# Hexanoic acid, 2-ethyl-, tin(2+) salt: Human health tier II assessment

**10 March 2017**

## CAS Number: 301-10-0



## 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.

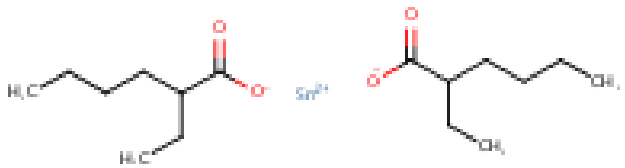
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

**Disclaimer**

Acronyms & Abbreviations

## Chemical Identity

| | |
|---|---|
| Synonyms | stannous octoate<br>tin 2-ethylhexanoate<br>2-ethylhexanoic acid stannous salt<br>tin bis(2-ethylhexanoate) |
| Structural Formula |  |
| Molecular Formula | C8H16O2.1/2Sn |
| Molecular Weight (g/mol) | 405.119 |
| Appearance and Odour (where available) | Clear to pale yellow, viscous liquid. |
| SMILES | C(=O)(C(CCCC)CC)O{-}.[Sn]{2+}.O{-}C(=O)C(CCCC)CC |

## Import, Manufacture and Use

### Australian

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was <100 tonnes per annum (tpa). No specific use was specified.

The chemical has reported commercial use in industrial adhesives and tapes.

### 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 the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR).

The chemical has reported domestic use, including in:

- paints, lacquers and varnishes;

- fillers, putties and plasters; and
- adhesives and binding agents.

The chemical has reported commercial use, including as a:

- lubricant agent or additive; and
- reprographic agent.

The chemical has reported site-limited use, including as a polymerisation catalyst.

## Restrictions

### Australian

The chemical is the tin salt of 2-ethylhexanoic aid, therefore, it is covered by the listing of 2-ethylhexanoic acid in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 6 (SUSMP, 2016).

Schedule 6:

'2-ETHYLHEXANOIC ACID and its alkyl esters except in preparations containing 5 per cent or less calculated as 2-ethylhexanoic acid.'

Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2016).

### International

No known restrictions have been identified.

## Existing Work Health and Safety Controls

### Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

### Exposure Standards

#### Australian

No specific exposure standards are available.

#### International

No specific exposure standards are available.

## Health Hazard Information

While limited health hazard information are available for this specific chemical, it is the tin salt of 2-ethylhexanoic acid, and under biologically-relevant conditions it exists as a solution, almost completely dissociated into its 2-ethylhexanoate anion and tin (II) cation (REACH). The chemical 2-ethylhexanoic acid (2-EHA; CAS RN 149-57-5) has been assessed by NICNAS (NICNAS), and where relevant, available information for 2-EHA has been included in this report. Information from a World Health Organisation (WHO) Concise International Chemical Assessment Document (CICAD) for tin compounds (WHO, 2005) has been included in this report where relevant.

### Acute Toxicity

### Oral

The chemical is expected to have low acute toxicity based on results from animal tests (test guidelines not specified) following oral exposure. The median lethal dose (LD50) values in rats are reported to be 3400–5870 mg/kg bw (REACH). Observed sub-lethal effects included raised fur, loss of coordination and changes in motor activity.

### Dermal

The chemical is expected to have low acute toxicity based on results from animal tests following dermal exposure, conducted according to OECD Test Guideline (TG) 402. The dermal LD50 in rats is reported to be >2000 mg/kg bw (REACH). Dermal irritation in some of the animals was the only clinical observation reported.

A dermal LD50 of >2000 mg/kg bw in rabbits was also reported from another acute dermal toxicity study (REACH). However, only limited study details are available.

### Inhalation

No data are available.

## Corrosion / Irritation

### Skin Irritation

While the chemical is unlikely to be irritating to the skin following a single exposure, it may cause irritation following repeated or cumulative exposures based on the result from skin irritation and skin sensitisation studies (see **Sensitisation - Skin** section) in animals.

The chemical was reported to be a slight skin irritant in rabbits (REACH). While a test guideline is not specified, the chemical was applied to the intact and abraded skin of six albino rabbits, for an exposure period of 24 hours. A primary irritation score of 1.54 was reported (no further details available) from the results up to the end of the 72-hour observation period. The effects were not sufficient to warrant hazard classification.

