2-Furanmethanol, tetrahydro-: Human health tier II assessment

02 March 2018

CAS Number: 97-99-4

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.

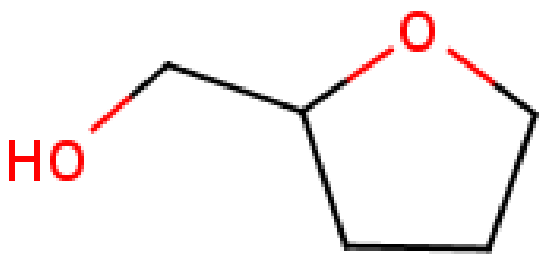
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	THFA oxolan-2-yl methanol tetrahydrofuran carbinol tetrahydrofurfuryl alcohol
Structural Formula	
Molecular Formula	C5H10O2
Molecular Weight (g/mol)	102.13
Appearance and Odour (where available)	Clear colourless liquid with a mild odour.
SMILES	C1(CO)CCCO1

Import, Manufacture and Use

Australian

The chemical has a reported commercial use as a component in screen and stencil wipes, and printing inks.

The chemical also has a non-industrial use in plant protection products.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development Screening Information Data Set (OECD SIDS) Initial Assessment Report (SIAR); Galleria Chemica; the Substances in Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature Cosmetic Ingredients (INCI) Dictionary; the OECD High Production Volume chemical program (OECD HPV); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic uses as:

- a fragrance ingredient (e.g. in air-fresheners);
- a masking agent; and
- a solvent for nail-cleaning products.

The chemical is not listed in the compilation of ingredients used in cosmetic products in the US (CIUCUS, 2011).

The chemical has reported domestic uses, including as a solvent for paints, floor polish removers and oven cleaners.

The chemical has reported commercial uses, including as:

- an adhesive agent or sealant in general manufacturing;
- a fuel additive; and
- a solvent (e.g. in graffiti removers).

The chemical has reported site-limited uses, including as:

- an adhesive agent or sealant in manufacture of paper, plastic, rubber, wood products and furniture;
- a synthetic intermediate, including in the manufacturing of petroleum products;
- a component of washing and cleaning products, including solvent-based products (electronics industry); and
- a solvent for fats, waxes, resins, leather dyes, coatings, paints, chlorinated rubber and cellulose esters.

The chemical also has non-industrial uses as an intermediate in the production of fungicides and pharmaceuticals. Use in plant protection products is the only consumer use included in the REACH dossier.

Restrictions

Australian

No known restrictions have been identified.

International

According to the draft CMR (carcinogenic, mutagenic, or reprotoxic) Omnibus proposal by the European Commission, the chemical was recommended for listing in Annex II of the Cosmetics Regulation CMR substances that are not authorised for use in cosmetic products (Cosmetics Europe, 2017).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

Eye irritation – category 2; H319 (Causes serious eye irritation)

Reproductive toxicity – category 1B; H360Df (May damage the unborn child. Suspected of damaging fertility)

Exposure Standards

Australian

No specific exposure standards are available.

International

An exposure standard is identified (Galleria Chemica):

TWA (time-weighted average): 0.5 ppm (American Industrial Hygiene Association).

Health Hazard Information

Toxicokinetics

No data are available.

By using physiologically-based toxicokinetic (PBTK) models, as well as irritation and genotoxicity studies, the following predictions were reported (REACH):

Absorption of the chemical would occur after oral, dermal and/or inhalation exposure with minimal distribution. The chemical is expected to be metabolised and excreted, mainly via the kidney.

Acute Toxicity

Oral

The chemical has low acute oral toxicity with a median lethal dose (LD50) >2000 mg/kg bw.

In an OECD Test Guideline (TG) 423 (Acute Oral Toxic Class Method) study (non-Good Laboratory Practice (GLP) compliant), Sprague Dawley (SD) rats (six females) were administered 2000 mg/kg bw of THFA via gavage and observed for 15 days. Mild hypotonia and severely decreased locomotor activity were observed in all animals within one hour after treatment. The effects disappeared on day two and no clinical signs or mortality were observed thereafter. The LD50 was >2000 mg/kg bw (REACH).

The chemical also has reported oral LD50 values of 1600–3200 mg/kg bw in rats, 2300 mg/kg bw in mice, 800–1600 mg/kg bw in guinea pigs (Hirata-Koizumi et al., 2007; Galleria Chemica). However, supplemental information for deriving these values is not available.

Dermal

Based on the available data, the chemical is expected to have low acute dermal toxicity.

A dermal LD50 of 5000 mg/kg bw was reported in guinea pigs (Galleria Chemica). No further information is available.

Inhalation

Limited information on the acute inhalation toxicity of the chemical is available. The chemical has a median lethal concentration (LC50) of >3.1 mg/L.

