2(1H)-Pyrimidinone, tetrahydro-1,3-dimethyl-: Human health tier II assessment

05 February 2016

CAS Number: 7226-23-5

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.

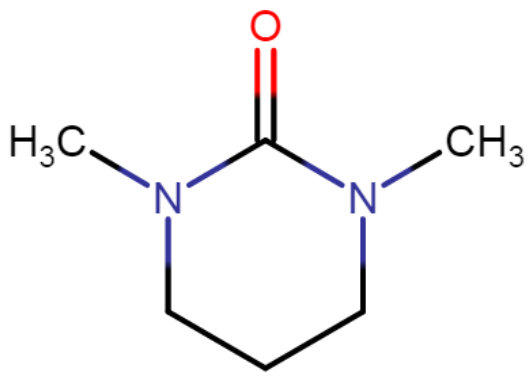
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone N,N'-dimethylpropylene urea (DMPU) tetrahydro-1,3-dimethyl-1H-pyrimidin-2-one
Structural Formula	
Molecular Formula	C6H12N2O
Molecular Weight (g/mol)	128.17
Appearance and Odour (where available)	colourless to light yellow liquid
SMILES	C1(=O)N(C)CCCN1C

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through:

- the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; and
- Galleria Chemica.

The chemical has reported site-limited use as an aprotic dipolar manufacturing solvent for highly reactive nucleophiles and bases. The chemical was shown to be a suitable replacement for the carcinogenic hexamethylphosphoramide (HMPA), which has a similar use.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Repr. Cat. 3; R62 (Reproductive toxicity);
- Xn; R22 (Acute toxicity); and
- Xi; R41 (Irritation).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). The data available (median lethal dose—LD50—1770 mg/kg bw) support this classification.

In a study conducted in Wistar rats (five animals/sex/dose), a single dose of the chemical at 681, 1470 or 2000 mg/kg bw was administered by gavage. Most of the animals in the high dose group died after 14 days (4/5 animals among both males and females). In the 1470 mg/kg group, only one female died. No deaths occurred in the low dose group. Pathological examination of the deceased animals showed general congestion and intensified hyperaemia in the lungs (REACH).

Dermal

The chemical has low acute toxicity following dermal exposure with a reported LD50 > 2000 mg/kg bw in a study conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 402. Semi-occlusive application of the undiluted chemical in Wistar rats (five animals/sex/dose) at a dose of 1000 or 2000 mg/kg bw caused the following effects: impaired general state, dyspnoea, and piloerection. Erythema was also noted in some females in both exposed groups but not in males (REACH).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical is not irritating to rabbit skin. In a study conducted in six Vienna White rabbits (two males and four females), the undiluted chemical (0.5 mL) was applied to shaved skin for four hours. The chemical was determined to be non-irritating based on erythema and oedema scores of 0.8 and 0.0, respectively (REACH).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Risk of serious damage to eyes' (Xi; R41) in the HSIS (Safe Work Australia). The available data support this classification.

In a study conducted in three Vienna White rabbits, the chemical (0.1 mL) was applied to the conjunctival sac of the right eye for 24 hours. The mean cornea, iris, conjunctivae and chemosis scores were 1, 0.8, 2.2 and 1.7, respectively. With the exception of the effects in the iris, all the other effects were not reversible after 21 days. Thus, the chemical was determined to be seriously damaging to rabbit eyes (REACH).

Sensitisation

Skin Sensitisation

The chemical was not sensitising based on a study conducted in accordance with OECD TG 429 (mouse local lymph node assay). Application of the chemical (in acetone/olive oil (4:1 v/v)) at concentrations of up to 25% (w/w) in CBA/CaOlaHsd mice gave a maximum stimulation index of 0.77 (REACH). Thus, a recommendation to classify the chemical for this particular endpoint is not warranted.

Repeated Dose Toxicity

Oral

Repeated oral exposure to the chemical is not considered to cause serious damage to health.

