Morpholine, 4,4'-methylenebis-: Human health tier II assessment

30 June 2017

CAS Number: 5625-90-1

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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.

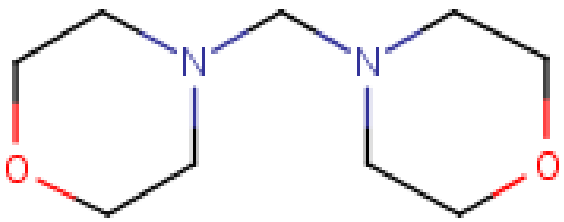
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	4,4'-methylenedimorpholine N,N'-methylenebismorpholine dimorpholinomethane
Structural Formula	
Molecular Formula	C9H18N2O2
Molecular Weight (g/mol)	186.25
Appearance and Odour (where available)	pale yellow liquid with slight amine-like odour
SMILES	C1CN(CN2CCOCC2)CCO1

Import, Manufacture and Use

Australian

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was less than 100 tonnes in 2006.

The chemical has reported commercial use in Australia as fuel additive and in hydraulic fluids. It is used in metalworking fluids (MWF) and soluble cutting oils, at concentrations up to 5 %.

International

The following international uses have been identified through: Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; and various international assessments including the European Competent Authority Report (CAR, 2014), the Classification, Labelling and Harmonisation report (CLH, 2014) and the Committee for Risk Assessment report (RAC, 2015).

The chemical has reported domestic uses in the SPIN database in cleaning and/or washing agents.

However, it should be noted that SPIN does not distinguish between direct use of the chemical, or use of the products that are produced from chemical reactions involving the chemical.

The chemical has reported commercial use:

- in corrosion inhibitors;
- as preservative in metalworking fluids at concentrations up to 0.15 % (CAR, 2014); and
- as preservative in fuels at concentrations up to 0.1 % (CAR, 2014).

The chemical has reported non-industrial use in non-agricultural pesticides and preservatives (SPIN).

Restrictions

Australian

No known restrictions have been identified for the chemical. However, the chemical is a formaldehyde donor.

Formaldehyde (CAS No. 50-00-0) is listed in Schedules 2, 6 and 10 of the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons) (SUSMP, 2017) as follows:

- in Schedule 2:

'FORMALDEHYDE' (excluding its derivatives) for human therapeutic use **except**:

a) in oral hygiene preparations containing 0.1 per cent or less of free formaldehyde; or

b) in other preparations containing 0.2 per cent or less of free formaldehyde.'

Schedule 2 chemicals are 'substances, the safe use of which may require advice from a pharmacist and which should be available from a pharmacy or, where a pharmacy service is not available, from a licensed person.' They are labelled with 'Pharmacy Medicine' (SUSMP, 2017).

- in Schedule 6:

'FORMALDEHYDE' (excluding its derivatives) in preparations containing 0.05 per cent or more of free formaldehyde **except**:

a) for human therapeutic use;

b) in oral hygiene preparations;

c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde;

d) in nail hardener cosmetic preparations containing 0.2 per cent or less of free formaldehyde when labelled with the statement: PROTECT CUTICLES WITH GREASE OR OIL;

e) in all other cosmetic preparations; or

f) in other preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement: CONTAINS FORMALDEHYDE.'

Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label.' Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2017).

- in Schedule 10:

'FORMALDEHYDE' (excluding its derivatives):

a) in oral hygiene preparations containing more than 0.1 per cent of free formaldehyde;

b) in aerosol sprays for cosmetic use containing 0.005 per cent or more of free formaldehyde;

c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde; or

d) in all other cosmetic preparations containing 0.05 per cent or more of free formaldehyde **except** in preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement: CONTAINS FORMALDEHYDE.'

Schedule 10 chemicals are 'substances which are prohibited for the purpose or purposes listed for each poison. They are labelled with 'Substances of such danger to health as to warrant prohibition of sale, supply and use' (SUSMP, 2017).

'Free formaldehyde' includes all hydrated and non-hydrated formaldehyde present in aqueous solution, including methylene glycol and formaldehyde released from formaldehyde donors.

International

No known restrictions have been identified for the chemical (Galleria Chemica). However, the chemical is a formaldehyde donor and may be subject to the restrictions on formaldehyde, under certain conditions.

Using formaldehyde in cosmetics in the European Union is subject to the restrictions described in EU Regulation Annexes III and V (CosIng).

