Stannane, butyltris[(2-ethyl-1-oxohexyl)oxy]-: Human health tier II assessment

12 December 2019

CAS Number: 23850-94-4

Preface

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

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

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

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

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

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

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

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

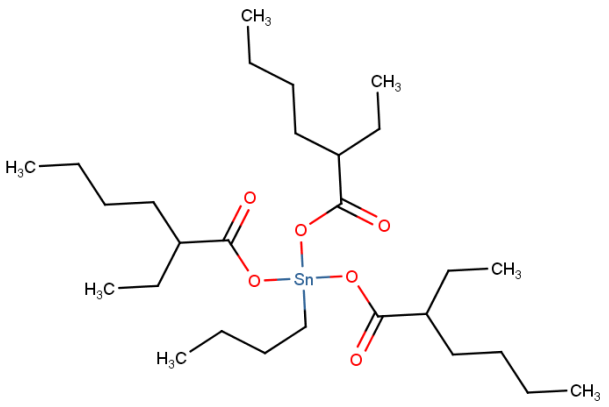
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	butyltin tris(2-ethylhexanoate) butyltris((2-ethyl-1-oxohexyl)oxy)stannane
Structural Formula	
Molecular Formula	C28H54O6Sn
Molecular Weight (g/mol)	605.43
SMILES	C(=O)(C(CCCC)CC)O[Sn](CCCC)(OC(=O)C(CCCC)CC)OC(=O)C(CCCC)CC

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacture information has been identified. 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) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database and international reports (Environment Canada, 2009).

The chemical has reported domestic uses in paint, lacquers and varnishes in the Substances and Preparations in 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 are produced from chemical reactions involving the chemical.

The chemical is not listed in the US Household Products database (US HPD), indicating that domestic use of the chemical may not be widespread.

The chemical has reported site-limited uses, including as a catalyst for the manufacture of coatings and resins (REACH). Monoalkyltins are reported to be used as a polyvinyl chloride (PVC) stabilisers; and in depositing tin oxide coatings on reusable glass bottles (REACH; Environment Canada, 2009).

Polyester resins manufactured with the chemical have use in food contact articles. The concentration of the chemical in the final resin is not to exceed 0.2 % (US FDA, 2019).

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

Organic tin compounds—which includes the chemical in this assessment—are listed on the following:

- 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 (Council of Europe, 1992).
- 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, respectively (European Parliament and Council, 2009).
- Council of Europe Resolution ResAP(2008)1 on requirements and criteria for the safety of tattoos and permanent make-up —Table 3 Maximum allowed concentrations of impurities in products for tattoos and PMU; a limit of 50 ppm tin (Sn) applies (Council of Europe, 2008).

Organotin compounds—which includes the chemical in this assessment—are listed in Annex XVII to the REACH regulations with restrictions relating to biocide and water treatment uses (ECHA).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is 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 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

Limited data are available for the chemical. The chemical contains a monobutyl (BuSn-) group and three labile ligands (X). Data available indicate that the chemical is hydrolysed to release 2-ethylhexanoic acid (2-EHA; CAS No. 149-57-5). Although there is no evidence that the chemical is hydrolysed to monobutyltin trichloride (MBTC; CAS No. 1118-46-3), 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 chemical being assessed are not available, health hazard information for the mono-butyl tin compound MBTC and a metabolite, 2-EHA, have been included in this report for read across for systemic toxicity endpoints.

The Tier II Human Health assessment reports for monobutyltin trichloride, and 2-ethylhexanoic acid are available at https://www.nicnas.gov.au. These reports should be read in conjunction with this Tier II Human Health assessment.

Toxicokinetics

In a hydrolysis study (OECD test guideline (TG) 111) the chemical was hydrolytically stable under simulated gastric conditions (at pH 1.2 and pH 4). At pH 7 and pH 9, the chemical hydrolysed to form monobutyltin bis (2-ethylhexanoate) indicating the release of 2-EHA (REACH). The lack of hydrolysis at low pH and presence of hydrolysis at pH 7 is contrary to hydrolysis observed with other monoorganotins.

