Esters of tetrahydrofurfuryl alcohol: Human health tier II assessment

26 October 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
2-Furanmethanol, tetrahydro-, acetate	637-64-9
2-Furanmethanol, tetrahydro-, propanoate	637-65-0
Butanoic acid, (tetrahydro-2-furanyl)methyl ester	2217-33-6
Benzeneacetic acid, (tetrahydrofuranyl)methyl ester	5421-00-1
2-Propenoic acid, 3-phenyl-, (tetrahydro-2-furanyl)methyl ester	65505-25-1

Preface

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

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

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

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

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

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

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

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

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

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group are esters of tetrahydrofurfuryl alcohol (THFA, CAS No. 97-99-4). According to the Cramer decision tree approach, tetrahydrofurfuryl esters and the alcohol were assigned to structural class III (i.e. 'having structural features that permit no strong initial presumption of safety, or may even suggest significant toxicity'). However, they were not subject to

further evaluation because consumption of the chemicals was determined to be of no safety concern (JECFA, 2006; EFSA, 2008). THFA derivatives (also known as tetrahydrofuran derivatives) do not form epoxides, i.e. reactive metabolites (JECFA, 2006).

Following absorption, the chemicals are expected to hydrolysed to THFA and the corresponding carboxylic acids. The corresponding carboxylate ions produced by ester hydrolysis in vivo are all expected to have low toxicity. On the basis of similar uses and that the toxicity effects of the chemicals are dependent on the formation of THFA, the assessment of these chemicals as a group is considered appropriate.

Import, Manufacture and Use

Australian

The three chemicals tetrahydrofurfuryl acetate, propionate and butyrate have reported site-limited uses in manufacture of substances (Sigma Aldrich SDS).

No specific Australian use, import, or manufacturing information has been identified for tetrahydrofurfuryl cinnamate and phenylacetate.

International

The following international uses have been identified through Galleria Chemica; the European Commission (EC) Cosmetic Ingredients and Substances (CosIng) database; and the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary.

Tetrahydrofurfuryl acetate (CAS No. 637-64-9) has reported cosmetic uses as a masking agent and as a solvent (CosIng). The chemical is used to dissolve eosins and make them miscible with fats and waxes used in make-up preparations such as lipstick and cream rouges (Poucher, 1991).

Tetrahydrofurfuryl propionate (CAS No. 637-65-0) and tetrahydrofurfuryl butyrate (CAS No. 2217-33-6) have reported cosmetic use as fragrance ingredients.

The chemicals have reported non-industrial use as flavouring agents.

There is no documented use of the chemicals in the US (CIUCUS, 2011). The chemicals are not listed on the International Fragrance Association (IFRA) transparency list.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Limited data are available. In general, esters are of low local toxicity. Systemic human health effects of the chemicals are expected to be driven by their metabolite THFA. Therefore, where relevant, information from THFA is considered for data gap filling (read-across), particularly for systemic long-term toxicity (NICNASa). The other metabolites are corresponding carboxylic acids, which are all expected to have low toxicity (NICNASb, NICNASc).

In animals, THFA derivatives are observed to be rapidly absorbed following exposure. THFA derivatives are considered to be efficiently metabolised and would not saturate the metabolic pathways; therefore, distribution is expected to be low. Following hydrolysis of the esters, usually via carboxylesterases or esterases, THFA is oxidised to the carboxylic acid, conjugated with glucuronic acid and excreted primarily in the urine. The corresponding carboxylic acids are also expected to undergo similar metabolism and elimination pathways (JECFA, 2006; EFSA, 2008).

The dermal permeability constant is reported to be 0.00199 cm/hour for tetrahydrofurfuryl propionate (CAS No. 637-65-0) (Galleria Chemica).

No data for acute toxicity, skin and eye irritation, skin sensitisation and carcinogenicity are available for the chemicals in this group.

Limited genotoxicity data are available for tetrahydrofurfuryl propionate (CAS No. 637-65-0):

- negative in bacterial reverse mutation assay with several strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98 and TA100) up to 3600 µg/plate, without metabolic activation (JECFA, 2006); and

- negative in a bone marrow micronucleus test when administered intraperitoneally at doses 316, 632 or 949 mg/kg bw in male and female mice. However this study was not considered valid due to the absence of a positive control, no reported polychromatic to normochromatic erythrocyte (PCE/NCE) ratio, and only one time point was assessed (EFSA, 2016).

The metabolite THFA is classified as hazardous with the hazard category and statement 'Reproductive toxicity – Category 1B (H360Df May damage the unborn child. Suspected of damaging fertility)' in the HCIS (Safe Work Australia). Based on the read-across information, this hazard classification is recommended for all members of the group.