In another study of limited reliability (test guideline not specified and only one animal studied), topical application of the chemical (0.5 mL), to the intact and abraded skin of one New Zealand White (NZW) rabbit did not produce any skin irritation reactions following a 24-hour exposure period (REACH). However, slight erythema was reported following repeated application of the chemical.

### Eye Irritation

In an eye irritation study, conducted similarly to OECD TG 405, 0.1 mL of the chemical was applied to the right eye of six NZW rabbits and the animals were observed over a 7-day period, with the left eye serving as a control. Mean scores of one, >1.5, >2 and >2 were calculated for corneal opacity, iris lesions, redness of the conjunctivae and chemosis, respectively, from the 24, 48 and 72-hour observations (REACH). In all cases, effects were not reversible within the 7-day study observation period. The chemical is considered to be highly irritating to the eyes, with effects sufficient to warrant hazard classification.

## Sensitisation

### Skin Sensitisation

In a skin sensitisation test in 60 female Himalayan guinea pigs, conducted according to OECD TG 406 (guinea pig maximisation test), induction exposure to the chemical was conducted by intradermal injections (2 % w/w in propylene glycol) followed by epidermal application seven days later (50 % w/w in propylene glycol) (REACH). Challenge exposures were applied two weeks later, as epidermal applications of the chemical at 2, 5 and 10 % in propylene glycol (20 animals/group). Sensitisation reactions were assessed 24 and 48 hours after challenge application.

Skin reactions were observed in 13/20, 16/20 and 17/20 animals, following challenge exposure of the chemical at 2, 5 and 10 %, respectively. Redness and scaliness were reported at all doses, and crust formation and swelling were reported in the 10 % dose group. The authors concluded the chemical to be extremely sensitising based on the 85 % reaction response rate in the 10 % dose group. However, it is noted that slight to severe erythema and slight to well-defined oedema were reported in test animals following the epidermal induction exposure to the chemical (no further details are available). Therefore, it is difficult to evaluate whether the chemical is a specific skin sensitiser.

In another skin sensitisation test of limited reliability (due to lack of study details), the chemical was applied to 10 male Hartley guinea pigs at a concentration of 10 % (0.4 mL) for the induction exposure (route or number of exposures not specified) (REACH). The challenge exposure

(concentration not specified) was applied two weeks later, with slight to moderate erythema reported in 6/10 animals. While the authors considered the chemical to be sensitising to the skin based from this study, no data are available on skin reactions in test animals following the induction phase.

The dermal sensitisation potential of this chemical remains unclear, as the above studies do not clearly identify the chemical as a specific skin sensitier. Additionally, one of the chemical's hydrolysis products, 2-ethylhexanoic acid, was not found to induce dermal sensitisation in guinea pigs in a maximisation study similar or equivalent to OECD TG 406 (NICNAS). The chemical's other hydrolysis products, the tin (II) cation, is also not considered to be a significant contact allergen (WHO, 2005).

## Repeated Dose Toxicity

### Oral

Limited data are available.

In a short-term, repeated oral dose toxicity study, conducted similarly to OECD TG 407 (deviation to TG being that a 14-day study period, rather than a 28-day study period, was used), the chemical was administered by oral gavage to Wistar rats (5 animals/sex/dose) at 75, 250 or 750 mg/kg bw/day, daily for 14 days (REACH). No mortalities were reported. No significant differences in mean body weights, food consumption, or organ weights were reported between the groups. No treatment-related changes in the kidney or liver were reported at histopathological examination. Changes in the stomach (instances of red areas) were noted in 1/10, 1/10 and 7/10 animals in the 75, 250 and 750 mg/kg bw/day groups, respectively; however, these were considered to be due to local irritation effects from ingestion of the chemical. Atrophy of the thymus was observed in three female rats in the 750 mg/kg bw/day group. The authors considered this to be a secondary response to decreased body weight or food consumption in these animals.

While no other statistically significant findings were observed in this study, the study authors considered the no observed adverse effect level (NOAEL) to be 250 mg/kg bw/day, based on instances of weight loss and less than normal food consumption at the higher dose.

### Dermal

No data are available.

### Inhalation

No data are available.

## Genotoxicity

The chemical gave negative results in one available in vitro study (a bacterial reverse mutation assay), conducted similarly to OECD TG 471, in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 at test concentrations of 0.5, 5, 100 or 500 µg/plate, with and without metabolic activation (REACH). However, this study is of limited reliability due to lack of specific information on the test chemical.

