2-Propenamide, N-(hydroxymethyl)-: Human health tier II assessment

01 July 2016

CAS Number: 924-42-5

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.

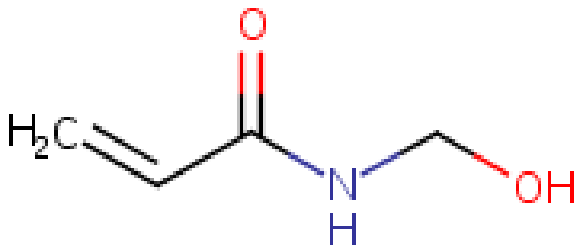
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	N-(hydroxymethyl)-2-propenamide N-(hydroxymethyl)acrylamide N-methylolacrylamide NMA
Structural Formula	
Molecular Formula	C4H7NO2
Molecular Weight (g/mol)	101.10
Appearance and Odour (where available)	White crystalline solid, slight formaldehyde odour.
SMILES	C(=O)(C=C)NCO

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 site-limited use in Australia in the manufacture of process regulators.

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 Organisation for Economic Co-operation and Development (OECD) High Production Volume chemical program list (OECD HPV); the US National Library of Medicine Hazardous Substances Data Bank (HSDB); the US Environmental Protection Agency Aggregated Computer Toxicology Resource (ACToR); the US Environmental Protection Agency Chemical and Product Categories (CPCat) database; and the US Food and Drug Administration (US FDA, 2015) - List of Indirect Additives Used in Food Contact Substances.

The chemical has reported domestic uses, including as a component in:

- paints, lacquers and varnishes; and
- household adhesives and sealants.

The chemical has reported commercial uses, including as a:

- component of adhesives, binders, surface-coatings and resins used in construction;
- component of food contact substances such as adhesives, coatings, paper and cardboard components; and
- durable-press agent (textiles).

The chemical has reported site-limited uses, including:

- in the manufacture of adhesives, surface coatings and binders;
- as an intermediate in the manufacture of chemicals such as polymers;
- in the manufacture of fabric, textiles and leather;
- in the manufacture of pulp and paper;
- in the manufacture of process regulators; and
- in the manufacture of lubricants and other additives.

Restrictions

Australian

There are no restrictions specific to this chemical in Australia; however, the chemical is a known formaldehyde donor.

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

- 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 labelled with 'Poison' and are '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'.

- 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, other than those included in Schedule 9, of such danger to health as to warrant prohibition of sale, supply and use'.

Formaldehyde donors are mentioned in the definition of free formaldehyde in Part I of the *Poisons Standard* (SUSMP) as follows:

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

International

The chemical is regulated for use as a component of food contact substances under the US FDA - List of Indirect Additives Used in Food Contact Substances (US FDA, 2015) with the following limitations:

- resin-bonded filters used in producing, manufacturing, processing and preparing food: the finished copolymers contained in the resins shall contain no more than 2 % w/w of total polymer units derived from the chemical; and
- plastic articles intended for single-use food contact: the polymers used in these plastics must not contain more than 5 % w/w of total polymer units derived from the chemical.

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available for the chemical.

International

No specific exposure standards are available for the chemical.

Health Hazard Information

The chemical N-methylolacrylamide (NMA) (CAS No. 924-42-5) is an α,β–unsaturated carbonyl compound, containing a highly reactive functional group and common structural alert for several toxicological endpoints. The chemical is also a known formaldehyde donor, as the chemical is unstable in dilute aqueous solutions at neutral pH (US EPA, 2002), and can hydrolyse to generate acrylamide and formalin (the aqueous form of formaldehyde)—both critical drivers for toxicity. The toxicology of formaldehyde (CAS No. 50-00-0) and acrylamide (CAS No. 79-06-1) have previously been assessed by NICNAS, and have been considered in this assessment (NICNAS, 2002; NICNAS, 2006). Where appropriate, data for these chemicals are read across to fill data gaps in the assessment, as hydrolysis of the chemical NMA can occur in biological systems to generate both compounds.

Toxicokinetics

There are limited data available; however, the chemical is expected to have a similar toxicokinetic profile to the hydrolysis product, acrylamide.

Based on excretion data, NMA is well absorbed following oral administration, with 66–77 % of the chemical excreted in urine and CO_2 within 72 hours, and only 9 % recovered in faeces (REACH). The chemical is expected to have a similar dermal and inhalation absorption profile to acrylamide, which is systemically available via the dermal and inhalation routes in animal and human studies (NICNAS, 2002).