Acute Toxicity

Oral

The median lethal dose (LD50) values in rats indicate that the chemical has low acute oral toxicity. A sex-related difference was noted in one study with LD50 values of >5000 and 3200 mg/kg bw in male and female rats, respectively (REACH).

On the day of dosing, treatment related effects included ataxia, discharge from the nose, mouth and eyes, reduced activity, faecal and urinary staining and irregular breathing. The following day hypothermia, abdominal griping, soft stool and/or decreased food consumption were reported. In some animals abnormalities lasted for several days (REACH).

Dermal

The LD50 value in rabbits indicates that the chemical has low acute oral toxicity.

In a combined dermal toxicity/irritation study the chemical was applied to the skin of rabbits under an occlusive patch for 24 hours. The LD50 was determined as >8000 mg/kg bw. Some incidence of lethargy, drooping eyelids, reduced number of faecal pellets and yellow nasal discharge were reported (REACH).

Inhalation

No data are available for the chemical.

Corrosion / Irritation

Corrosivity

The chemical was corrosive in a guideline in vitro assay. While in vivo assays report use of a 24 hour exposure time, and cannot be used for classification, worsening symptoms over the 14 day observation period supports observations in vitro. Based on this data, the chemical is recommended for classification (see **Recommendation** section).

In an in vitro skin corrosion assay conducted in accordance with OECD TG 431 (reconstructed human epidermis) the chemical resulted in a reduction in tissue viability (27 % and 21.2 % at 3 minutes and 1 hour, respectively) (REACH). A reduction in viability to less than 50 % relative to negative controls supports classification (OECD, 2019).

In a combined dermal toxicity/irritation study the chemical (2000, 4000, 8000 and 16000 mg/kg bw) was applied to the skin of rabbits under an occlusive patch for 24 hours (REACH). Dermal reactions were scored at 24 hours and on days 3, 7 and 14. After 24 hours the mean erythema and oedema scores were 2.5 and 2.0 in the 8000 mg/kg bw treatment group. At day 14, the mean erythema and oedema scores were 4.0 and 2.0. Slight eschar and skin flaking were reported for all animals in the 8000 and 16000 mg/kg bw groups (REACH).

In an eye irritation/corrosion study 0.1 mL of the chemical was applied to the eyes of rabbits. The treated eye either remained unwashed (n=6) or washed with warm tap water 30 seconds after treatment (n=3). Reactions were severe in 4/6 and 1/3 test animals with unwashed and washed eyes, respectively. The mean cornea, iris, conjunctivae and chemosis scores in the unwashed eye treatment group across the 24, 48 and 72 hour time points were 0.78, 0.38, 1.22 and 1.55, respectively. Reactions cleared in all but one animal within 7 days (REACH).

Sensitisation

Skin Sensitisation

No data are available for the chemical.

Repeated Dose Toxicity

Oral

No data are available for the chemical.

The structurally related chemical, MBTC (CAS No. 1118-46-3), was reported to have a no observed adverse effect level (NOAEL) of 96 mg/kg bw/day and 101 mg/kg bw/day in male and female rats, respectively (NICNASb). At the highest dose level (521 mg/kg bw and 533 mg/kg bw in males and females, respectively) treatment-related effects included changes in haematology, clinical chemistry and liver weights indicating liver damage. Adverse effects on the thymus were not observed (NICNASb).

The metabolite, 2-EHA (CAS No. 149-57-5), has a reported lowest adverse effect levels (LOAEL) of 917 mg/kg bw/day and 1040 mg/kg bw/day in two 90-day dietary studies in rats. Reported effects included reduced body weight gain and reduced food consumption (NICNASa).

Dermal

No data are available.

Inhalation

No data are available for the chemical.

The structurally related chemical, MBTC, was not considered to cause serious damage to health through repeated exposure by the inhalation route. Observed effects were consistent with the corrosive nature of the chemical and were not considered relevant for classification for systemic toxicity (NICNASb).

