Formamide, N,N-dimethyl-: Human health tier II assessment

22 March 2013

CAS Number: 68-12-2

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.

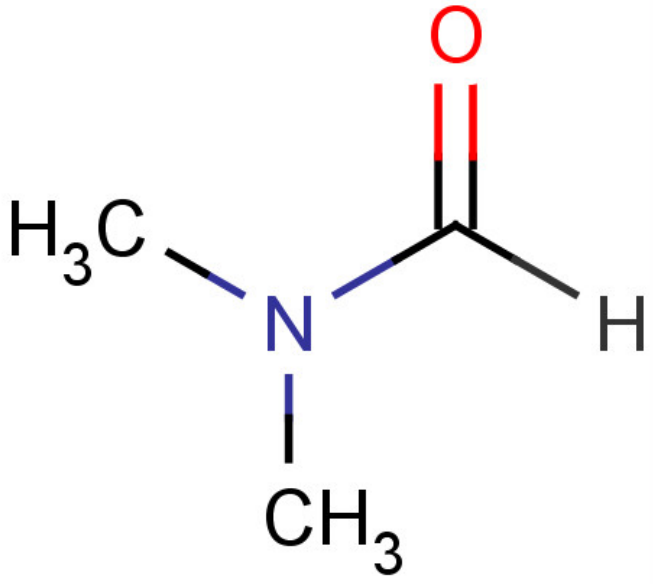
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Dimethylformamide N,N-Dimethylformamide DMF
Structural Formula	
Molecular Formula	C3H7NO
Molecular Weight (g/mol)	78.09
Appearance and Odour (where available)	Colorless to very slightly yellow liquid with a faint amine odour.
SMILES	C(=O)N(C)C

Import, Manufacture and Use

Australian

The following Australian uses were reported under previous NICNAS calls for information.

The chemical has reported commercial use including:

- peptide production;
- furniture industry;
- plate-making in printing industry;
- shoe paint; and
- mining waste water treatment.

The chemical has reported site-limited use including:

- manufacture of laboratory reagents.

International

The following International uses have been identified through the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR), European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) Dossiers, Canadian Assessments (Second Priority Substances List- PSL2), Galleria Chemica and the Substances and Preparations In the Nordic countries (SPIN):

The chemical has reported domestic use including:

- in cleaning/washing agents.

The chemical has reported commercial use including:

- as a solvent in manufacturing industry;
- in coatings (paints, lacquers, varnishes), adhesives, films and printing (use in the electronics industry);
- in synthetic leather, acrylic fibres & polyurethanes; and
- in construction materials.

The chemical has reported site limited use including:

- in the oil and gas/petrochemical sector mainly for gas stream separation; and
- as an intermediate in the manufacture of laboratory & fine chemicals.

The chemical is in the US FDA List of "Indirect" additives used in food contact substances.

Restrictions

Australian

The chemical is listed in the Poisons Standard (for the Uniform Scheduling of Medicines and Poisons (SUSMP)) in:

Schedule 5 - in preparations containing 10 per cent or less of dimethylformamide except in silicone rubber mastic containing 2 per cent or less of dimethylformamide; and

Schedule 6 - except (a) when included in Schedule 5; or (b) in silicone rubber mastic containing 2 per cent or less of dimethylformamide.

International

ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

Canada List of Prohibited and Restricted Cosmetic Ingredients (The Cosmetic Ingredient "Hotlist").

EU Cosmetics Regulation (EC) No 1223/2009 Annex II: List of substances which must not form part of the composition of cosmetic products.

New Zealand Cosmetic Products Group Standard - Schedule 4: Components cosmetic products must not contain - Table 1.

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. 2; R61

Xn; R20/21 (acute toxicity)

Xi; R36 (irritation)

Exposure Standards

Australian

The chemical has an exposure standard of 30 mg/m³ (10 ppm) TWA.

International

The following are identified (Galleria Chemica):

Occupational exposure limit (OEL) of 0.2 - 30 mg/m³ (0.005 - 10 ppm) in USA (Alaska, Hawaii), Canada (Yukon), Norway and Switzerland; and

STEL of 35 - 120 mg/m³ (10 - 20 ppm) in USA (Alaska, Hawaii), Canada (Yukon), Norway and Switzerland.

