retaining the TWA. The recommended TWA is considered protective for effects on the central nervous system and other systems. A STEL was not recommended due to insufficient data relating to acute exposures (SWA 2020). At the time of publication of this evaluation statement, these workplace exposure standards were yet to be finalised.

International regulatory status

Exposure standards

The following exposure standards were identified for tin, organic compounds (as Sn) (Chemwatch):

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), Denmark, Egypt, Estonia, France, Greece, Malaysia, Mexico, Norway, Philippines, Singapore, South Africa, Spain, Sweden, Taiwan, the United Kingdom and the United States of American (California, Hawaii, Minnesota, Tennessee, Vermont, Washington).

European Union

Four of the chemicals (CAS Nos. 10039-33-5; 15535-79-2; 15571-60-5; 68109-88-6) are listed in the European Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food - Annex I - Table 1 (EC 2011).

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

- 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
- 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 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 to di-n-octyltin (COE 1992).

Tin or tin organic compounds—which includes the chemicals in this assessment—are listed on the following:

- European Commission 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 (COE 2009)
- 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 (COE 2008).

Health hazard information

Toxicokinetics

Studies have shown that in general, sulfur or carboxylate-based ligands of organotin compounds are easily displaced under mild physiological conditions (OECD 2006). Abiotic hydrolysis of an analogue has been studied. However, no data are available regarding the in vivo metabolism of these chemicals.

In a study conducted according to Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 111, a solution of the chemical with CAS No. 15535-79-2 identified as DOTTG (assumed to be dioctyltin thioglycolate based on the dossier details) was exposed to simulated gastric conditions (0.1 M HCl/pH 1.2/ 37ºC) for 4 hours and monitored using ^{119}Sn NMR. The chemical hydrolysed completely to dioctyltin monochlorothioglycolic acid (REACHc).

Acute toxicity

Based on data for 8 of the chemicals and read across data from dioctyltin dichloride, dioctyltin alkyl mercaptoacetates, dioctyltin oxide, and dioctyltin dicarboxylates, the chemicals may have low to moderate acute oral and low dermal toxicity. There are no data on inhalation toxicity.

Oral

The following lethal median doses (LD50s) were reported, indicating low to moderate toxicity:

- >2000 mg/kg bw in Sprague Dawley (SD) rats, 5/sex/dose, OECD TG 401 conducted with Good Laboratory Practice (GLP), sub-lethal signs of toxicity included piloerection, soft faeces production and a swollen abdomen (CAS No. 3033-29-2) (REACHa)
- 1850 mg/kg bw in rats (species not specified) (CAS No. 3033-29-2) (CCOHS 2021a)
- 2700 mg/kg bw in white mice (6/sex), sub-lethal signs of toxicity included seizure, respiratory depression, hyperaemia in the gastrointestinal tract and the liver, sporadic haemorrhages in the lungs and enlarged liver and spleen (CAS No. 10039-33-5) (CCOHS 2021; REACHb)
- 2760 mg/kg bw in rats (species not specified) (CAS No. 10039-33-5) (CCOHS 2021b)
- 300–2000 mg/kg bw in Wistar rats (5/sex), OECD TG 420 conducted with GLP, sub-lethal signs of toxicity included ataxia and hunched posture at 300 mg/kg bw and hunched posture, pilo-erection, tiptoe gait, emaciation, dehydration, pale extremities and hypothermia at 2000 mg/kg bw, (CAS No. 15535-79-2) (REACHc)
- 2294 mg/kg bw in SPF rats (5/sex/dose), OECD TG 401, sub-lethal signs of toxicity included lethargy, dyspnoea, exophthalmos, ruffled fur, diarrhoea, and hunched posture (CAS No. 15535-79-2) (REACHc)
- 943–2290 mg/kg bw in 4 non-guidelines studies with no reported details, (CAS No. 15535-79-2) (CCOHS 2021c; REACHc)
- 4500 mg/kg bw in rats, no reported details (CAS No. 16091-18-2) (CCOHS 2021d)
- 775 mg/kg bw in mice, no reported details (CAS No. 16091-18-2) (CCOHS 2021d)
- 4000 mg/kg bw in mice (species not specified), sub-lethal signs of toxicity included fatty liver degeneration and hyperaemia in the kidney (CAS No. 22205-30-7) (CCOHS 2021e).
- 1673 mg/kg bw in rats (species not specified), no reported details (CAS No. 60494-19-1) (CCOHS 2021f).
- 3793 mg/kg bw in SPF rats, (5/sex/dose), OECD TG 401 conducted with GLP, (CAS No 68109-88-6), sub-lethal signs of toxicity included sedation, dyspnoea, exophthalmus, ruffled fur and hunched posture (REACHe).
- >2000 mg/kg bw in Wistar rats (6 female), OECD TG 423 conducted with GLP, reported sub-lethal signs of toxicity included piloerection and hunched posture (CAS No. 93925-43-0) (REACHf).