Formaldehyde may be present in the following cosmetic products and personal care products (CosIng):

- nail hardening products at a maximum concentration of 5 % in ready for use preparation; if the concentration exceeds 0.05 %, the label must indicate 'Contains formaldehyde';
- preservatives for oral products with a maximum concentration of 0.1 % as free formaldehyde in ready for use preparation; and
- preservatives for other products with a maximum concentration of 0.2 % as free formaldehyde in ready for use preparation.

Another hydrolysis product of the chemical, morpholine (CAS No. 110-91-8) is listed on the EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products (CosIng).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

The chemical is currently subject to a proposal (CLH, 2014) for harmonised classification and labelling under the CLP regulation. The RAC issued an opinion (RAC, 2015) in which the following hazard classes and hazard statements are proposed:

- Carcinogenicity – category 1B; H350 (May cause cancer)
- Mutagenicity – category 2; H341 (Suspected of causing genetic defects)
- Acute Toxicity – category 4; H332 (Harmful if inhaled)
- Acute Toxicity – category 4; H312 (Harmful in contact with skin)
- Acute Toxicity – category 4; H302 (Harmful if swallowed)
- Specific target organ toxicity (repeated exposure) STOT RE – category 2; H373 (May cause damage to organs – gastrointestinal tract, respiratory tract – through prolonged or repeated exposure)
- Skin Corrosion – category 1B; H314 (Causes severe skin burns and eye damage)
- Skin Sensitisation – category 1; H317 (May cause an allergic skin reaction)

Hydrolysis products of the chemical are currently classified as hazardous, with the following hazard categories and hazard statements for human health in the HCIS:

Formaldehyde (CAS No. 50-00-0):

- Carcinogenicity – category 1B; H350i (May cause cancer by inhalation)
- Acute toxicity (inhalation) - category 2; H330 (Fatal if inhaled)
- Acute toxicity (ingestion) - category 3; H301 (Toxic if swallowed)
- Acute toxicity (dermal) - category 3; H311 (Toxic in contact with skin)
- Skin corrosion – category 1; H314 (Causes severe skin burns and eye damage)
- Skin sensitisation – category 1; H317 (May cause an allergic skin reaction)

Morpholine (CAS No. 110-91-8):

- Acute Toxicity – category 4; H332 (Harmful if inhaled)
- Acute Toxicity – category 4; H312 (Harmful in contact with skin)
- Acute Toxicity – category 4; H302 (Harmful if swallowed)
- Skin corrosion – category 1B; H314 (Causes severe skin burns and eye damage)

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

The chemical is a formaldehyde donor. Upon contact with aqueous media such as biological tissues, it hydrolyses into morpholine and formaldehyde (CAR, 2014), both critical drivers for toxicity. The human health hazards of morpholine and formaldehyde have previously been assessed by NICNAS (NICNAS, 2015; NICNAS, 2006). Where appropriate, health hazard information for these two chemicals has been included in this report, as hydrolysis of the chemical is expected to occur in biological systems.

Toxicokinetics

Studies show that the chemical is converted into two main hydrolysis products, morpholine and formaldehyde, in water and upon contact with biological tissues. Distribution of these compounds depends on the route of exposure, which is critical for toxicity considerations.

In an in vitro percutaneous absorption study following OECD Test Guideline (TG) 428, human skin samples were exposed for eight hours to four different preparations of labelled chemical in aqueous solutions, at the following concentrations (CAR, 2014; CLH, 2014):

- test preparation 1: 3 % for a mixture of radiolabelled chemical containing (a) ^{14}C-labelled methylene group and (b) ^{14}C-labelled morpholine (detecting formaldehyde, morpholine and parent chemical);
- test preparation 2: 0.15 % for a mixture of radiolabelled chemical containing (a) ^{14}C-labelled methylene group and (b) ^{14}C-labelled morpholine (detecting formaldehyde, morpholine and parent chemical);
- test preparation 3: 0.15% of the chemical solely labelled at the methylene group (detecting formaldehyde and parent chemical); and
- test preparation 4: 0.15% of the chemical solely labelled with ^{14}C-morpholine (detecting parent chemical and morpholine).