The chemical's hydrolysis product, 2-ethylhexanoic acid (2-EHA; CAS RN 149-57-5), has been assessed by NICNAS and is not considered to be genotoxic based on both in vitro and in vivo studies (NICNAS). The tin (II) cation is also not expected to contribute any significant genotoxic effects based on both in vivo and in vitro studies of tin compounds (WHO, 2005).

## Carcinogenicity

One non-guideline dietary carcinogenicity study in inbred August hooded rats is available, with the chemical reported not to cause any carcinogenic effects (REACH). However, this study is of low reliability due to the lack of guidelines followed, and pulmonary disease and other non treatment-related issues noted in test animals prior to administration of the chemical.

While no specific data are available on the chemical's hydrolysis product, 2-EHA (CAS RN 149-57-5), 2-EHA is a major metabolite of 2-ethylhexanol (CAS RN 104-76-7) which was reported to not be carcinogenic in a two-year study (equivalent or similar to OECD TG 451) in rats (NICNAS).

2-Ethylhexanol was administered via oral gavage to male and female Fischer F344 rats at 0 (water), 0 (vehicle), 50, 150 or 500 mg/kg bw/day, for two years, five days per week. It was reported that the number of primary, benign and malignant tumours was lower in the top dose group than in either of the control groups.

The tin (II) cation is also not expected to have any significant carcinogenic potential, based on studies for other tin (II) compounds (WHO, 2005).

## Reproductive and Developmental Toxicity

No data are available for this specific chemical. However, the chemical almost completely dissociates under biologically-relevant conditions to produce the 2-ethylhexanoate anion (2-EHA) and tin (II) cation, at a ratio of 2:1 (REACH).

While the tin (II) cation is not expected to contribute to any reproductive or developmental toxicty (WHO, 2005), 2-EHA (CAS RN 149-57-5) is classified as hazardous, as a Category 3 reproductive toxin, with the risk phrases 'Possible risk of impaired fertility' (Xn; R62) and ‘Possible risk of harm to the unborn child’ (Xn; R63) in HSIS (Safe Work Australia).

Developmental toxic effects were reported in several studies in rats following treatment via the oral route (NICNAS). These effects were noted in the absence of signs of maternal toxicity. The lowest observed adverse effect level (LOAEL) for developmental toxicity was reported to be 100 mg/kg bw/day. Effects on the male reproductive system (reduction in sperm motility) and fertility were also observed at 100 mg/kg bw/day.

The hazard classification for 2-EHA is also considered appropriate for this chemical.

# Risk Characterisation

## Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects of reproductive and developmental toxicity. The chemical can also cause severe eye irritation, and may cause skin irritation following repeated dermal exposure. The potential for the chemical to be a dermal sensitiser cannot be ruled out.

## Public Risk Characterisation

The chemical is the tin salt of 2-ethylhexanoic acid, therefore, it is currently covered by the listing of 2-ethylhexanoic acid on Schedule 6 of the Poisons Standard (SUSMP) for preparations containing >5 % calculated as 2-ethylhexanoic acid. Additionally, a number of warning statements, first aid instructions and safety directions relating to use of the chemical at any concentration, apply.

The function of the chemical is to act as a catalyst by delivering the tin 2+ ion to a chemical reaction, and is used in products available to consumers, including two-component coating products, paints and do-it-yourself epoxy adhesives (DOW, 2011).

While use of the chemical in domestic products in Australia is not known, it is reported to be used in these types of domestic products overseas. The chemical is not reported to be used in cosmetic products in Australia or overseas.

No specific information is available in regard to use concentration in domestic products. However, it has been reported that chemical concentrations are likely to be less than 1 % by weight, with consumer exposure expected to be low due to infrequent use of these products (DOW, 2011).

## Occupational Risk Characterisation

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

During product formulation, dermal and ocular 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 health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise 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.

# 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

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2016).

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.

| Hazard | Approved Criteria (HSIS)[a] | GHS Classification (HCIS)[b] |
|---|---|---|
| Irritation / Corrosivity | Risk of serious eye damage (Xi; R41) | Causes serious eye damage - Cat. 1 (H318) |
| Reproductive and Developmental Toxicity | Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62) Repro. Cat 3 - Possible risk of harm to the unborn child (Xn; R63) | 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 the chemical should be used according to the instructions on the label.

## Advice for industry

***Control measures***

Control measures to minimise the risk from 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;
- 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

Approved Criteria for Classifying Hazardous Substances [NOHSC: 1008(2004)] Third edition. Accessed at http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

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