Available data for dioctyltin alkyl mercaptoacetates, dioctyltin oxide, and dioctyltin dicarboxylates indicate that the chemicals have low to moderate acute oral toxicity (NICNAS 2018a; NICNAS 2018b; NICNAS 2018c; NICNAS 2019).

Dermal

Based on the available data, 2 of the chemicals (CAS Nos. 68109-88-6 and 93925-43-0) have low acute toxicity following dermal exposure. No data are available for the other chemicals in this group.

In 2 GLP compliant acute dermal toxicity studies conducted in accordance with OECD TG 402, Wistar rats (5/sex) were treated with a single dose of the following chemicals and reported LD50 values were >2000 mg/kg bw.

- CAS No. 68109-88-6. Sub-lethal effects of toxicity included very slight erythema, crust formation and desquamation were reported in the treated skin area of the animals (REACHe).
- CAS No. 93925-43-0. Sub-lethal signs of toxicity included lethargy, chromodacryorrhoea, piloerection and hunched posture (REACHf).

Available data for dioctyltin alkyl mercaptoacetates, dioctyltin oxide, and dioctyltin dicarboxylates indicated that these chemicals have low acute dermal toxicity (NICNAS 2019; NICNAS 2018b; NICNAS 2018c).

Inhalation

No studies are available.

Corrosion/Irritation

Limited data for some of the chemicals in this group indicate that they are at most slightly irritating to skin or eyes apart from one chemical (CAS No. 68109-88-6) which is irritating to eyes, warranting classification. It is also reported to cause necrosis after 24 hours of occluded skin exposure. However, due to the severe conditions used in this study, no conclusions can be drawn regarding the skin irritation potential of this chemical under standard conditions. No data are available for the other chemicals in this group.

Skin irritation

In a GLP compliant in vitro skin corrosion assay conducted in accordance with OECD TG 431, the chemical was applied to RhE EpiDerm™ for 3 and 60 minutes. The mean tissue viability was 78.2 and 101.5% after 3 and 60 minutes respectively. Substances that reduce viability to less than 15% after 60 minutes are classified as corrosive. Therefore, the chemical is considered to be unlikely to have potential to cause corrosion in vivo following application (REACHa). In a GLP compliant in vitro skin irritation study conducted in accordance with OECD TG 439 (in vitro reconstructed human epidermis (RHE) test method for skin irritation), the chemical with CAS No. 3033-29-2 was applied to RhE EpiSkin™, for an exposure period of 15 minutes, followed by an observation period of 42 hours. A mean tissue viability value of 93.1% was reported for the chemical in this study, and it was determined to not be irritating to the skin. Interpretation of results obtained from OECD TG 439 studies do not allow for distinction between irritation and corrosion (REACHa).