Once absorbed, NMA is widely distributed throughout the body, with most radioactivity detected in the blood in radiolabelling studies. Lower levels of radioactivity were detected in the liver, testes and other tissues. However, the available radiolabelling studies with NMA were carried out with the radioactive carbon on the methylol group (Witt et al., 2003; REACH), which can be cleaved under physiological conditions. The reported distribution patterns may not fully account for the remainder of the molecule, acrylamide, which can bind to RNA, DNA and proteins such as haemoglobin (Hb) (NICNAS, 2002). Intense and delayed uptake of acrylamide over a nine-day period in the male reproductive tract was demonstrated in a whole-body radiography study following oral administration of acrylamide to mice. This effect was particularly prominent compared with the uptake observed in other organs (Marlowe et al., 1986).

The major urinary metabolite (10–45 %) of NMA was identified as mercapturic acid derived from direct conjugation of NMA with glutathione and subsequent metabolism (Witt et al., 2003; REACH). About 10 % of the administered dose was recovered in the urine, unchanged (Witt et al., 2003). The

chemical possesses an activated carbon-carbon double bond that can undergo addition reactions with amino and thiol groups on proteins and nucleosides to form stable, protein-bound adducts. These are primarily found in the blood as Hb adducts. Only acrylamide-Hb adducts have been detected following NMA administration, suggesting that the release of formaldehyde occurs either prior to, or following adduct formation. This is thought to be due to chemical processes at physiological pH without the involvement of metabolism (Fennell et al., 2013). Acrylamide can also be oxidised via metabolic processes to the reactive epoxide species, glycamide. Low levels of acrylamide metabolites (including glycamide adducts) have been detected following NMA administration (Fennell et al., 2013).

The chemical is excreted primarily in the urine and faeces (68–77 %), with a small amount (10 %) in expired air as CO_2. The large percentages of chemical recovered collectively from urine and breath indicate that bioaccumulation is low, with less than 5 % of the dose remaining in tissues sampled 72 hours after dosing (REACH).

Acute Toxicity

Oral

The chemical has moderate acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) in rats is 400–474 mg/kg bodyweight (bw), and 400–677 mg/kg bw in mice. Observed sub-lethal effects included ataxia, muscle tremors and hyperirritability (NTP, 1989; US EPA, 2002).

Dermal

The chemical has low acute toxicity based on results from animal tests following dermal exposure. The lowest dermal lethal dose (LDLo) published is >16000 mg/kg bw in rabbits. Observed sub-lethal effects included tremors and hind leg impairment. Irritant effects were also observed (US EPA, 2002).

Inhalation

Limited data are available for the chemical. No mortalities or clinical effects were observed when mice, rats or guinea pigs were exposed to a nearly saturated atmosphere of the chemical, with a no observed adverse effect level (NOAEL) for each species determined as 39 mg/m^3 (equivalent to >9.4 ppm) (US EPA, 2002).

Corrosion / Irritation

Respiratory Irritation

There are no data available for the chemical. Based on the potential for formaldehyde—a known respiratory irritant (NICNAS, 2002)—to be released upon contact with mucous membranes, there is a potential for irritation of the respiratory system following inhalation of NMA, warranting hazard classification (see **Recommendation** section). There is also some evidence that respiratory irritation can occur in occupational settings (see **Observation in humans** section).

Skin Irritation

The limited data available from animal and human studies indicate that there is potential for skin irritation upon dermal exposure to the chemical, warranting hazard classification. The chemical was reported to induce irritating effects in a single acute dermal toxicity assay, although the study was not well-reported and the observed effects occurred at high doses. These effects may be due to the release of formaldehyde—a known skin irritant (NICNAS, 2006)—which is expected to occur in aqueous solutions of the chemical. Acrylamide is also irritating to the skin (NICNAS, 2002). Skin irritation was also observed following occupational exposure to NMA (see **Observation in humans** section).

In a non-guideline acute dermal toxicity study, the chemical was applied as an aqueous paste under occlusive conditions in single doses at 2000, 4000, 8000 or 16000 mg/kg bw. Following a 24-hour exposure period, the patch and excess remaining chemical on the skin were removed. The skin was observed for five days following dose administration. Evidence of skin irritation, including erythema, oedema and desquamation, was observed at all dose levels, with caustic burns observed at the highest dose (16000 mg/kg bw). The chemical was concluded to be moderately irritating. No details on the reversibility of effects were reported, nor were individual irritation scores (US EPA, 2002).

