# Acetamide, N-methyl-: Human health tier II assessment

**21 April 2016**

## CAS Number: 79-16-3



## 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.

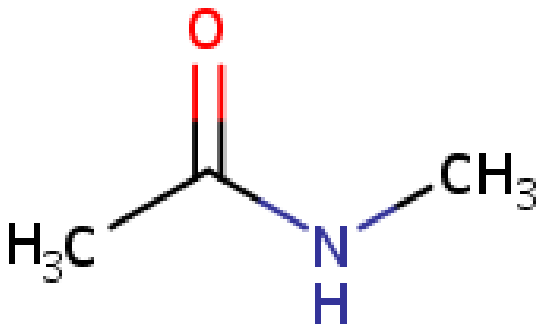
For more detail on this program please visit:www.nicnas.gov.au

**Disclaimer**



Acronyms & Abbreviations

## Chemical Identity

| | |
|---|---|
| Synonyms | N-methylacetamide<br>acetamide, N-methyl-<br>monomethylacetamide |
| Structural Formula |  |
| Molecular Formula | C3H7NO |
| Molecular Weight (g/mol) | 73.09 |
| SMILES | C(C)(=O)NC |

## 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; Galleria Chemica; the Substances and 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 of Cosmetic Ingredients (INCI) Dictionary; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR) and; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported commercial uses including;

- in construction materials;
- as a solvent;
- in electrochemistry; and
- in capacitors in automobile parts.

The chemical has reported non-industrial uses including;

- as a cryoprotectant; and
- as a pesticide.

## Restrictions

### Australian

No known restrictions have been identified.

### International

The chemical is listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard - Schedule 4: Components Cosmetic Products Must Not Contain; and
- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

## Existing Work Health and Safety Controls

### Hazard Classification

The chemical is classified as hazardous, with the following risk phrase for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia): R61; Repr. Cat. 2 (reproductive toxicity).

### Exposure Standards

#### Australian

No specific exposure standards are available.

#### International

No specific exposure standards are available.

## Health Hazard Information

Limited health hazard information is available for the chemical. The data for structurally similar chemicals, acetamide (CAS No. 60-35-5) and N,N-dimethylacetamide (CAS No. 127-19-5) are considered relevant and are included in this assessment for certain endpoints. Due to expected differences in dermal absorbancy and absence of clear dose-dependent liver toxicity in a repeated-dose study by the oral route, hazard information for the structurally similar chemicals is not considered in this assessement for the dermal and inhalation routes upon repeated exposure.

### Toxicokinetics

The metabolism of N-methylacetamide was investigated by a single intraperitoneal (i.p.) injection in male CBA/CA mice at 40 mg/kg bw (6 animals/dose). Urine was collected 24 hours after administration. The main metabolite excreted was N-hydroxymethylacetamide at 54 ± 10 % of the applied dose and the unchanged parent was excreted as 2.0 ± 2.0 % of the applied dose (REACH).

N-methylacetamide and N-hydroxymethylacetamide are the main metabolites of N-dimethylacetamide in animals and humans (NICNAS), indicating similar metabolism and excretion pathways for these chemicals.

### Acute Toxicity

#### Oral

The chemical has low acute toxicity based on results from animal tests following oral exposure. The reported median lethal dose (LD50) was > 2000 mg/kg bw in rats.

In a study according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401, rats (strain unspecified, 10 animals/ sex/dose) were administered a single dose of the chemical at 0, 200, 1600, 3200, 4000, 5000 or 6400 mg/kg bw by oral gavage. The LD50 was determined at 4000 mg/kg bw. Observed sub-lethal effects include unexcited behaviour immediately after application, increased respiration rate, dyspnoea, and ruffled coat. The effects were reversible within 7–13 days in surviving animals. At the highest dose, mortalities occurred for all animals within 7 days of administration. Diarrhoea with possible intestinal atony (loss of peristalsis) and fatty liver were observed in deceased animals. No treatment-related effects were seen in surviving animals (REACH).

In another study, Sprague Dawley (SD) rats were treated once with 1600, 3200, 4000, 5000 or 6400 µL/kg bw of the chemical by oral gavage. Observed sub-lethal effects include ruffled coat, apathy, and lateral recumbency. At the highest dose, adhered eyes and tremor, with mortality occuring within two days were observed. Congestion of the liver and lung, degeneration of the

heart, dark yellow coloured liver and reduced weight gain were observed in deceased animals. No treatment-related effects were seen in surviving animals. The oral LD50 is 4200 µL/kg bw corresponding to 3950 mg/kg bw (REACH).