Genotoxicity

Based on the weight of evidence from an available in vitro study and data from a structurally related chemical and the metabolite, the chemical is not expected to be genotoxic.

The chemical was negative in a bacterial reverse mutation assay in *Salmonella typhimurium* TA 1535, TA 1537, TA 98 and TA 100, and *Escherichia coli* WP2 uvrA conducted according to OECD TG 471 with and without metabolic activation at concentrations of up to 5000 µg/plate (REACH).

The structurally related chemical, MBTC, was negative in most in vitro assays including a bacterial reverse mutation assay, chromosomal aberration assay in Chinese hamster ovary (CHO) cells and a mammalian gene mutation assay in CHO cells. In vivo MBTC was negative in a mouse micronucleus assay at doses up to 250 mg/kg bw) (NICNASb).

A metabolite, 2-EHA, gave mixed results in vitro (negative in a bacterial reverse mutation assay, induced DNA damage in rat hepatocytes, and increased frequency of sister chromatid exchange in CHO cells). In vivo, 2-EHA was not mutagenic in a mouse micronucleus assays (NICNASa).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

No data are available for the chemical. Based on available information for its metabolite 2-ethylhexanoic acid the chemical is considered to have potential to cause developmental and reproductive toxicity.

No evidence of reproductive toxicity was reported for the structurally related chemical, MBTC. Developmental effects were observed; however, effects were secondary to maternal toxicity and consistent with that of a corrosive chemical. The developmental toxicity associated with di-substituted alkyltins is not exhibited in the corresponding mono-substituted compound (WHO, 2006; NICNASb).

The metabolite, 2-EHA, is classified as hazardous with hazard category ‘Reproductive Toxicity – Category 2’ and the hazard statement ‘Suspected of damaging fertility or the unborn child (H361)’. Known adverse developmental and reproductive effects include dose dependent increases in foetal skeletal variations and malformations, reduced foetal body weights, early foetal deaths, impaired sperm motility and increased abnormal sperm, delays in mating, and complete infertility in some animals (NICNASa).

Risk Characterisation

Critical Health Effects

Based on information for the chemical, an analogue—MBTC, and its metabolite—2-EHA, the critical health effects for risk characterisation include systemic long-term effects (reproductive toxicity and developmental toxicity), and local effects (corrosivity).

Public Risk Characterisation

Although use in domestic products in Australia is not known, the chemical is reported to be used in domestic products overseas. However, data indicate that use in products that could expose the public directly to the chemical, 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 chemical is not considered unreasonable.

The public could be exposed to the chemicals at low levels based on their use as PVC stabilisers, catalysts to manufacture coatings and resins and use in food contact applications. At these levels the acute and local effects are not expected. Internationally, a group tolerable daily intake (TDI) of (0.1 µg/kg bw as Sn) for organotins in foodstuff based on systemic effects has been established (European Commission, 2009). To reduce the identified risk of organotins transferred from food packaging to foodstuffs, the overall exposure should be lower than the TDI. The dominant contribution to human intake of organotins (mainly tributyltin) is via consumption of fish. Exposure to other organotins, including these chemicals is expected to be generally low both from food contact and handling PVC articles. The cumulative estimated daily intake (CEDI) for the chemical as a result of use in food contact substances is 0.09 µg/kg bw/day (US FDA). Hence, the public risk from these chemicals is not considered to be unreasonable. If data becomes available indicating specific uses in Australia that could significantly contribute to the overall TDI for organotins, further assessment of these chemicals may be required.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation (if aerosols are generated) 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 local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

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

NICNAS Recommendation

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

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical 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]
Irritation / Corrosivity	Not Applicable	Causes severe skin burns and eye damage - Cat. 1 (H314)
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 industry

Control measures

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

- using closed systems or isolating operations;

- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

References

American Conference of Governmental Industrial Hygienists (ACGIH), 2011. Documentation of the Threshold Limit Values for Chemical Substances, ACGIH Signature Publications, 7th Edition.