In an OECD TG 403 (Acute Inhalation Toxicity) study, Crl:CD BR rats (10/sex) were exposed to the saturated vapour of the chemical for four hours. No deaths or irreversible effects were noted during the study. The LC50 was reported to be >751 ppm (equivalent to 3.1 mg/L) (REACH).

An LC50 of 12650 ppm was reported for six-hour exposure (OECD SIAR). However, no information on the animal species used in the study was specified.

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is at most a slight skin irritant.

In a study equivalent to OECD TG 404 (Acute Dermal Irritation), four-hour exposure to THFA resulted in very slight erythema in 3/6 rabbits. The effect completely subsided by day three. There was no oedema or other dermal irritation findings (REACH).

Eye Irritation

The chemical is classified with the statement ‘Eye irritation – category 2 (H319 Causes serious eye irritation)’ in the HCIS (Safe Work Australia). The available data support this classification.

In an OECD TG 405 (Acute Eye Irritation/Corrosion) study, THFA was found to be irritating to the eyes of rabbits, based on corneal opacity ≥1 (3/6 animals); iritis ≥1 (4/6 animals); and conjunctival chemosis of ≥2 (3/6 animals) (REACH).

Sensitisation

Skin Sensitisation

Based on one available study, THFA is not considered a skin sensitiser.

In an OECD TG 429 (Skin Sensitisation: Local Lymph Node Assay (LLNA)) study using the chemical at concentrations of 25 and 50 % (v/v) in acetone/olive oil (4:1), none of the concentrations of the chemical resulted in a three-fold increase in stimulation index (REACH).

Repeated Dose Toxicity

Oral

Based on the available data, male reproductive organs were the main target for THFA toxicity after repeated oral exposure.

In a study similar to the OECD TG 408 (Repeated Dose 90-Day Oral Toxicity), SD rats (20/sex/dose) were treated with THFA in diet at 35, 69, 339 or 673 mg/kg bw/day (males); 42, 84, 401 or 781 mg/kg bw/day (females). Food consumption and body weights were significantly reduced in a dose-dependent manner at ≥69 and ≥401 mg/kg bw/day in male and female rats, respectively. Histopathological changes in spleen as well as dose-related decreases in haemoglobin, leukocytes, platelets, albumin and total protein were reported at ≥339–401 mg/kg bw/day (males-females). Effects on male reproductive organs included significant weight reductions and histopathological findings in testes, epididymides, seminal vesicles at ≥339 mg/kg bw/day, and in prostates at ≥673 mg/kg bw/day. The no observed adverse effect level (NOAEL) values were determined to be 35 mg/kg bw/day in males and 84 mg/kg bw/day in females, based on systemic toxicity reported at higher doses (OECD SIAR; REACH).

In an OECD TG 407 (Repeated Dose 28-Day Oral Toxicity) study, Crj:CD(SD) rats (5–10/sex/dose) were treated by gavage with THFA at 0, 10, 40, 150 or 600 mg/kg bw/day. High-dose effects on body weights, locomotor activity, haematological and biochemical parameters, histopathological changes of the spleen, atrophy of thymus and testes were similar to those reported in the 90-day repeated dose and reproductive toxicity studies (see **Reproductive and Developmental Toxicity** section). In this study, necrosis of seminiferous tubules was reported at ≥150 mg/kg bw/day. Therefore, the NOAEL was considered to be 40 mg/kg bw/day (OECD SIAR; REACH).

Dermal

Based on the available data, male reproductive system is the main target for THFA toxicity after repeated dermal exposure.

In an OECD TG 411 (Repeated Dose 90-day Dermal Toxicity) study, SD rats (12–17/sex/dose) were treated with THFA at 0, 100, 300 or 1000 mg/kg bw/day. Both male and female rats at 1000 mg/kg bw/day had a significantly lowered weight gain as compared to the controls. Spermatogenic effects of THFA were reported at ≥300 mg/kg bw/day. The NOAEL values were determined to be 100 mg/kg bw/day in males and 300 mg/kg bw/day in females (REACH).

Inhalation

Based on the available data, male reproductive system is the main target for THFA toxicity after repeated inhalation exposure.

In an OECD TG 413 (Repeated Dose 90-day Inhalation Toxicity) study, SD rats (10–14/sex/dose) were exposed to vapourised THFA at 0, 50, 150 or 500 ppm, six hours/day for five days/week. Intermittent whole-body spasms and dose-related hyperactivity were observed at ≥50 ppm (approximately 0.2 mg/L). Lowered food consumption, reduced body weight gain and prostate weight were seen at ≥150 ppm in males. Other male reproductive effects were also reported at 500 ppm (see **Reproductive and Developmental Toxicity** section). Yellow urogenital matting, salivation and haematological effects occurred at 500 ppm in both sexes. A no observed adverse effect concentration (NOAEC) value could not be determined (REACH).

Genotoxicity

The chemical was negative for mutagenicity or clastogenicity in several in vitro tests. No in vivo data are available.