The similar chemical, acrylamide, is classified as a skin irritant; however, the results in animal studies have been mixed. In a dermal irritation study carried out according to OECD Test Guideline (TG) 404, acrylamide (0.5 g) was moistened with water and applied to the shaved, intact skin of three New Zealand White rabbits under semi-occlusive conditions for four hours. The chemical was reported to be non-irritating, with no erythema or oedema at any of the time points (24, 48 and 72 hours post-application). In a similar study carried out according to the same guidelines, there were no signs of skin irritation using 0.5 mL 50 % aqueous acrylamide (EU RAR, 2002). Despite the lack of demonstrable skin irritation in these well-conducted studies, a number of non-guideline dermal studies in rabbits have demonstrated slight to moderate irritation following applications of 12.5–51 % aqueous

acrylamide under semi-occlusive and occlusive conditions. These are also supported by many case reports and workplace surveys that have demonstrated skin effects attributable to aqueous solutions of acrylamide in occupational settings (EU RAR, 2002; NICNAS, 2002).

Eye Irritation

Based on the limited animal data available, the chemical is not expected to cause serious damage to the eyes. However, the chemical may release low levels of formaldehyde and acrylamide—both known eye irritants (NICNAS, 2002; NICNAS, 2006)—upon contact with mucous membranes, warranting hazard classification (see **Recommendation** section). In addition, incidences of eye irritation have been reported following occupational exposure to the chemical (see **Observation in humans** section).

In a non-guideline study, the pure compound (3 mg) was administered to one eye of three rabbits. The eyes remained unwashed, and were observed over a five-day period. Mild irritation was noted immediately following application; however, this was reversed after one hour. No further details were reported (US EPA, 2002).

Observation in humans

Out of 210 tunnel workers in Sweden who were repeatedly exposed to NMA and acrylamide during tunnel construction over a two-month period, 38 workers who were identified as having higher exposure levels to the chemical experienced significant irritation of the skin, eyes and respiratory tract during grouting operations. Signs included peeling of the skin, coughing and wheezing. The respiratory tract signs were reported to be acute in nature and disappeared after the end of the workday (Hagmar et al., 2001).

Skin, eye and respiratory irritation was observed in a case study involving 24 tunnel workers exposed to NMA- and acrylamide-containing grout in Norway. A number of subjects (35 %) experienced peeling of the skin during tunnel work. Symptoms persisted for four months following exposure. Other local effects such as eczema, skin irritation and symptoms in the upper airways that developed during grouting operations were all significantly reduced 16 months after exposure compared to an initial examination after cessation of grouting activities. However, the investigators expressed some uncertainty with regards to whether additional industrial chemicals were responsible for the observed local effects (NIOH, 2002).

Sensitisation

Skin Sensitisation

The available information supports the classification of NMA as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in the HSIS (Safe Work Australia) (see **Recommendation** section). The chemical is considered to be a weak to moderate skin sensitiser, based on the limited animal and human studies available (see **Observation in humans** section). The chemical may also release formaldehyde and acrylamide—both of which are known skin sensitisers (NICNAS, 2002; NICNAS, 2006).

In a non-guideline adjuvant study, animals were injected intradermally with 0.1 mL of Freund's complete adjuvant. This was followed by topical administration of a 0.5 M (5 %) solution of NMA in petrolatum under occlusive conditions during the induction phase, with a 0.1 M (1 %) open epicutaneous challenge dose in methyl ethyl ketone/peanut oil (ratio 2:1). Following a two-week rest period, the first challenge dose resulted in positive reactions in 1/8 animals (13 %), with 4/8 animals (50 %) showing a positive reaction following a second challenge dose (Waegemaekers, 1985).

Observation in humans

There are limited human data available for the chemical NMA. A single study was carried out on patients presenting at dermatology clinics with dermatitis following repeated occupational exposure to grouts and tunnel-water containing a mixture of NMA and acrylamide. Out of 210 Swedish tunnel workers exposed over a two-month period, 24 subjects presented to dermatology clinics with contact dermatitis. A series of contact allergy tests were carried out, including against a specific series of 50 compounds relevant to the occupational setting (including acrylates, isocyanates and compounds present in grouting agents, protective gloves and soaps). One subject patch-tested positive to the chemical NMA, but not formaldehyde (Hagmar et al., 2001).