Other reported LD50 values in rats were between 5000-7000 mg/ kg bw (Buhler, 1990; HSDB; RTECS).

### Dermal

No data are available for the chemical.

### Inhalation

The chemical is not considered to be acutely toxic by inhalation route. The reported effects were not sufficient to warrant hazard classification.

In an inhalation study conducted similarly to OECD TG 403, rats (six animals/sex/dose; strain unspecified) were exposed to vapours of the chemical for eight hours at a single dose of 2.19 mg/L. No clinical signs or mortalities were observed during treatment and up to seven days after administration (REACH).

## Corrosion / Irritation

### Skin Irritation

The chemical is reported in animal studies to slightly irritate the skin. Effects were not sufficient to warrant hazard classification.

In a study conducted similarly to OECD TG 404, Vienna white rabbits (two animals/dose) were dermally administered the chemical under occlusive conditions. The chemical was applied undiluted for 1, 15 minutes or 20 hours' exposure time. The mean erythema scores observed at 24, 48 and 72 hours post application were 1.5, 1.0, and 0.5, respectively, for animals exposed to the chemical for 20 hours. The effects were reversible within 8 days (REACH).

### Eye Irritation

The chemical is not considered to be an eye irritant based on animal studies. Effects were not sufficient to warrant hazard classification.

In a study conducted similarly to OECD TG 405, Vienna white rabbits (two animals/dose) had 0.05 mL of the chemical instilled into the conjunctival sac. The mean chemosis and conjunctivae scores at 24 hours were 1 and 2 respectively. All effects were reversible within the observation period of 72 hours (REACH).

## Sensitisation

### Skin Sensitisation

No human or animal data are available for the chemical. A weight of evidence approach supports the conclusion that the chemical is not considered to be a skin sensitiser.

The chemical contains one structural alert for binding to protein based on the mechanistic profilers of the OECD Quantitiative Structure–Activity Relationship (QSAR) Application Toolbox (v. 3.3). However, QSAR modelling using OASIS–TIMES (Optimized Approach based on Structural Indices Set–Tissue Metabolism Simulator) resulted in a prediction as a non–sensitiser. The prediction was within the applicability domain of the model. Additionally, acetamide resulted in a prediction as a non-sensitiser and was within the domain of the model.

The structurally similar chemical N,N-dimethylacetamide was negative for skin sensitisation in a non-guideline guinea pig study (NICNAS). No human or animal data were available for acetamide.

## Repeated Dose Toxicity

### Oral

Based on the data available, the chemical is not considered to cause serious damage to health through repeated oral exposure.

In a study conducted similarly to OECD TG 408, rats (strain not specified; 20 animals/dose) were administered the chemical in drinking water at doses of 0, 50, 400 or 1000 mg/kg bw/day for 90 days. The relative and/or absolute organ weights for spleen, kidneys, adrenals, brain, testes and liver were significantly different in all treated animals compared to controls. At the highest dose, significantly reduced bodyweight gain, food and water consumption, and increased mortality were reported. Histopathological analysis revealed changes in the bone marrow, lymph nodes and thymus in males and females and the liver of males only. Tubular nephrosis was observed in males (in the 50 mg/kg bw/day group and higher) and in females (in the 1000 mg/kg bw/day group). Although a lowest observed adverse effect level (LOAEL) was determined to be 50 mg/kg bw/day based on tubular nephrosis in the kidney, the effects were not considered toxicologically relevant to humans (REACH).

### Dermal

While the chemical is the main metabolite of N,N-dimethylacetamide in animals (see **Toxicokinetics**) and the epidemiological/occupational health studies in humans exposed dermally to N,N-dimethylacetamide indicate adverse effects in the liver (NICNAS), no animal data on repeated exposure by the dermal route are available for the chemical. Based on available information, classification is not warranted for the chemical.

### Inhalation

While the chemical is the main metabolite of N,N-dimethylacetamide in animals (see **Toxicokinetics**) and the epidemiological/occupational health studies in humans exposed by the inhalation to N,N-dimethylacetamide indicate adverse effects in the liver (NICNAS), no animal data on repeated exposure by the inhalation route are available for the chemical. Based on available information, classification is not warranted for the chemical. The liver effects seen in repeated oral dose studies with N,N-dimethylacetamide are not seen for N-methylacetamide after repeated oral dosing.

### Observation in humans

No human data for the chemical are available.

