Furan, tetrahydro-: Human health tier III assessment

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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 III because the Tier II assessment indicated that it needed further investigation. The report should be read in conjunction with the Tier II assessment.

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

Disclaimer

Acronyms & Abbreviations

Synopsis

Under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) Framework, it was determined that further work is required to fully assess the carcinogenicity data of the chemical tetrahydrofuran (THF). A human health Tier III assessment was recommended.

In this assessment, the available data are considered insufficient to either characterise a mechanism of tumour formation or demonstrate a species-specific mode of action (MOA) in THF-induced kidney tumours in male rats and liver tumours in female mice. On this basis, the tumours induced by THF must be considered relevant to a human health risk assessment. NICNAS has made a recommendation for risk mitigation through classification.

Therefore, the Tier III assessment conclusions concur with the current classification of THF for carcinogenicity in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Human Health Tier II assessment for the chemical is available at: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=117 and contains detailed assessment information that remains valid (NICNAS). New or updated information is included in the Tier III human health report, in the relevant sections. The Tier II and Tier III reports for this chemical should be read together.

Rationale for Tier III Assessment

In order to determine if a recommendation for carcinogenicity classification of THF in Hazardous Substances Information System (HSIS, Safe Work Australia) is warranted, NICNAS reviewed the current information on THF and carcinogenicity, and considered the human relevance of the adverse effects and modes of action observed in animal studies. The carcinogenicity assessment for THF is based on the collective results of all available studies through analysing weight of evidence and conclusions drawn from previous international reviews.

The two-year inhalation studies conducted by the United States (US) National Toxicology Program (NTP 1998) were considered critical carcinogenicity studies for THF. These concluded that there was:

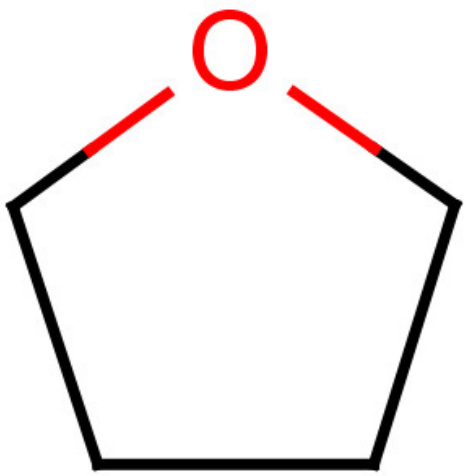
- *some evidence of carcinogenic activity* of THF in male Fischer 344 (F344/N) rats based on increased incidence of combined renal tubule neoplasms (either adenoma or carcinoma); and
- *clear evidence of carcinogenic activity* of THF in female B6C3F1 mice based on increased incidence of hepatocellular adenoma or carcinoma.

In the NTP (1998) studies, groups (50/sex) of rats and mice were exposed by inhalation to THF at 0, 200, 600 or 1800 ppm (0, 590, 1770 or 5310 mg/m^3, respectively) for 6 hours/day, 5 days/week for 105 weeks. There was a dose-related trend in the incidence of combined renal tubule neoplasms (either adenoma or carcinoma) in exposed male rats (1/50, 1/50, 4/50, 5/50, respectively). The increased incidences at 600 and 1800 ppm were not statistically significant, but exceeded the incidence

reported for historical controls. In the female mice, neoplastic effects observed included hepatocellular adenoma (12/50, 17/50, 18/50, 31/48), hepatocellular carcinoma (6/50, 10/50, 10/50, 16/48), hepatocellular adenoma or carcinoma (17/50, 24/50, 26/50, 41/48, respectively). There was no evidence of carcinogenic activity or an increasing trend in renal tubule neoplasms in exposed female rats or hepatocellular neoplasms in male mice.

In the Tier II assessment, it was noted that there were different opinions as to the human relevance of the positive rat and mouse results. Normally, observation of carcinogenic responses in two different species would be sufficient to classify a chemical as a possible human carcinogen. However, carcinogenicity that can be attributed to a mechanism not relevant to humans may be disregarded for classification purposes. Therefore, the primary purpose of this assessment is to examine the evidence for whether or not the rat renal carcinogenicity is due to mechanisms that are relevant to humans.