Repeated Dose Toxicity

Oral

Based on the available animal studies, the chemical is considered to cause serious damage to health (neurotoxicity) from repeated oral exposure, warranting hazard classification (see **Recommendation** section).

In a 16-day study, the chemical was administered to rats and mice at doses of 0, 25, 50, 100, 200 or 400 mg/kg bw/day. Mortality was observed in the 200 mg/kg bw/day (3/5 males) and 400 mg/kg bw/day (all animals) groups. Non-lethal, treatment-related clinical signs in the 100 and 200 mg/kg bw/day groups included ataxia, muscle tremors, hyperirritability and decreased bodyweights. Compound-related lesions in rats included bronchiolar and tracheal

epithelial hyperplasia, nasal and tracheal epithelial dysplasia, centrilobular hepatocellular necrosis, lymphoid depletion of the spleen and myelin degeneration of the lumbar ventral spinal nerve (NTP, 1989).

In a non-guideline, seven-week study, the chemical was administered to rats in the diet at a concentration of 1800 ppm (equivalent to 27 mg/kg bw/day) for one week, followed by 900 ppm (equivalent to 18.6 mg/kg bw/day) for four weeks, producing slight ataxia after five weeks. Along with continued dosing in the diet (at 900 ppm) for two additional weeks, four intraperitoneal (i.p.) doses of the chemical (at 50 mg/kg bw/dose) were also administered. The severity of the ataxia had increased by the end of the seven-week mark of the study. The observed neuropathy was slowly reversed after the rats were returned to a normal diet (Edwards, 1975).

In a 13-week oral gavage study in rats, doses of 0, 12.5, 25, 50, 100 or 200 mg/kg bw/day were administered to animals. Lowest observed adverse effect levels (LOAELs) of 25 mg/kg bw/day for females, and 12.5 mg/kg bw/day for males were determined based on neurotoxic effects and a decrease in testes weights, respectively. Toxic effects observed at this dose and higher (25–200 mg/kg bw/day) included degeneration of peripheral nerves and decreased bodyweight (NTP, 1989; REACH).

Dermal

No data are available for the chemical. The chemical is expected to be readily absorbed by the skin and systemically available in a similar manner to acrylamide (NICNAS, 2002). While the chemical has low acute toxicity via the dermal route in rats (LD50 >16000 mg/kg bw), the sub-lethal treatment-related effects in these studies indicate that there may be some concerns for adverse health effects (such as neurotoxicity) from repeated exposure, warranting hazard classification. This is supported by evidence of harmful health effects in humans following occupational exposure to the chemical through the skin (see **Observation in humans** and **Neurotoxicity** sections).

Inhalation

No data are available for the chemical or the hydrolysis product, acrylamide. While the chemical is reported to have low vapour pressure, inhalation exposure to aerosols or mists containing the chemical could result in systemic availability of the chemical.

Observation in humans

There are several case studies in which adverse health effects were reported for workers exposed to the chemical when used as the major component of grouting agents (typically in mixtures with acrylamide). The grouting agents containing NMA have been mentioned previously in a Priority Existing Chemical report for acrylamide, with concerns raised for occupational health (NICNAS, 2002). Dermal exposure occurred during and after the grouting process, as well when workers came into contact with water containing leached NMA and acrylamide. Exposure also occurred, to a lesser extent, via inhalation. Quantification of exposure was carried out by measuring levels of Hb adducts that form in the blood in the presence of NMA and acrylamide (Hagmar et al., 2001).

Blood samples were collected from 210 tunnel construction workers in Sweden who were potentially exposed to NMA and acrylamide for two months from grouting agents, as well as from drainage water containing both chemicals. Elevated levels of acrylamide-Hb adducts (which are formed following both NMA and acrylamide exposure) were found in 163/210 subjects one week following exposure; however, these were not adjusted for levels of acrylamide-Hb adducts that can be attributed to smoking or alcohol consumption. Repeated sampling from five workers during the five months following exposure showed a decrease in the adduct levels that was compatible with the 120-day life span of human erythrocytes. There were obvious and significant dose-response associations between Hb adduct levels and the prevalence of peripheral nervous system (PNS) symptoms (tingling, pain and numbness in hands/feet), irritation of the skin, eyes and respiratory tract, and symptoms of general discomfort such as headache, nausea and dizziness. Out of all the subjects who reported PNS symptoms, all but two workers had recovered 18 months after cessation of exposure (Hagmar et al., 2001).