Several epidemiological/occupational health studies that investigated the long-term, combined low-level dermal and inhalation exposures to the structurally similar chemical, N,N-dimethylacetamide, are available and discussed extensively (NICNAS). Occupational exposure studies used N-methylacetamide as biomarker for exposure. Adverse effects on the liver have been observed consistently in these studies. Clinical studies based on accidental repeated exposures showed that N,N-dimethylacetamide can cause hepatitis. Additionally, when tested as anti-tumour agent in cancer patients, N,N-dimethylacetamide caused extreme disorientation, lethargy, and hallucinogenic effects. The liver is not implicated as a target organ for N-methylacetamide to the same extent.

## Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

***In vitro***

The chemical tested as positive in an *Escherichia coli* reverse mutation assay of limited reliability, at high doses (= 10 mg/mL) and without metabolic activation. A sister chromatid exchange assay in Chinese hamster ovary cells gave ambiguous results (REACH).

***In vivo***

The in vivo mutagenicity of the chemical was assessed in a study conducted in accordance with OECD TG 474 (mammalian erythrocyte micronucleus test); male NMRI mice (5 animals/dose) were administered doses of 0, 500, 100 or 2000 mg/kg bw by i.p. injection, twice, 24 hours apart. Slight inhibition of erythropoesis at the highest dose was reported. The chemical did not induce a relevant increase in the frequency of micronuclei at any dose (REACH).

In a study conducted in accordance with OECD TG 478 (rodent dominant lethal test) in male NMRI mice (20 animals/dose), the animals were administered the chemical at 660 mg/kg bw by single i.p. injection, and mated for a total of eight matings over eight weeks. No treatment-related effects in males or difference in mutation index, conception rates or number of implantations were reported. The chemical does not induce germ cell mutations (REACH).

## Carcinogenicity

No human and animal data are available for the chemical. The chemical is not expected to be carcinogenic.

The chemical is not considered carcinogenic in dermal and inhalation carcinogenicity studies in rodents (NICNAS). Given that N-methylacetamide is a known metabolite of N,N-dimethylacetamide, this suports a lack of carcinogenicity of the chemical. Furthermore, the chemical does not contain any structural alerts for binding to DNA based on the mechanistic profilers of the OECD QSAR Application Toolbox (v. 3.3).

## Reproductive and Developmental Toxicity

The chemical is classified as hazardous—Category 2 substance toxic to reproduction—with the risk phrase ‘May cause harm to the unborn child’ (T; R61) in the HSIS (Safe Work Australia). The available data support this classification.

Slight increase in foetal resorption occurred upon application of the chemical to the skin of pregnant rabbits (strain unspecified) at a dose of 600 mg/kg bw/day during gestation days (GD) 9 to 13 (Buhler, 1990; HSDB).

In an oral gavage study, the chemical was administered on GD 6 to 18 inclusively to pregnant rabbits at 10, 50 or 240 mg/kg bw/day. At the lowest dose, no adverse effects were reported. At 50 mg/kg bw/day five malformed kits from three litters were reported in the absence of maternal toxicity. At the highest dose, foetal malformations were reported in the presence of maternal toxicity (Buhler, 1990).

Pregnant Long Evans rats were administered the chemical by oral gavage in three dosing series:

- 280 mg/kg bw/day daily on GD 7 through 17 inclusive;
- 940 or 1900 mg/kg bw as a single dose on GD 7;
- 940 or 1900 mg/kg bw/day on GD 7 and 8.

No effects were reported at the lowest dose. In the second dosing series, 20 % and 96 % of implants were resorbed in the 940 and 1900 mg/kg bw/day group, respectively. In the third dosing series, 92 % of implants were resorbed at 940 mg/kg bw/day (REACH).

In other studies, doses of the chemical above 1000 mg/kg bw/day are embryotoxic (REACH, RTECS).

In a study conducted in rats exposed at 1000 mg/kg bw/d for 90 days (see **Repeated Dose Toxicity - oral**), the following effects on reproductive capacity were observed: epididymal aspermia, seminiferous tubule atrophy and reduced seminal vesicle secretory activity in males (REACH).

# Risk Characterisation

## Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (reproductive toxicity).

## Public Risk Characterisation

Given the uses identified for the chemical, 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 acute and long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal 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 Hazardous Substances Information System (HSIS) (Safe Work Australia) is considered appropriate.

# 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] |
|---|---|---|
| Reproductive and Developmental Toxicity | Repro. Cat 2 - May cause harm to the unborn child (T; R61)* | May damage fertility or the unborn child - Cat. 1B (H360D) |

[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 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

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