Twenty-four hours after application, the dermal absorption (percentage of the dose detected in exposed skin + receptor fluid and rinse) was 43, 21, 12 and 20 % of the applied dose for test preparations 1, 2, 3 and 4, respectively (CAR, 2014). Test preparation 2 had a higher amount of unabsorbed radioactivity (17 % detected in stratum corneum) than test preparation 1 (5 % detected in stratum corneum), which was interpretated as possible dose-dependent hydrolysis of the chemical. (CAR, 2014). Test preparation 3 had the highest amount detected in stratum corneum (23 %) and lowest amount detected in the receptor fluid (4 %), consistent with the retention of formaldehyde in the outer layers of the skin (CAR , 2014). In test preparation 4, dermal absorption (20 %) was comparable to that of test preparation 2 (21 %), with a slightly lower amount retained in the stratum corneum (13 % compared to 17 %) and slightly higher amount in the receptor fluid (15 % compared to 11 %), consistent with a better absorption of morpholine compared to formaldehyde (CAR, 2014). Based on this study, the following relative absorption amounts corrected for recovery were (CLH, 2014): 70 % and 60 % for the parent chemical at a concentration of 3 % and 0.15 % respectively, and 50 % for morpholine at a concentration of 0.15 % for the parent chemical (CLH, 2014).

Groups of 12 Wistar rats (n = 6/sex) were dosed with 2.5 mg/kg bw radiolabelled chemical by single intratracheal instillation in two separate experiments (morpholine-labelled in the first experiment and methylene-labelled in the second). The first experiment showed that the parent chemical and morpholine were rapidly absorbed with a maximum concentration (C_{max}) being reached after two hours. Blood half-life of these chemicals was five hours. Approximately 100 % of the detected dose (as parent chemical, morpholine and morpholine metabolites) was excreted in the urine within seven days. The second experiment showed that 60 % of the detected dose was expired as formaldehyde and carbon dioxide (CO_2) within seven days. About 25 % of the dose as the parent chemical, formaldehyde and formaldehyde metabolites was excreted in the urine, 5 % in the faeces and 10 % remained in the carcass. Unlike the first experiment, blood levels of these compounds declined slowly (half-life of 29 h) (CLH,

2014). This study showed that the chemical was readily converted into morpholine, which was absorbed into the body and excreted mostly in the urine, and formaldehyde, mostly expired into air (CLH, 2014).

Acute Toxicity

Oral

The chemical has moderate acute toxicity following oral exposure, warranting hazard classification. The median lethal dose (LD50) in rats is between 500 and 2000 mg/kg bw.

In an acute toxicity study compliant with OECD TG 423, Sprague Dawley (SD) rats (n = 3/sex/group) were administered the chemical by gavage at doses of 200, 500 or 2000 mg/kg bw. The chemical was undiluted for mid and high doses, and diluted at 2 % in aqueous solution for the low dose. The median lethal dose (LD50) was between 500 (one rat died) and 2000 mg/kg bw (all rats died). Reported signs of toxicity include hunched posture, lethargy, ataxia, ptosis (drooping of the upper eyelid), piloerection, prostration, decreased respiratory rate, noisy respiration and tiptoe-gait. No effects were seen at the low dose, and in females at the mid dose. Animals that died showed 'varying degrees' of mucosal lesions in the gastrointestinal tract (GIT) (CAR, 2014), possibly due to corrosive properties of the chemical (see **Corrosion/Irritation** section).

Dermal

No data are available on the chemical. Based on the available data on hydrolysis products and toxicokinetic considerations, the chemical is expected to have moderate acute toxicity following dermal exposure, warranting hazard classification.

The toxicokinetic data indicated that the parent chemical and hydrolysis product (morpholine) are expected to be absorbed; whereas formaldehyde is expected to have limited dermal absorption, reacting preferentially with outer layers of the skin (CLH, 2014; RAC, 2015). Dermal exposure to the chemical is expected to generate similar systemic toxicity as morpholine, while formaldehyde release would mostly cause local effects (corrosion).

Based on molar read across from the total releasable amount of morpholine (factor 1.06), the chemical is predicted to have a comparable dermal toxicity as morpholine, qualifying for dermal acute toxicity (RAC, 2015). Morpholine is classified as hazardous, with hazard category and hazard statement, "Acute toxicity – category 4; H312 (Harmful in contact with skin)" in the HCIS (Safe Work Australia).

Inhalation

No data are available on the chemical. Based on the available data on hydrolysis products and toxicokinetic considerations, the chemical is expected to have moderate acute toxicity following inhalation exposure, warranting hazard classification.