Chemical Identity

Synonyms	tetrahydrofuran (THF) 1,4-epoxybutane butylene oxide diethylene oxide cyclotetramethylene oxide
Structural Formula	
Molecular Formula	C4H8O
Molecular Weight (g/mol)	72.11
Appearance and Odour (where available)	Colourless clear liquid.
SMILES	C1CCCO1

Health Hazard Information

Carcinogenicity

Relevance of kidney tumours in male rats to humans

Some reviews of THF mechanistic data suggest that the observed renal tubule tumours (RTT) in the male rat were associated with advanced or end-stage chronic progressive nephropathy (CPN) and/or α_{2u}-globulin nephropathy, and therefore conclude that they are not relevant to humans (Bruner et al. 2010; Fowles et al. 2013; Hard et al. 2013). Age-related degenerative-regenerative disease of the kidney, such as CPN, occurs spontaneously with a high incidence in both sexes of laboratory rats, while α_{2u}-globulin nephropathy appears unique to the male rat (Hard et al. 2013; Melnick et al. 2012; US EPA 2012).

However, the European Chemical Agency Risk Assessment Committee (ECHA RAC 2010) and the United States Environmental Protection Agency (US EPA 2012) were of the opinion that there is no definite evidence to support either CPN or α_{2u}-globulin as a MOA in THF-induced kidney tumours in the rat (see ECHA 2010; US EPA 2012 for review).

In the ECHA RAC opinion, histopathological analyses of kidney lesions by Bruner et al. (2010), submitted by the European Chemical Industry Council (CEFIC) during the public consultation on an initial proposal for harmonised classification of THF, had contributed to clarifying the nature of kidney tumours seen in male rats. The ECHA RAC concluded that, although small, the increase in male kidney tumours should be considered indicative of a carcinogenic effect. The histopathological findings in the majority of adenomas and carcinomas in rats with severe CPN were considered not to conclusively demonstrate a causal relationship between tumour occurrence and CPN. Therefore, it was not possible to dismiss this carcinogenic hazard in considering the classification of THF (ECHA 2010).

The US EPA (2012) emphasised that the NTP two-year study on THF reported no dose-related increase in the incidence or severity of CPN in exposed male rats. It would be expected that, were the tumours related to chemically induced CPN, the CPN would have displayed a similar dose-related response to that of the tumours. There was also no direct evidence, either to support the role of THF in development of proliferative lesions within CPN-affected tissue, or to characterise mechanistic key events leading to induction of male rat kidney tumours, based on a detailed analysis of various mechanistic studies.

Supplementary information on the relationship between CPN and RTT

Melnick et al. (2012) examined the correlation between reported signs of chemically exacerbated CPN and RTT in multiple NTP studies (58 studies in male and 11 studies in female F344 rats). The results indicated that the relationship was inconsistent, providing no good evidence of a causal relationship between CPN and RTT in this analysis. The study emphasised that, although cell proliferation is one of the critical biological processes in the development of cancer, neither chemically exacerbated cell division nor histopathological findings alone could reliably justify or confirm mechanistic key events of chemically induced tumours, including tumour development in the rat kidney.

Using a different approach to statistical analyses including consideration of CPN severity grades (on a 0-8 scale), Hard et al. (2013) demonstrated a strong correlation between high-grade CPN (i.e. grades 7 and 8 CPN) and incidence of proliferative lesions and RTT, which is not consistent with the Melnick et al. findings above.

While the two studies have raised an issue of the criteria required for evaluating exacerbation of CPN as a MOA for RTT in rats, the lack of a dose-response for incidence or severity of CPN in the NTP (1998) rat study does not suggest that CPN is a mechanistic basis for causing RTT.

Regarding α_{2u}-globulin nephropathy as a MOA, there was some evidence of α_{2u}-globulin accumulation (as indicated by protein hyaline droplets) in repeated dose studies, following 5 or 20 days or 13 weeks of exposure to THF (see US EPA 2012 for review). However, the response in α_{2u}-globulin accumulation and cell proliferation induced by THF were weak, compared with other well-characterised inducers of α_{2u}-globulin accumulation, in these short-term studies. Furthermore, in the absence of detectable histopathological lesions characteristic of this MOA in the two-year NTP study, the evidence for THF-induced carcinogenicity associated with α_{2u}-globulin nephropathy is considered equivocal (NTP 1998; US EPA 2012).