The metabolite THFA was reported to cause toxicity to the male reproductive system in Sprague-Dawley (SD) rats following 90-day repeated oral and dermal exposure at ≥339 and ≥300 mg/kg bw/day, respectively. In a 90-day repeated inhalation study in SD rats, male reproductive toxicity effects were observed at ≥150 ppm (approximately 0.6 mg/L). In a reproductive and developmental toxicity study in Crj:CD(SD)IGS rats, parental toxicity was observed at ≥150 mg/kg bw/day and reproductive and developmental toxicity at 500 mg/kg bw/day. The no observed adverse effect level (NOAEL) for reproductive toxicity is 69 mg/kg bw/day (NICNASa).

Risk Characterisation

Critical Health Effects

The critical health effects of this group for risk characterisation includes systemic long-term effects (reproductive and developmental toxicity).

Public Risk Characterisation

While cosmetic or domestic uses in Australia were not identified, the chemicals are reported to be used in cosmetic products overseas. The general public could be exposed through the skin or inhalation when using cosmetic products containing the chemicals.

While the metabolite THFA has reported male reproductive and developmental toxicity, exposure of the public by any route to its toxic levels would be unlikely. In addition, the chemicals are assessed as 'no safety concern' when used as flavouring agents in food based on current estimated (combined) intakes (up to 40 µg/person per day) given as they would not exceed the human intake threshold. For THFA derivatives class III, the threshold is 90 µg/person per day based on a survey conducted by the US National Academy of Sciences/National Research Council (NAS/NRC). Intake data is calculated assuming survey poundage accounts for 60 % of actual usage, 10 % of population exposed, and US population of 240 million in 1987 (JECFA, 1996; JECFA, 2006; EFSA, 2008).

Assuming a concentration of 1 % of the chemical for cosmetic uses, and a maximum use amount of 0.23 g/day (RIVM, 2012) for perfume sprays, the estimated dermal margin of exposure (MoE) is >10000. Considering the magnitude of the MoE from this rough calculation, it is not expected that more detailed scenarios would lead to an unacceptably low MoE.

Therefore, the public health risk from identified cosmetic uses of these chemicals is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

Based on the available data, an amendment to the hazard classification in the HCIS (Safe Work Australia) is considered appropriate (refer to **Recommendation** section).

NICNAS Recommendation

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

If any information becomes available to indicate significant consumer exposure to the chemical in Australia (i.e. higher concentrations or quantities in cosmetics), risks to public health and safety may have to be managed by changes to the Poisons Standard.

Regulatory Control

Work Health and Safety

The chemicals are recommended for classification and labelling in alignment with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This assessment does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Reproductive and Developmental Toxicity	Not Applicable	May damage the unborn child. Suspected of damaging fertility - Cat. 1B (H360Df)