Toxicokinetic data indicated that the chemical is likely to be converted into formaldehyde and morpholine upon contact with mucosa following inhalation exposure. Formaldehyde is the main driver for inhalation toxicity. Based on a four hour inhalation median lethal concentration (LC50) of 0.6 mg/L for formaldehyde and molar read across from the total releasable amount of formaldehyde (16%), an LC50 (4h) of 4 mg/L is predicted for the chemical (CLH, 2014; RAC, 2015). Formaldehyde is classified as hazardous, with hazard category and hazard statement, "Acute toxicity – category 2; H330 (Fatal if inhaled)" in the HCIS (Safe Work Australia).

Corrosion / Irritation

Corrosivity

Based on the available data, the chemical is corrosive to the skin and eyes, warranting hazard classification.

In a study following OECD TG 404, the chemical (undiluted) was applied on the skin of three New Zealand White (NZW) rabbits for four hours under occlusive patches. One hour after removing the patches, moderate to severe erythema, described by 'hardened dark brown/black coloured scab, scab ondulating, or sunken hardened brown/black-coloured scab resembling a crater' was observed (score: 3) in three rabbits, and progressed into severe erythema in one rabbit within 24 hours. Severe oedema (score: 4) was observed in all three rabbits after one hour. The effects were not reversible and the rabbits were euthanised after nine days (CAR, 2014).

Sensitisation

Respiratory Sensitisation

No data are available on the chemical. Formaldehyde is not classified as a respiratory sensitiser, nor is it likely to be volatile when present at low concentration in aqueous solutions in products containing the chemical.

Skin Sensitisation

Based on the available data, the chemical is expected to cause skin sensitisation, warranting hazard classification. While the experimental data on the chemical were inconclusive, the hydrolysis of the chemical into formaldehyde, a well-known skin sensitiser, must be considered (CLH, 2014; RAC, 2015).

In a guinea pig maximisation test (GPMT) conducted according to OECD TG 406, groups of female Dunkin/Hartley guinea pigs (n = 20/group, 10 for control group) were administered with solutions of the chemical in Alembicol D. The following concentrations were used:

a) for induction:

- intradermal injection on day 0 at 0.1 % (v/v);
- topical application on day 7 at 10 % (v/v) for 48 hours; and

b) for challenge on day 21: topical applications of 5 % (v/v) and 1 % (v/v) for 24 hours.

Three animals (3/20) challenged with 5 % presented with slight erythema within 24 hours post-exposure (CAR, 2014). No effects were seen at 1 % challenge. The chemical did not show any sensitising properties. However, this study was considered as inconclusive because of the low doses used for induction. While the intradermal induction at 0.1 % induced slight irritation (in 16/20 animals) to well-defined irritation (in 4/20 animals), a higher concentration of 10 % induced no skin irritation (CLH, 2014; RAC, 2015).

Formaldehyde is classified as hazardous, with hazard category and hazard statement 'Skin sensitisation – category 1; H317 (May cause an allergic skin reaction)' in the HCIS (Safe Work Australia).

Observation in humans

Metal workers (n=144) exposed to metal working fluids (MWF) containing formaldehyde releasers were patch tested using 1% 4,4'-methylenebismorpholine in petrolatum. Seven patients (4.9 %) had a positive reaction to the chemical, including two patients that also reacted to formaldehyde (De Groot et al., 2010).

In another study, 1166 patients with suspected occupational dermatitis were investigated for reaction to formaldehyde and formaldehyde releseasers. A total of 81 patients showed positive reactions to formaldehyde, of which eight patients were tested with 4,4'-methylenebismorpholine and five (83 %) had a positive response to this chemical. One patient showed positive reaction to the chemical 'without clear formaldehyde allergy'. Overall, allergic reactions were assumed to be caused by formaldehyde release (Aalto-Korte et al., 2008).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not expected to cause systemic toxicity following repeated oral exposure. Local signs of toxicity, likely related to the corrosive properties of the chemical, were seen in the GIT and the upper respiratory tract at doses ≥50 mg/kg bw/day.