In another occupational exposure incident, 73 tunnel workers in Norway were examined following exposure to grout containing NMA and acrylamide during injection operations. Slight effects on the PNS, the visual system, local effects and possible genotoxic effects were reported (NIOH, 2002).

Genotoxicity

Based on the information available from animal studies, the chemical has genotoxic potential, warranting hazard classification as a Category 2 mutagen with the risk phrase "May cause heritable genetic damage" (T; R46).

The chemical did not induce gene mutations in any tested strains of *Salmonella typhimurium*. In single studies with Chinese hamster ovary (CHO) cells in vitro, NMA induced chromosomal aberrations and sister chromatid exchanges. Micronuclei were not observed in bone marrow cells of mice exposed to NMA in vivo by single and subchronic i.p. injections; however, the chemical induced dominant lethal mutations in male germ cells upon repeated oral exposure. Similar effects have been observed with acrylamide (NICNAS, 2002).

In vitro

In a bacterial reverse mutation assay, the chemical was tested for point mutations in *S. typhimurium* strains TA 1535, TA 97, TA 98 and TA 100 at test concentrations of 0, 100, 333, 1000, 3333 and 10000 µg/plate. No increase in the number of histidine revertants was observed at any dose concentration tested (NTP, 1989; REACH).

In an in vitro mammalian chromosome aberration test using CHO cells at test concentrations of 0, 250, 375, 438, 500, 2500, 3750 or 5000 µg/mL, the chemical caused a dose-related increase in chromosomal aberrations both with and without metabolic activation (NTP, 1989; REACH).

When tested for cytogenic effects in cultured CHO cells, NMA induced dose-related increases in sister chromatid exchanges at all doses tested (17, 50, 125, 167, 250, 500 and 1700 µg/mL) compared to controls, with and without metabolic activation (NTP, 1989).

In vivo

In several mouse micronucleus tests using different routes of acute exposure and vehicles, mice were administered two daily doses of NMA—either via i.p. injections (at 0, 37.5, 75 or 112/150 mg/kg bw/day in phosphate-buffered saline (PBS) or corn oil) or via oral gavage (at 0, 37.5, 75 or 112/150 mg/kg bw/day in PBS). No significant increases in the frequencies of micronucleated polychromatic erythrocytes were observed following administration by either route of exposure.

In two additional studies, mice were administered doses of NMA via oral gavage for 31 days (at 0, 42, 84 or 168 mg/kg bw/day in water) or in the drinking water for 13 weeks (at total administered doses of 0, 37, 68, 90–95 or 120–125 mg/kg bw/day). No significant increases in the frequencies of micronucleated polychromatic erythrocytes or normochromatic erythrocytes were observed in the bone marrow or peripheral blood, respectively, of treated mice compared with controls (Witt et al., 2003).

In a dominant lethal assay, the chemical was administered by i.p. injection using either a single bolus dose (at 150 mg/kg bw) or a series of five single daily i.p. injections (at 50 mg/kg bw/day) to male mice before mating with untreated females a few hours after the final injection. No dominant lethal effects were observed in these acute i.p. studies. However, a dose-related increase in dominant lethal effects was observed in a 13-week drinking water study, with NMA concentration levels of 0, 180, 360, 540 and 720 ppm (equivalent to 0, 37, 68, 90–95 and 120–125 mg/kg bw/day) administered to male mice prior to three separate mating intervals with untreated females. The germ cell effects appeared to plateau after eight weeks of treatment at the three highest dose levels. It was concluded that total dose, which correlates with exposure duration, may be a key factor in the observed mutagenicity of NMA (Witt et al., 2003).

The chemical induced dominant lethal mutations in a 27-week continuous breeding study, in which NMA was administered to male mice before, during and following a mating period with untreated females, at 0, 60, 180 or 360 ppm in drinking water (equivalent to 0, 13, 37 and 68 mg/kg bw/day). A dose-related increase in early resorptions was observed at all dose levels, which was attributed to dominant lethal effect in males. Based on the timing associated with mouse spermatogenesis and epididymal transit, it was postulated that the dominant lethality was mediated by an effect of NMA on late testicular or epididymal germ cells (Chapin et al., 1995).