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

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

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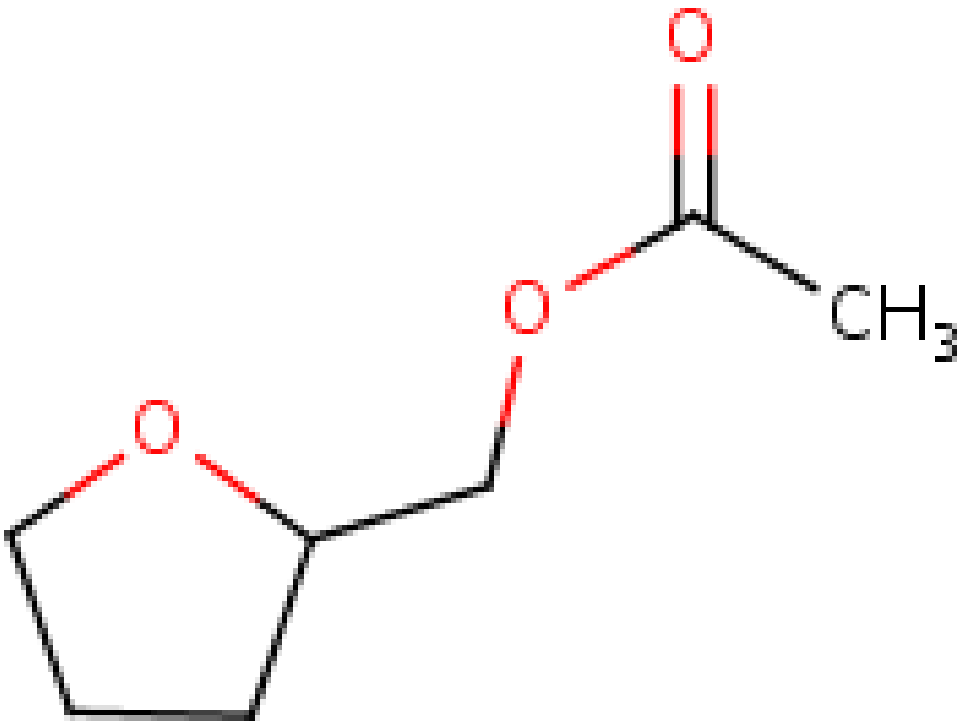
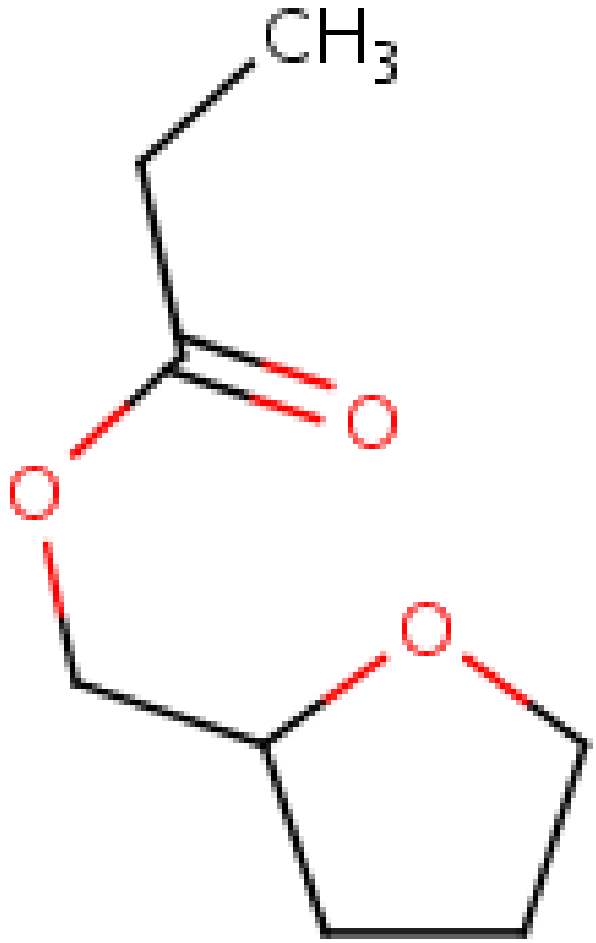
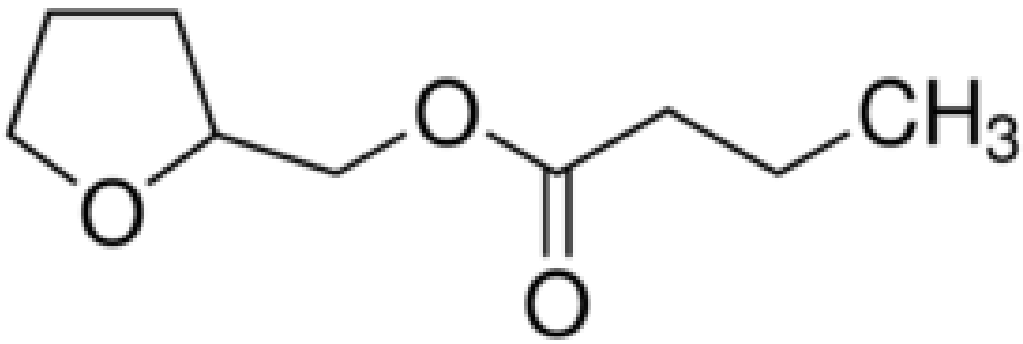
Last Update 26 October 2018