Health Hazard Information

Toxicokinetics

The chemical is readily absorbed via all exposure routes in animals. N-hydroxymethyl-N-methyl formamide is the main urinary metabolite. To a minor extent but with greater toxicological relevance, the metabolite mono-N-methylformamide (MMF) occurs which may partially be conjugated to glutathione forming S-methyl carbamoyl glutathione. The glutathione (GSH) and its sequel adducts (S-methylcarbamoylcysteine and the corresponding mercapturic acid S-methylcarbamoyl-N-acetyl-cysteine) appear to be responsible for the developmental toxic effects. At higher doses, the chemical inhibits its own metabolism, i.e. the formyloxidation to MMF which precedes the GSH binding (OECD, 2003).

In humans, the chemical is absorbed by inhalation and through the skin. Persons who repeatedly inhaled the chemical excreted the mercapturic acid at ~13% of the dose with a total half-life of 23 h. Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of the chemical and conversely, the chemical inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces cytochrome P450 2E1 which facilitates the initial hydroxylation of the chemical. Thus, exposure to the chemical can cause a severe alcohol intolerance (OECD, 2003).

Acute Toxicity

Oral

The chemical is of low acute toxicity via the oral route, based on the reported LD50 of 3040 mg/kg bw in rats. Main symptoms following oral exposure were apathy and staggering (OECD, 2003).

Dermal

The chemical is currently classified with the risk phrase 'Harmful in contact with skin' (Xn; R21) in Australia (HSIS, Safe Work Australia). However, the data available show the chemical to be of low acute toxicity via the dermal route. Therefore, the existing hazard classification is not recommended.

The following dermal LD50 values are reported (OECD, 2003):

- >3160 mg/kg bw in rats (GLP compliant);
- 5000 - 11,000 mg/kg bw in rats (no GLP);
- >5000 mg/kg bw in mice; and
- between 1500 mg/kg bw to 12,350 mg/kg bw in rabbits. However it is noted that the lower LD50 value was for pregnant animals.

Inhalation

The chemical is currently classified with the risk phrase 'Harmful by inhalation' (Xn; R20) in Australia (HSIS, Safe Work Australia). The data available support this classification.

The following LC50 values are reported (OECD, 2003):

- LC50 (vapour) > 5900 mg/m³/4 h in rats; and
- LC50 (saturated air) between 9 - 15 mg/L/4 h in rats.

Irregular or intermittent respiration was observed in the treated animals.

Corrosion / Irritation

Skin Irritation

The undiluted chemical was not irritating to the intact skin of rabbits or abraded skin of rats (OECD, 2003).

Eye Irritation

The chemical is currently classified with the risk phrase 'Irritating to eyes' (Xi; R36) in Australia (Safe Work Australia – HSIS). The data available support this classification.

There are several studies reporting the chemical as an eye irritant (OECD, 2003). One study reported severe signs of inflammation (redness, chemosis and purulent secretion) as well as transient opacity of the cornea in one of two test animals received the undiluted test substance. In another study, after instillation of 0.1 mL of the neat chemical the primary irritation index (Draize method) was 50.8 after 1 h, decreasing to 35.8 after 72 h and 35.0 on day 4, decreasing to 3.3 on day 13. All animals in the latter study showed large blisters on the inside of upper and lower eye lids at the 1 h and 4 h readings. Blisters decreased in size at the 24 h reading and disappeared by 48 h (OECD, 2003).

Sensitisation

Skin Sensitisation

The chemical is not considered a skin sensitiser.

A guinea pig maximisation test reported the chemical as non-sensitising (OECD, 2003). In a murine local lymph node assay 25 µL of the chemical was applied on the dorsum of both ears of six mice for three consecutive days. The treatment led to slight ear-draining lymph node activation as expressed by increased weight and cell count, in comparison to the untreated animals. However, this observation was not reproducible in a second experiment. Therefore, there was no clear indication of a sensitising potential of the chemical (OECD, 2003).

Repeated Dose Toxicity

Oral

Based on the data available, the chemical is not considered to cause severe effects from repeated oral exposure.

In a 90-day feeding study in CD rats, a NOAEL of 200 ppm (12 mg/kg bw/d) was established. The LOAEL was 1000 ppm (60 mg/kg bw/d) based on increased liver weights and hypercholesterolaemia and elevated phospholipid values observed in females. Increased relative liver weights above 1000 ppm together with mild liver injury in the histological examination were found in both sexes. There were some haematological effects in both sexes such as decreased red blood cells and leucocytosis at 1000 ppm and anaemia and leucocytosis at 5000 ppm (OECD, 2003).