In a subchronic toxicity study following OECD TG 408, groups of SD rats (n = 10/sex/dose) were administered the chemical by gavage at doses of 0, 5, 15, 50 or 250 mg/kg bw/day for 90 days. The highest dose was reduced to 150 mg/kg bw/day from week 10 onwards. No treatment-related effects were observed up to 15 mg/kg bw/day throughout the study. Clinical signs of toxicity were observed at doses ≥50 mg/kg bw/day, including noisy respiration, increased salivation, hunched posture and general deterioration of physical condition in animals that subsequently died (tiptoe gait, emaciation, vocalisation and distended abdomen). Mortality was reported in the 50 mg/kg bw/day group (one male) and in the highest dose group (4/10 males and 6/10 females). Local signs of irritation were seen at doses ≥50 mg/kg bw/day in male and females rats, including acanthosis, hyperkeratosis and inflammation in the forestomach. At the highest dose, a statistically significant decrease in plasma glucose and an increase in inorganic phosphorus in males were seen. Males had slight, but statistically significant, increased urine volume. Histopathological lesions in the GIT and respiratory tract were observed at doses ≥50 mg/kg bw/day, consistent with the corrosive properties of the chemical. A lowest observed adverse effect level (LOAEL) of 50 mg/kg bw/day and a no observed adverse effect level (NOAEL) of 15 mg/kg bw/day were determined (CAR, 2014).

Based on the results from the above study, the European Chemicals Agency's (ECHA) Committee for Risk Assessment (RAC) proposed that the chemical should be classified for Specific Target Organ Toxicity–Repeated Exposure (STOT RE – category 2) with the rationale that 'local effects in the gastrointestinal tract (such as chronic oesophagitis, gastritis) after repeated/prolonged exposure are toxicogically relevant as they impair not only the morphology and/or function of the locally targeted organ, but also bear the potential to impair adherent tissues/organs by transmural extension of the chronic inflammation (e.g. peritonitis, pleuritis) or to cause delayed mortalities (after ulceration into body cavities)' (RAC, 2015).

Neither formaldehyde nor morpholine are classified for repeat dose toxicity. The effects seen following repeated exposure were attributed to their corrosive properties (NICNAS, 2006; NICNAS, 2015).

Dermal

No data are available on the chemical. Based on the read across from available data on morpholine (NICNAS, 2015) and formaldehyde (NICNAS, 2006), the chemical is not expected to have systemic toxicity following repeated dermal exposure.

Only limited information is available on morpholine. In a subacute toxicity study, seven albino rabbits were exposed by topical applications of morpholine at 900 mg/kg bw/day for 30 days. All rabbits died after the tenth application. Signs of toxicity included necrosis of the treated skin, inflammation and congestion of the underlying organs, and microscopic lesions of the liver and effects on kidneys and spleen (details not provided) (NICNAS, 2015).

Inhalation

No data are available on the chemical. Based on the read across from available data on morpholine and formaldehyde and toxicokinetic considerations, the chemical is not expected to cause systemic toxicity following repeated inhalation exposure. Local effects related to the corrosivity of the chemical may be observed, as in the case for formaldehyde.

Genotoxicity

Based on the available data, the chemical is not considered to be genotoxic. Positive results from three in vitro studies indicated clastogenic activity, but two in vivo studies gave negative results.

In vitro

- In a bacterial gene mutation test following OECD TG 471, the chemical was tested at concentrations up to 5000 µg/plate in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2uvrA-. There was a slight but significant increase in the number of revertant colonies in TA100, at 500 µg/plate with and without metabolic activation, in a first experiment; and at 300 µg/plate with metabolic activation only, in a second experiment (CAR, 2014; CLH, 2014).

- In a chromosome aberration test following OECD TG 473, the chemical was tested on Chinese hamster lung (CHL) cells at concentrations up to 120 µg/mL and 60 µg/mL with and without metabolic activation, respectively. Dose-dependent and statistically significant clastogenic activity was observed at concentrations ≥ 60 µg/mL with metabolic activation and ≥ 30 µg/mL without metabolic activation (CAR, 2014; CLH, 2014).

- In a mammalian cell gene mutation assay (OECD TG 476), the chemical was tested in mouse lymphoma L5178Y cells at concentrations up to 60 µg/mL. A dose-dependent and statistically significant increase in mutant frequency was observed at concentrations ≥ 30 µg/mL, with and without metabolic activation (CAR, 2014; CLH, 2014).

In vivo

- In a micronucleus test following OECD TG 474, the chemical was administered to male Crl:CD1 mice at single oral doses of 0, 250, 500 or 1000 mg/kg bw. No increases in the number of micronucleated erythrocytes were seen in any treated groups. Cytotoxic effects were seen at the highest dose (CAR, 2014; CLH, 2014).