In a study conducted in accordance with OECD TG 407 in Wistar rats (five animals/sex/dose), the chemical was administered by gavage at a dose of 0, 10, 50 or 250 mg/kg bw/d for 28 days. No deaths occurred in any dose groups. No effects were reported in the 10 and 50 mg/kg bw/d groups. In the high dose group, effects observed during weeks 2 and 3 of the dosing period included ruffled fur, slight sedation, reduced food consumption, and lower body weight gain. After the dosing period, the high dose group exhibited slight anaemia which was supported by other haematological findings such as increased haemosiderin deposits in the spleen and compensatory effects through slight increases in reticulocytes, nucleated erythrocytes and platelets. Decreased lymphocyte count was correlated to the lymphoid atrophy in the spleen and thymus (REACH).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

The chemical is not mutagenic based on the negative results from the following *in vitro* tests (REACH):

- bacterial reverse mutation test in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 (OECD TG 471) with and without metabolic activation at doses up to 5000 µg/plate;
- bacterial reverse mutation test in *Escherichia coli* strain WP2 uvr A with and without metabolic activation at unspecified doses;
- mammalian cell gene mutation assay (OECD TG 476) in Chinese hamster lung fibroblasts (V79) with and without metabolic activation at doses up to 1300 µg/mL; and
- mammalian chromosome aberration test (OECD TG 473) in Chinese hamster lung fibroblasts (V79) with and without metabolic activation at doses up to 1290 µg/mL.

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

The chemical is classified as hazardous—Category 3 (substance toxic to reproduction)—with the risk phrase 'Possible risk of impaired fertility' (Xn; R62) in the HSIS (Safe Work Australia). No data are available to support this classification. The available developmental toxicity data are not considered to require hazard classification.

In a study conducted in accordance with OECD TG 414 in female Wistar rats (five animals/sex/dose), the chemical was administered once daily by gavage at doses of 0, 60, 120 or 180 mg/kg bw/d from day 6 – 20 post-coitum. No mortalities occurred in the dams. Food consumption, mean bodyweight, and mean bodyweight gain were reduced in all exposed groups (statistically significant in the high dose group only). Statistically significant decreased foetus weight was observed in the 120 and 180 mg/kg bw/d groups. Malformations in the foetuses were observed in the 120 and 180 mg/kg bw/d groups, including head abnormalities, shortened jaws and malformed thoracic area. However, these effects were not considered to be treatment-related since the type and frequency of these malformations were consistent with historical control data. No foetal effects were noted in the 60 mg/kg bw/d group (REACH). The no observed adverse effect levels (NOAELs) were 120 mg/kg bw/d for maternal effects and 60 mg/kg bw/d for the developmental effect of slightly reduced pup weight.

In another study conducted in accordance with OECD TG 414 in female Wistar rats (25 animals/sex/dose), the chemical was administered by gavage at doses of 0, 5, 15 or 60 mg/kg bw/d from day 6 – 20 post-coitum. Females in the high dose group showed reduced food consumption which was correlated with reduced mean bodyweights and bodyweight gain. Mean placental weights in the 15 and 60 mg/kg bw/d dose groups were reduced compared to controls (statistically significant only in the 60 mg/kg bw/d group). In the high dose group, a slight but statistically significant reduction in mean foetal body weights of the litters was observed. Although skeletal variation, specifically wavy ribs, was observed in the 5 and 15 mg/kg bw/d groups, these effects were not considered to be treatment-related (REACH). The NOAEL for both maternal and developmental effects was 15 mg/kg bw/d.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from oral exposure). The available data are not sufficient to determine the fertility effects of the chemical. The chemical can also cause eye irritation.

Public Risk Characterisation

Given the site-limited use of the chemical (refer to **Import, Manufacture & Use**), it is unlikely that the public will be exposed. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

Given the critical systemic long-term and acute health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral and ocular 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

Current risk management measures are considered adequate to protect public and workers' 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. No further assessment is required.

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 (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)*	Harmful if swallowed - Cat. 4 (H302)
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)*	Suspected of damaging fertility - Cat. 2 (H361f)

[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 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;
- 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;
- 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

Galleria Chemica. Accessed December 2015 at http://jr.chemwatch.net/galleria/

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. Tetrahydro-1,3-dimethyl-1H-pyrimidin-2-one (CAS No. 7226-23-5). Accessed December 2015 at http://apps.echa.europa.eu/registered/data/dossiers/DISS-d6b29dbc-75b1-5991-e044-00144f67d031/AGGR-dfd13d98-2871-4ffc-9e4a-8cf1e18dc5b0_DISS-d6b29dbc-75b1-5991-e044-00144f67d031.html#AGGR-dfd13d98-2871-4ffc-9e4a-8cf1e18dc5b0

Safe Work Australia (SWA). Hazardous Substances Information system (HSIS). Accessed December 2015 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

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