Council of Europe 1992. Resolution AP(92)2 on control of aids to polymerisation (technological coadjuvants) for plastic materials and articles intended to come into contact with foodstuffs. Accessed Novemeber 2019 at https://rm.coe.int/16804d0d41

Council of Europe 2008. Resolution ResAP(2008)1 on requirements and criteria for the safety of tattoos and permanent make-up (superseding Resolution ResAP(2003)2 on tattoos and permanent make-up. Adopted by the Committee of Ministers on 20 February 2008 at the 1018th meeting of the Ministers' Deputies.

Environment Canada 2009. Follow-up to the 1993 ecological risk assessment of organotin substances on Canada's domestic substance list. Accessed November 2019 at http://www.ec.gc.ca/lcpe-cepa/documents/substances/org/final/followup_organotin-eng.pdf

European Chemicals Agency (ECHA). Information on Chemicals Substances restricted under REACH Substances restricted under REACH. Accessed November 2019 at https://echa.europa.eu/substances-restricted-under-reach

European Commission, 2009. COMMISSION STAFF WORKING DOCUMENT Impact Assessment Report Proposal for a COMMISSION DECISION amending Council Directive 76/769/EEC on the approximation of the laws, regulationsand administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations (Organostannic compounds). Accessed November 2019 at http://ec.europa.eu/growth/sectors/chemicals/reach/studies/index_en.htm

European Parliament and Council 2009. Directive 2009/48/EC, Official Journal of the European Union, Publications Office of the European Union. Accessed Novemeber 2019 at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32009L0048

Galleria Chemica. Accessed November 2019 at http://jr.chemwatch.net/galleria/

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

National Industrial Chemicals Notification and Assessment Scheme (NICNASa). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for 2-ethylhexanoic acid (CAS No. 149-57-5). Accessed November 2019 at http://www.nicnas.gov.au

National Industrial Chemicals Notification and Assessment Scheme (NICNASa). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human health Tier II Assessment for monobutyltin trichloride (CAS No. 1118-46-3). Accessed November 2019 at https://www.nicnas.gov.au/

National Pollutant Inventory (NPI). Accessed November 2019 at http://www.npi.gov.au/index.html

Organisation for Economic Cooperation and Development (OECD) 2019. Guidelines for the Testing of Chemicals. In vitro Skin Corrosion: Reconstructed Human Epidermis (RhE) Test Method. Accessed November 2019 at https://doi.org/10.1787/9789264264618-en

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. Butyltris[(2-ethyl-1-oxohexyl]oxy]stannane (CAS no. 23850-94-4). Accessed November 2019 at https://echa.europa.eu/registration-dossier/-/registered-dossier/25558/1

Safe Work Australia (2019). Model Work Health and Safety Regulations. Accesed November 2019 at http://www.safeworkaustralia.gov.au/system/files/documents/1902/model-whs-regulations-15-january-2019.pdf

Safe Work Australia. Hazardous Chemical Information System (HCIS). Accessed November 2019 at http://hcis.safeworkaustralia.gov.au/

The Poisons Standard October 2019. The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) No. 25. Accessed November 2019 at https://www.tga.gov.au/publication/poisons-standard-susmp

US Food and Drug Administration (US FDA). Code of Federal Regulations, Title 21, Volume 3. Revised April 1, 2019. Accessed November 2019 at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm

US Foof and Drug Administration (US FDA). Cumulative Estimated Daily Intake (CEDI) Database. Accessed November 2019 at https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=edisrev

US Household Products Database. US Department of Health and Human Services. Accessed November 2019 at http://householdproducts.nlm.nih.gov/advancedsearch.htm

World Health Organization (WHO), Concise International Chemical Assessment Document 73 (CICAD),2006. Mono and disubstituted methyltin, butyltin, and octyltin compounds. Accessed November 2019 at http://www.inchem.org/documents/cicads/cicads/cicad73.pdf

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