In an in vitro skin corrosion assay conducted in accordance with OECD TG 431, the chemical with CAS No. 15535-79-2 was applied to RhE EpiSkin™ for 3, 60 and 240 minutes. The mean tissue viability was 104, 124.5 and 110.5% after 3, 60 and 240 minutes respectively. Therefore, the chemical is considered to be unlikely to have potential to cause corrosion in vivo following application (REACHc). In an in vitro skin irritation study conducted in accordance with OECD TG 439 (in vitro RHE test method for skin irritation), the chemical was applied to RhE EpiSkin™, for an exposure period of 15 minutes. A mean tissue viability value of 92.7% was reported for the chemical in this study, and it was determined not to be irritating to the skin (REACHc).

In a GLP compliant in vitro skin corrosion assay conducted in accordance with OECD TG 431, the chemical with CAS No. 22205-30-7 was applied to RhE EpiDerm™ for 3 and 60 minutes. The mean tissue viability was 95.1 and 97.8% after 3 and 60 minutes respectively. Therefore, the chemical is considered to be unlikely to have potential to cause corrosion in vivo following application (REACHd). In a GLP compliant in vitro skin irritation

study conducted in accordance with OECD TG 439 (in vitro RHE test method for skin irritation), the chemical was applied to RhE EpiSkin™, for an exposure period of 15 minutes, followed by an observation period of 42 hours. A mean tissue viability value of 98.1% was reported for the chemical in this study, and it was determined not to be irritating to the skin (REACHd).

In a GLP compliant skin irritation study similar to OECD TG 404, New Zealand White (NZW) rabbits (n=6) were treated with the chemical with CAS No. 68109-88-6 for 24 hours under occluded conditions on intact and abraded skin on each animal. Observations were recorded at 24, 48 and 72 hours after patch removal. The following mean scores were reported for observations at 24, 48 and 72 hours: 3, 3, 3, (intact) and 3, 2.8, 2.8 (abraded) for erythema and 2.8, 2.5, 2.7 (intact) and 2.7, 2.5, 2.5 (abraded) for oedema respectively (maximum score of 4). Signs of irritation include necrosis and extended erythema. The erythema and oedema were not reversible in all animals within 7 days (REACHe).

In a skin irritation study conducted in accordance with OECD TG 404, NZW rabbits (n=3) were treated with the chemical with CAS No. 93925-43-0 for 4 hours under semi-occlusive conditions. Observations were recorded at 24, 48 and 72 hours after patch removal. The following mean scores for individual animals were reported for observations at 24, 48 and 72 hours: 1.3, 1.3, 0.7 for erythema and 1, 0.7 and 0.3 for oedema respectively (maximum score of 4). Erythema and oedema were reversible in all animals within 7 days (REACHf).

Available data for dioctyltin dichloride, dioctyltin alkyl mercaptoacetates, dioctyltin oxide, and dioctyltin dicarboxylates reported the chemicals to be at most slightly irritating to skin (NICNAS 2018a; NICNAS 2018b; NICNAS 2018c; NICNAS 2019).

Eye irritation

In a GLP compliant ex vivo eye corrosivity/irritation study conducted according to OECD TG 437, the chemical with CAS No. 3033-29-2 was applied to 3 bovine corneas per experiment. The mean in vitro irritancy score (IVIS) was 0.2 after 4 hours of treatment (IVIS >55 is regarded as serious eye damage and IVIS ≤3 is UN GHS No Category). Based on the criteria of the assay, the chemical was not considered to be corrosive or a severe irritant to the eye (REACHa).

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, the chemical (pure, CAS No. 15535-79-2) was instilled into one eye each of 2 male NZW rabbits. Observations were recorded at one, 24, 48, 72 hours. The following mean scores were reported at 24, 48 and 72 hours; corneal opacity 0/4, iritis 0/2, conjunctival redness 0.66/3, chemosis 0/4. The observed effects were reversible in both animals within 72 hours (REACHc). In a GLP compliant non-guideline in vitro eye irritation study, the chemical (pure) was applied to reconstituted human corneal SkinEthic™ HCE and tissue viability was measured following exposure and a post treatment incubation period of 10 minutes. The tissue viability was determined to be 100.4%. Based on the decision criteria for this test (tissue viability >60%), the chemical is not predicted to meet the criteria for serious eye damage or eye irritation and should not be classified (REACHc).