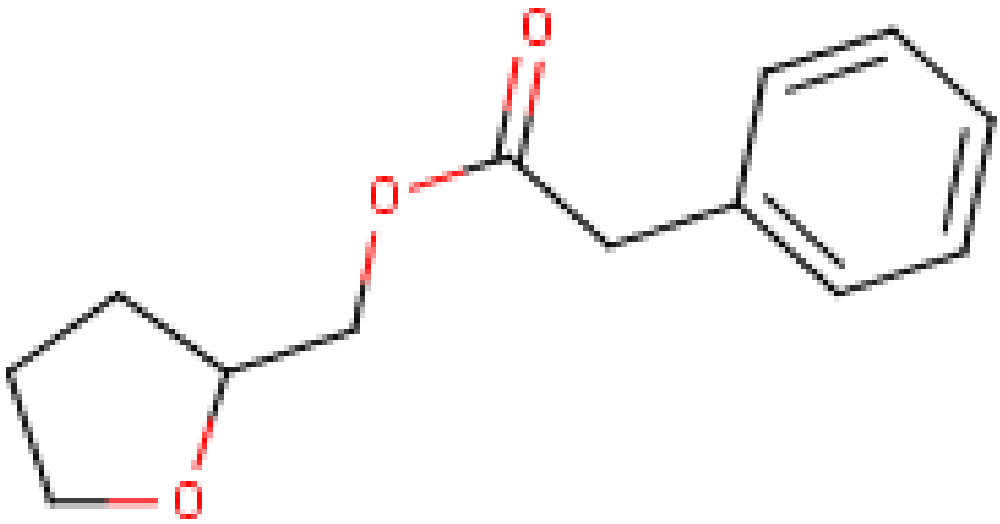
Chemical Identities

Chemical Name in the Inventory and Synonyms	**2-Furanmethanol, tetrahydro-, acetate** tetrahydrofurfuryl acetate furfuryl alcohol, tetrahydro-, acetate tetrahydro-2-furylmethyl acetate
CAS Number	637-64-9
Structural Formula	
Molecular Formula	C7H12O3
Molecular Weight	144.17

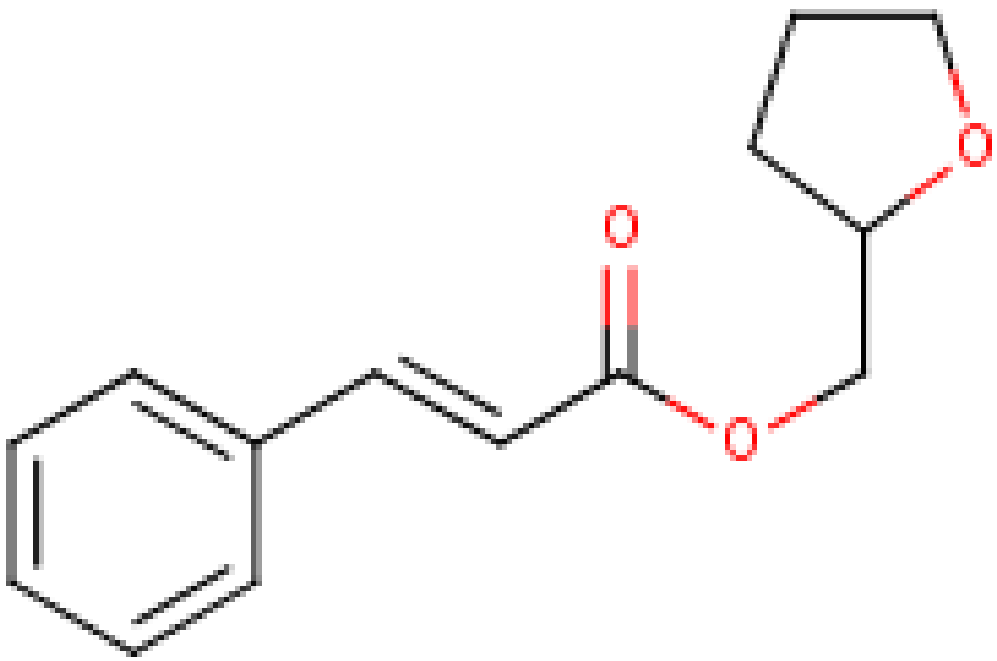
Chemical Name in the Inventory and Synonyms	**2-Furanmethanol, tetrahydro-, propanoate** tetrahydrofurfuryl propionate propionic acid, tetrahydrofurfuryl ester furfuryl alcohol, tetrahydro-, propionate
CAS Number	637-65-0
Structural Formula	

	
Molecular Formula	C8H14O3
Molecular Weight	158.20

Chemical Name in the Inventory and Synonyms	**Butanoic acid, (tetrahydro-2-furanyl)methyl ester** tetrahydrofurfuryl butyrate butyric acid, tetrahydrofurfuryl ester (tetrahydro-2-furyl)methyl butyrate
CAS Number	2217-33-6
Structural Formula	
Molecular Formula	C9H16O3
Molecular Weight	172.22

Chemical Name in the Inventory and Synonyms	**Benzeneacetic acid, (tetrahydrofuranyl)methyl ester** tetrahydrofurfuryl phenylacetate (tetrahydrofuryl)methyl phenylacetate (tetrahydrofuryl)methyl phenylacetate
CAS Number	5421-00-1
Structural Formula	
Molecular Formula	C13H16O3
Molecular Weight	220.27

Chemical Name in the Inventory and Synonyms	**2-Propenoic acid, 3-phenyl-, (tetrahydro-2-furanyl)methyl ester** tetrahydrofurfuryl cinnamate tetrahydrofurfuryl 3-phenylpropenoate
CAS Number	65505-25-1
Structural Formula	

	
Molecular Formula	C14H16O3
Molecular Weight	232.28

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