In an OECD TG 471 (Bacterial Reverse Mutation Assay) study, THFA produced negative results in *Salmonella typhimurium* (TA 1535, TA 1537, TA 98, TA 100) and *Escherichia coli* (WP2 uvrA/pKM101), with or without metabolic activation (REACH).

In an OECD TG 473 (In vitro Mammalian Chromosome Aberration Test) study, THFA produced negative results for induction of chromosome aberrations, with or without metabolic activation (REACH).

In an OECD TG 476 (In vitro Mammalian Cell Gene Mutation Test) study, THFA did not cause an increase in mutation frequency, cytotoxicity or in the ratio of small to large colonies, with or without metabolic activation (REACH).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

The chemical is classified with the statement 'Reproductive toxicity – category 1B (H360Df May damage the unborn child. Suspected of damaging fertility)' in the HCIS (Safe Work Australia). The available data support this classification.

In an OECD TG 421 (Reproduction/Developmental Toxicity Screening Test) study, Crj:CD(SD)IGS rats (12/sex/dose) were treated by gavage with THFA at dose levels of 0, 15, 50, 150 or 500 mg/kg bw/day. For parental toxicity, reduced body weight gain, locomotor activity changes and histopathological changes in spleen (capsule inflammation and/or decreased extramedullary haematopoiesis in females) were reported at ≥150 mg/kg bw/day. Reduced weights of body, thymus, testes and epididymides, including histopathological changes such as atrophy of seminiferous tubule, hyperplasia of interstitial cells, cell debris and/or decreased sperm were seen at 500 mg/kg bw/day.

At 150 mg/kg bw/day, although copulation index, fertility index or implantation index were not impaired, other reproductive effects (prolonged gestation length and reduced gestation index) and developmental effects (decreased number of newborn, live birth index, litter size, viability index and live pups on postnatal date four) were significant. At 500 mg/kg bw/day, there was a total embryonic/foetal loss in pregnant females. A NOAEL of 50 mg/kg bw/day was determined for maternal, reproductive and developmental toxicity (Hirata-Koizumi et al., 2008; OECD SIAR; REACH).

In the 90-day repeated oral dose study (see **Repeated Dose Toxicity – Oral** section), reduced testes, epididymis and seminal vesicle weights, including small and/or soft testes, degeneration of seminiferous tubules and interstitial (peritubular) oedema in the testes, and accumulation of cellular debris in the epididymides were seen at ≥339 mg/kg bw/day. Prostate weight was significantly lowered at 673 mg/kg bw/day. A NOAEL of 69 mg/kg bw/day was determined based on male reproductive toxicity at higher doses (OECD SIAR; REACH).

In the 28-day repeated oral dose study (see **Repeated Dose Toxicity – Oral** section), necrosis of the seminiferous epithelium of the testes was noted at ≥150 mg/kg bw/day, and decreased ratio of spermatid:sertoli cells at 600 mg/kg bw/day (REACH).

In the 90-day repeated dermal study (see **Repeated Dose Toxicity – Dermal** section), a NOAEL of 100 mg/kg bw/day was determined, based on decreases in sperm motility, sperm number and production rate at ≥300 mg/kg bw/day (REACH).

In the 90-day repeated inhalation study (see **Repeated Dose Toxicity – Inhalation** section), reduced weights of prostates at ≥150 ppm, as well as epididymides and seminal vesicles at 500 ppm were reported. At 500 ppm, multifocal atrophy of testes, reduced sperm motility and numbers, as well as a higher incidence of sperm abnormalities were also observed. On this basis, the NOAEC for male reproductive effects was considered to be 50 ppm (approximately 0.2 mg/L) (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation includes eye irritation and systemic long-term effects (reproductive and developmental toxicity).

Public Risk Characterisation

Considering the range of domestic, cosmetic products that may contain the chemical, the main route of public exposure is expected to be through the skin, and inhalation from products applied as aerosols. Accidental oral ingestion of the chemical in small quantities can also occur.

While the chemical has toxicity to the male reproductive system, exposure of members of the public by any route to toxic levels is extremely improbable. Very few cosmetic or domestic products containing the chemical has been identified in the US and EU. While uses in fragrances cannot be ruled out, this is expected to give rise to only low levels and very short-term exposure, and thus exposure is not expected to be as high in males compared with females. Therefore, the risk to public health is not expected to be high.

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 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.

Oral exposure is also possible but can be prevented by good hygiene practices.

Given the critical systemic long-term 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.

Based on the available data, the hazard classification in the HCIS (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and worker health and safety, provided that all 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 or domestic products), risks to public health and safety may have to be managed by changes to the Poisons Standard.

Regulatory Control

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2017).

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Not Applicable	Causes serious eye irritation - Cat. 2A (H319)*
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 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 oral, dermal, inhalation and/or 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;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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

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