In a GLP compliant ex vivo eye corrosivity/irritation study conducted according to OECD TG 437, the chemical (CAS No. 22205-30-7) was applied to 3 bovine corneas per experiment. The mean in vitro irritancy score (IVIS) was 0.8 after 2 hours of treatment (IVIS >55 is regarded as serious eye damage and IVIS ≤3 is UN GHS No Category). Based on the criteria of the assay, the chemical was not considered to be corrosive or a severe irritant to the eye (REACHd).

In a GLP compliant eye irritation study similar to OECD TG 405, the chemical (pure, CAS No. 68109-88-6) was instilled into one eye each of 9 NZW rabbits. The eyes were observed at 24, 48, 72 hours, 4, 7 days. For 3 of 9 animals, the eyes were washed out after 30 seconds. The following mean scores were reported at 24, 48 and 72 hours: corneal opacity (1/4, 1/4, 1/4), iritis (0/2, 0/2, 0/2), conjunctival redness (3/3, 3/3, 3/3) and chemosis (2.7/4, 3/4, 2.3/4) for rinsed eyes and corneal opacity (1/4, 1/4, 1/4), iritis (0.5/2, 0.5/2, 0.5/2), conjunctival redness (3/3, 2.8/3, 3/3) and chemosis (2.8/4, 2.7/4, 2.8/4) for unrinsed eyes. The irritation effects were not reversible in all animals within 7 days. No observations were made at 21 days, but the severity of effects was starting to reduce by day 7 indicating potential reversibility (REACHe).

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, the chemical (pure, CAS No. 93925-43-0) was instilled into one eye each of 3 male NZW rabbits. The eyes were washed out after 24 hours and observed at one, 24, 48, 72 hours. The following mean scores for individual animals were reported: corneal opacity (0/4, 0/4, 0/4), iritis (0/2, 0/2, 0/2), conjunctival redness (0.3/3, 0.3/3, 0.3/3) and chemosis (0/4, 0/4, 0/4). Observed effects were reversible in all animals within 72 hours (REACHe).

Available data for dioctyltin dichloride, dioctyltin alkyl mercaptoacetates, dioctyltin oxide, and dioctyltin dicarboxylates reported the chemicals to be at most slightly irritating to eyes (NICNAS 2018a; NICNAS 2018b; NICNAS 2018c; NICNAS 2019).

Sensitisation

No data are available.

Based on the available data for dioctyltin dichloride and dioctyltin oxide, the chemicals in this group are not expected to be skin sensitisers (NICNAS 2016a; NICNAS 2016b). Dioctyltin alkyl mercaptoacetates are skin sensitisers (NICNAS 2019). However, read across for this group of chemicals is not appropriate for local effects.

Repeat dose toxicity

No data are available.

Based on read across data, the chemicals are expected to cause serious systemic health effects following repeated exposure. Consistent effects on the thymus following repeated oral exposure at low doses including decreased thymus weights and associated lymphoid depletion were observed in studies with dioctyltin dichloride, dioctyltin alkyl mercaptoacetates and dioctyltin oxide. Adverse effects on the thymus were also observed in F0 and F1 animals treated with dioctyltin dichloride in a combined repeated dose toxicity and reproduction/developmental screening study and in reproductive and developmental toxicity studies with dioctyltin alkyl mercaptoacetates (NICNAS 2016a; NICNAS 2016b; NICNAS 2019).

Genotoxicity

Based on the available in vitro data for 4 of the chemicals and read across data from dioctyltin dichloride, dioctyltin alkyl mercaptoacetates and dioctyltin oxide, the chemicals are not expected to be genotoxic.