Normally, carcinogenicity that can be attributed to a mechanism not relevant to humans (such as CPN and/or α_{2u}-globulin nephropathy) may be disregarded for classification purposes. On the basis that neither of these mechanisms could be sufficiently supported by the available data, the male rat RTT induced by THF must be considered potentially relevant to humans.

Relevance of liver tumours in female mice to humans

Some data suggest that increased cell proliferation following exposure to THF could be a possible MOA for liver tumourigenesis in female mice, although this does not discount the human relevance of the effect.

ECHA RAC (2010) and US EPA (2012) were in agreement that the available data are insufficient to establish a MOA for liver tumours observed with THF. However, the conclusive findings of their reviews were different. The ECHA RAC considered that the liver tumours '*were most likely to have been specific to the strain and species tested'* (i.e. highly sensitive B6C3F1 strain of mouse) on the basis that the tumours occurred in the absence of hepatotoxic effects or any clinical signs of toxicity. It was also emphasised that THF is non-genotoxic and caused no increases in liver tumours in exposed rats.

In contrast, US EPA (2012) noted that, while THF induced cell proliferation in short-term studies, which could lead to a promotion in the growth of pre-initiated cells and subsequently to tumour formation, this cell proliferation was not consistently sustained in medium or long-term studies. Information on key precursor events linked to the observed cell proliferation or specific mediators of tumourigenesis was not identified. In the absence of definite species-specific mechanistic information, the tumours observed in female mice must be considered relevant to a human health risk assessment of carcinogenic potential of THF.

Overall, based on the weight of evidence analysis, the positive findings in both rat and mouse species must be considered relevant to humans, leading to the conclusion that a carcinogenic classification for THF is warranted. According to the Approved Criteria under HSIS (Safe Work Australia) and the International Agency for Research on Cancer (IARC) criteria, there is limited evidence of a carcinogenic effect for THF (i.e. THF shows no genotoxicity in vitro and in vivo, and causes carcinogenic activity only at high doses levels). There is also an increased incidence of an appropriate combination of benign and malignant neoplasms in two species of animals treated with THF. Therefore, this assessment conclusion is consistent with both ECHA RAC (2010) and US EPA (2012) findings. The carcinogenic potential should be considered to apply to all routes of exposure, given that there is no information to indicate otherwise.

Risk Characterisation

Critical Health Effects

The critical effects to human health are irritation to the eyes, skin and respiratory system from short term exposure. While rodent carcinogenicity data are considered relevant to humans, the exposures leading to these tumours are outside the range considered relevant for long term human exposure, particularly as the irritant concentrations in rodents are lower than the concentrations at which tumours were observed. Transient neurotoxic effects may also be possible from short term exposure.

Public Risk Characterisation

Although domestic uses in Australia are not known, the chemical is reported to be used in domestic products overseas, including in the fabrication of articles for packaging or storing of food (if the residual amount does not exceed 1.5 % of the film), in cleaning agents, adhesives and stain removers. Considering the existing control measures for possible irritant effects of the chemical through classification, the risks to the public through exposure to domestic products containing the chemicals are expected to be low.

Occupational Risk Characterisation

Given the critical local irritant and carcinogenic effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalational exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) or an employer at a workplace has adequate information to determine the appropriate controls.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to work health and safety be managed through changes to classification and labelling.

Should additional information become available on potentially high public exposure to the chemical, a recommendation that the chemical be risk managed for public safety through scheduling may be warranted.

Assessment of the chemical is considered to be sufficient provided that risk management recommendations are implemented and all 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.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification
Irritation / Corrosivity	Irritating to eyes (Xi; R36)* Irritating to skin (Xi; R38)* Irritating to respiratory system (Xi; R37)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)	Suspected of causing cancer - Cat. 2 (H351)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[*] Existing Hazard Classification. No change recommended to this classification

Public health

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

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, ocular and inhalation 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.

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