In a 28-day gavage study in Sprague–Dawley rats, a NOAEL of 250 ppm (238 mg/kg bw/d) and a LOAEL of 500 ppm (475 mg/kg bw) were established. The liver was the predominant target organ of toxicity. Hepatic injury was observed from 1000 ppm, characterised by changes in increased enzyme activities and increases in relative liver weights, in both sexes. Histological examination revealed an acute to subacute haemorrhagic liver dystrophy with necrosis in both sexes above 1000 ppm. Disturbances in kidney function (elevated urea in 2 of 9 female animals and increased creatinine values in all animals) were reported at the highest dose of 950 mg/kg bw/d (OECD, 2003).

Dermal

Based on the limited data available, the chemical is not considered to cause severe effects following repeated dermal exposure.

In a 30-day dermal study in rats (strain not reported), a NOAEL of 215 mg/kg bw/d was established based on dose-related changes seen in liver enzymes and cholinesterase in the serum and liver homogenate (OECD, 2003).

Inhalation

Based on the data available, the chemical is not considered to cause severe effects from repeated inhalation exposure.

In 13-week inhalation studies, Fischer 344 rats and B6C3F1 mice were exposed to vapour concentrations of 50, 100, 200, 400 and 800 ppm (about 150, 300, 610, 1210 and 2430 mg/m³) for 6 h/day, 5 days per week. Based on liver effects, the NOAEC was 100 ppm in rats and 400 ppm in mice. In a 13-week inhalation study with a limited number of Cynomolgus monkeys, no treatment-related effects occurred at the highest dose tested (NOAEC was 500 ppm (~ 1500 mg/m³)) (OECD, 2003).

In repeated-dose inhalation toxicity studies in rats with chronic exposure over 2 years, the predominant target organ was the liver. The reported NOAEC was 25 ppm (about 80 mg/m³) and LOAEC was 100 ppm. The LOAEC was based on changes in reduction in body weight gain, increase in serum sorbitol dehydrogenase activity, increased mean relative liver weights and centrilobular hepatocellular hypertrophy, as well as an increased centrilobular accumulation of lipofuscin/haemosiderin (OECD, 2003).

In repeated dose inhalation toxicity studies in mice with chronic exposure up to 18 months, the NOAEC could not be established but the reported LOAEC was 25 ppm (about 80 mg/ m³). This was based on: significantly increased incidence of hepatocellular hypertrophy in males (slight increase in females); dose related and significantly increased incidence of hepatic single cell necrosis in both sexes; dose related increased incidence of hepatic kupffer cell hyperplasia in males; and pigment accumulation that occurred in most cases in a dose-related manner (OECD, 2003).

Genotoxicity

The chemical is not considered to have genotoxicity.

The chemical did not induce chromosome aberrations or gene mutations in various test systems *in vivo* and *in vitro* (OECD, 2003).

Carcinogenicity

Based on the data available the chemical is not considered a carcinogen.

The IARC evaluated the carcinogenicity data and concluded that there is *inadequate evidence* in humans for the carcinogenicity of dimethylformamide and there is *evidence suggesting lack of carcinogenicity* of dimethylformamide in experimental animals. The overall IARC evaluation was dimethylformamide is *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1999).

Animal carcinogenicity data: In chronic inhalation studies in rats (two years) and mice (18 months), animals exposed to 25, 100 and 400 ppm (5 days/w, 6 h/d) showed no compound related lesions in the nose or respiratory tract. Incidences of hepatic tumors and testicular tumours in both species were similar to control values. Cell-labelling indices in the liver (measured in 5 randomly selected animals per sex and group after 2 weeks, 3 months and 12 months of exposure) showed no substance related effect at any exposure level in the mice. The rat cell-labelling indices for hepatocytes were not statistically different between control and 400 ppm animals, but rates were slightly higher for 400 ppm males at 2 weeks and 3 months but not at 12 months. The chronic exposure to the chemical did not cause a compound-related increase of tumours in rats or mice up to the highest dose tested i.e. 400 ppm (OECD, 2003).

Human carcinogenicity data: Case reports of testicular cancer in aircraft repair and leather tannery facilities suggested possible association with dimethylformamide. Further research has failed to confirm this relationship. A screening effort at a leather tannery, where a cancer cluster had been noted, identified no additional cases. Mortality and cancer incidence studies and nested case–control

investigations of testicular cancer and several other tumours, at several facilities with exposure to the chemical, noted no convincing associations with the chemical (IARC, 1999).