Genotoxicity information was available for 4 of the chemicals. Negative results were reported for the following GLP compliant in vitro assays (REACHa; REACHc; REACHe; REACHf):

- Two bacterial reverse mutation assays (OECD TG 471) in *Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and TA102 TA100 with and without metabolic activation at concentrations up to 200 µg/plate (CAS No 3033-29-2).
- Two experiments using bacterial reverse mutation assays (OECD TG 471), *Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and *Escherichia coli* strain WP2uvrA with and without metabolic activation at concentrations up to 5000 µg/plate (CAS No. 15535-79-2, 68109-88-6 and 93925-43-0).
- Two in vitro mammalian chromosome aberration assays (OECD TG 473) in Chinese hamster ovary (CHO) cells with and without metabolic activation at concentrations up to 100 µg/plate (CAS No. 3033-29-2).
- Two mammalian gene mutation assays (OECD TG 476) in the 6-thioguanine locus in Chinese hamster fibroblast V79 cells with and without metabolic activation at concentrations up to 150 µg/mL (CAS No. 3033-29-2).

Negative results were reported in all in vitro and in vivo test with dioctyltin dichloride, dioctyltin alkyl mercaptoacetates, dioctyltin oxide (NICNAS 2018a; NICNAS2018b; NICNAS 2019).

Carcinogenicity

No data are available. Limited data available using mixtures containing dioctyltin compounds are insufficient to draw conclusions regarding carcinogenicity (NICNAS 2018a).

Reproductive and development toxicity

No data are available.

Based on read across data, the chemicals are expected to cause specific adverse effects on development following exposure. Consistent effects on developmental toxicity including increased post implantation loss, increased incidence of resorption, decreased number of live pups, increased pup mortality and decreased foetal bodyweight were observed in studies with dioctyltin dichloride, dioctyltin alkyl mercaptoacetates and dioctyltin oxide. An increased incidence of foetal malformations (including missing bones bilaterally in the forepaws and cleft palates) and skeletal abnormalities or variations was observed in studies with dioctyltin dichloride and dioctyltin alkyl mercaptoacetates (NICNAS 2018a; NICNAS 2018b; NICNAS 2019). Following public consultation, another dioctyltin compound study became available. It was consistent with previous results.

In a GLP compliant prenatal developmental toxicity study conducted similarly to OECD TG 414, time-mated female Crl:WI(Han) rats (20/dose) were administered dioctyltin dilaurate (CAS No 3648-18-8) in feed ad libitum at 0, 20, 80 and 500 ppm (nominal dose levels equivalent to 0, 0.8, 3.9 and 25.4 mg/kg bw/day) on gestational days (GD) 6–21. Dams were sacrificed on GD 21 and the foetuses examined. Substantial reductions in food consumption and body weight losses were observed in dams treated with 500 ppm, resulting in early sacrifice of 2 animals and adverse pregnancies (2 total in utero litter losses, foetal deaths, increased post-implantation loss, lower foetal, gravid uterus and placental weights and skeletal malformations in one litter). Other maternal effects included reduced liver weights, necrosis and other microscopic changes in the liver, thyroid effects, reduced thymus weights accompanied with smaller thymuses and decreased thymic lymphocytes. Similar microscopic changes observed in the liver and thymus of animals treated with 500 ppm were also observed at 80 ppm and a dose response relationship was evident. A dose response relationship was reported for increased incidences of incomplete ossification of cervical arches in foetuses from dams in the mid and high dose groups, although the values for the

mid dose group were within the historical control data ranges. The maternal no observed adverse effect level (NOAEL) was 20 ppm (0.8 mg/kg bw/day) based on liver and thymus effects and the no adverse effect level for foetal effects was 80 ppm (3.9 mg/kg bw/day) (unpublished data, 2022).

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