- In an unscheduled DNA synthesis (UDS) test following OECD TG 486, the chemical, when administered in single oral doses of 0, 300 or 900 mg/kg bw to SD male rats, gave negative results. Clinical signs of toxicity were reported at the highest dose (CAR, 2014; CLH, 2014).

Formaldehyde is genotoxic in vitro, and weakly genotoxic at the site of contact in vivo (NICNAS, 2002). This may explain the positive results observed for the chemical in vitro and the negative results in vivo.

Carcinogenicity

No data are available on the chemical. Based on the read across from available data on formaldehyde and morpholine, and considering toxicokinetics, the chemical is not expected to be carcinogenic.

In toxicokinetic studies (see **Toxicokinetics** section), hydrolysis of the chemical has been demonstrated to occur via dermal and inhalation routes.

In a combined chronic/carcinogenicity study, rats showed no carcinogenic effects following exposure to morpholine by inhalation route (NICNAS, 2015). Formaldehyde is classified for Carcinogenicity category 1B based on nasal tumours observed in rats and humans following inhalation (RAC, 2012; RAC; 2015). Formaldehyde being the main driver for toxicity, the chemical has the potential to exert similar effects at sites of contact, as the reported maximum releasable amount of formaldehyde is 16 % (CLH, 2014; RAC, 2015). It is important to note, however, that formaldehyde is not likely to be volatile from the low concentration aqueous solutions present in metalworking fluids. Therefore, there are no carcinogenicity concerns relating to these products. During formulation of the products, formaldehyde gas may be present.

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not expected to cause reproductive or developmental toxicity. Toxicokinetic considerations support this conclusion, as formaldehyde (NICNAS, 2006) and morpholine (NICNAS, 2015) are not considered harmful to the reproduction and development.

In a prenatal developmental toxicity study following OECD TG 414, groups of pregnant female NZW rabbits (n = 22/dose) were orally administered the chemical at doses of 0, 10, 30 or 100 mg/kg bw/day during gestation days (GD) 6–28. All treated and control animals had white spots and haemorraghes in the stomach, possibly due to the gavage tube. At 100 and 30 mg/kg bw/day, stomach lesions were significantly increased, with erosion and granula aspect of the stomach, indicating corrosive effects of the chemical. Reproductive parameters (number of corpora lutea, implantation sites, pre and post implantation loss, number of early resorptions, number of live and dead foetuses, sex ratio) were not altered by treatment. However, at the highest dose, the gravid uterus weight was significantly lower compared to controls. Body weight gain and food consumption had also significantly decreased at 100 mg/kg bw/day. A LOAEL of 30 mg/kg bw/day and a NOAEL of 10 mg/kg bw/day for maternal

toxicity were determined in this study. Statistically significant delayed ossification was observed at all doses but was not dose-dependent. This effect was secondary to stomach effects and, therefore, considered as incidental and not treatment-related. A NOAEL of 100 mg/kg bw/day for teratogenicity was determined in this study (CAR, 2014).

Risk Characterisation

Critical Health Effects

In general, the critical health hazards relate to the hydrolysis products of the chemical, formaldehyde and morpholine.

The critical health effects for risk characterisation include:

- systemic acute effects (acute toxicity from oral, dermal and inhalation exposure); and
- local effects (corrosivity, skin sensitisation).

Public Risk Characterisation

Given the uses and volumes identified for the chemical in Australia, it is unlikely that the public will be exposed. Formaldehyde is not likely to be volatile considering the low concentrations of the chemical used in metalworking fluids. Therefore there are no carcinogenicity concerns relating to the chemical contained in these products.

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and inhalation exposure to the chemical may 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. Moreover, where the chemical is handled in a pure or highly concentrated form during formulation, formaldehyde and morpholine could be released.

Given the critical systemic acute and local health effects, and the potential release of formaldehyde, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, ocular and inhalation exposure are implemented. Epidemiological data showed that metalworking fluids were the most common source of skin sensitisation to formaldehyde (Aalto-Korte et al., 2008).

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. Appropriate risk management measures for formaldehyde should be applied in these cases.

The data available support an amendment to the hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

At present, the chemical falls within the scope of formaldehyde listing in Schedules 2, 6 and 10 of the SUSMP. Products containing the chemical 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]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312) Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Not Applicable	Causes severe skin burns and eye damage - Cat. 1B (H314)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (H317)

[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, 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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