Reproductive and Developmental Toxicity

The chemical is currently classified as hazardous with the risk phrase 'May cause harm to the unborn child' (T; R61) in HSIS (Safe Work Australia). The data available support this classification.

Reproductive toxicity was observed together with some general toxicity, in a continuous breeding study in mice, when the chemical was administered orally in the drinking water at doses of 1000, 4000 and 7000 ppm (about 219, 820 and 1455 mg/kg bw/day). The maximal tolerated dose for generalised toxicity (such as increased liver weights, hepatocellular hypertrophy and decreased body weight) was 1000 ppm (about 219 mg/kg bw/day) for the F0 and the F1 generation, thus a systemic NOAEL could not be determined. Significant reproductive toxicity effects reported at 4000 ppm or above include: reduced fertility and reproductive capacity (fecundity) characterised by reduced pregnancy and mating index (fecundity only observed at 7000 ppm); reduced number of litters; reduced average litter size and effects on prostate weight; and epididymal spermatozoa concentration (only in the high dose group) in F1 parental males. Reported developmental toxicity effects included reduced survival and growth of pups, increase in craniofacial and sternebral malformations occurred at 4000 ppm and above. The NOAEL for reproductive and developmental toxicity in F0 and F1 was 1000 ppm (about 219 mg/kg bw/day). Based on reduced pup weights found in F2 pups at 1000 ppm, the LOAEL for developmental toxicity in F2 was 1000 ppm (OECD, 2003). Based on the severity of the observed reproductive/developmental effects, these are not considered secondary to maternal toxicity.

Developmental toxicity and teratogenicity occurred in rats and rabbits in various studies (inhalation, oral or dermal administration) and in mice (oral administration). In rats embryo-/fetotoxicity and teratogenicity were mostly seen at maternally toxic doses, whereas in mice and in rabbits embryo-/fetotoxicity and teratogenicity occurred also at dose levels without maternal toxicity (OECD, 2003).

The rabbit appeared to be the most sensitive species to the developmental toxic effects of the chemical. Different studies in rabbits reported the following NOAEC/NOAEL (OECD, 2003):

- NOAEC (inhalation) for maternal toxicity and teratogenicity as well as embryo-/fetotoxicity was 50 ppm (about 150 mg/m³);
- NOAEL (oral, gavage) for maternal toxicity and embryo-/fetotoxicity was 65 mg/kg bw/day and NOAEL for teratogenicity was 44.1 mg/kg bw/day; and
- NOAEL (dermal) for maternal toxicity and teratogenicity as well as embryo- /fetotoxicity was 200 mg/kg bw/day.

Risk Characterisation

Critical Health Effects

The main critical effects to human health are reproductive and developmental toxicity, eye irritation and acute inhalation toxicity.

Public Risk Characterisation

No domestic uses were identified in Australia but the chemical is used in cleaning/washing agents overseas (use concentrations not available).

Considering the health effects, specifically reproductive/developmental toxicity, there is a concern in the use of this chemical as an ingredient in domestic products at high concentrations. The chemical is already listed in the SUSMP requiring cautionary labelling for products containing the chemical based on its concentrations. Therefore, the risk to public is considered low.

Occupational Risk Characterisation

The critical health effects the risk to workers from this chemical are considered high if adequate control measures to minimise occupational exposure to the chemical are not implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or an employee at a workplace has adequate information to determine appropriate controls.

NICNAS Recommendation

The chemical is sufficiently assessed and risk managed provided the recommendations for classification and labelling are adopted.

Regulatory Control

Public Health

Considering the available information to indicate low public exposure under existing regulatory settings to this chemical no additional regulatory controls are recommended.

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This does not consider classification of physical hazards and environmental hazards. Based on the data available, the current hazard classification for acute dermal toxicity on HSIS is not recommended.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful by inhalation (Xn; R20)*	Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)*	Causes serious eye irritation - Cat. 2A (H319)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May cause harm to the unborn child (T; R61)*	May damage 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 industry

Control measures

Control measures to minimise the risk from 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 storage, handling and use of a hazardous chemical are dependent on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include but are not limited to:

- use of closed systems or isolation of operations;
- use of 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;
- minimisation of manual processes and work tasks through automation of processes;
- work procedures that minimise splashes and spills;
- regular cleaning of equipment and work areas; and
- use of 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 be relied upon on its own to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selection of 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 assist with meeting 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 hazardous chemical are prepared; and
- management of risks arising from storage, handling and use of 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 physical hazards of the chemical has not been undertaken as part of this assessment.

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