Observation in humans

In an occupational exposure study in Norway, where 73 tunnel workers had been exposed to NMA/acrylamide during grouting operations, no significant differences between the 25 exposed subjects and control subjects for chromosome aberrations or breaks were detected; however, a significant increase in chromatid gaps was observed in the exposed subjects. The highest numbers of chromatid gaps were observed in workers who had reduced enzymatic capacity for acrylamide detoxification (NIOH, 2002; Kjuus et al., 2005).

Carcinogenicity

The limited data available from animal studies indicate that the chemical has carcinogenic potential, warranting hazard classification as a Category 3 carcinogenic substance with the risk phrase ‘Limited evidence of carcinogenic effect’ (Xn; R40) in the HSIS (see **Recommendation** section). This is supported by the transformation of the chemical into two carcinogenic substances, formaldehyde and acrylamide, in the body.

The International Agency for Research on Cancer (IARC) has classified the chemical as ‘Not classifiable as to its carcinogenicity to humans’ (Group 3) (IARC, 1994) based on inadequate evidence for carcinogenicity in humans and limited evidence in animals. The chemical was found to be carcinogenic in mice; however, it was not found to induce cancer in rats (NTP, 1989). The lack of biologically relevant toxic effects attributable to the chemical in the rat study suggests that somewhat higher doses could have been used to increase the sensitivity of the study for detecting the presence or absence of a carcinogenic effect.

In a two-year carcinogenicity study carried out according to OECD TG 451 (carcinogenicity studies), the chemical was administered to F344/N rats (50 animals/sex/dose) by oral gavage, at doses of 0, 6 or 12 mg/kg bw/day, five days per week. No biologically-relevant non-neoplastic or neoplastic lesions were attributed to treatment with the test compound. No evidence of carcinogenic activity for male or female rats receiving 6 or 12 mg/kg bw/day was observed. However, it was postulated that the administered doses were too low to determine the presence or absence of a carcinogenic response (NTP, 1989; REACH).

In a similar two-year study, B6C3F1 mice (~50 animals/sex/dose) were administered the chemical by oral gavage, at doses of 0, 25 or 50 mg/kg bw/day, five days per week. The chemical was found to induce tumours in all treated animals compared to controls. The incidence of adenomas of the Harderian gland was increased in males at both doses of NMA (control: 1/48; low dose: 14/49; high dose: 29/50), and in females at the highest dose (5/47; 8/45; 20/48). The incidence of carcinomas of the Harderian gland was not significantly increased. The incidence of hepatocellular adenomas was increased in male and female mice at 50 mg/kg bw/day (male: 8/50; 4/50; 19/50; female: 3/50; 4/50; 17/49). The incidence of hepatocellular carcinomas was also marginally increased in dosed males. The incidence of alveolar/bronchial adenomas and carcinomas (combined) was increased in male and female mice dosed at 50 mg/kg bw/day (males: 5/49; 10/50; 18/50; females: 6/50; 8/50; 13/49). Ovarian atrophy was observed in dosed female mice receiving NMA (3/50; 39/45; 38/47). The incidence of benign granulosa cell tumours was also increased in the dosed groups (0/50; 5/45; 5/47). The incidence of adenomas of the pars distalis in high dose female mice was significantly lower than in vehicle controls (13/49; 5/14; 4/43) (NTP, 1989; REACH).

Reproductive and Developmental Toxicity

The testicular effects observed in male mice in the absence of significant neurotoxicity or other systemic toxicity in some studies, indicates the potential for reproductive toxicity, warranting hazard classification. It is unclear whether these testicular effects are secondary to observed dominant lethal effects. In the absence of further information, it is recommended that the chemical be classified as a Category 3 reproductive toxin, with the risk phrase "Possible risk of impaired fertility" (Xn; R62) (see **Recommendation** section). There was no evidence of developmental toxicity.

Although the mechanism of action is unknown, the hydrolysis product, acrylamide—a suspected reproductive toxin (NICNAS, 2002)—has been shown to have an affinity for binding to protamine, which is only present in spermatids and not somatic cells (NICNAS, 2002; Sega et al., 1989). There is also some evidence of a delayed dispersal of acrylamide or its metabolites in the testes (see **Toxicokinetics** section; Marlowe et al., 1986), indicating that acrylamide may target the male reproductive system.

In a non-guideline reproductive toxicity study, male (12 animals/group) and female ddY mice (24 animals/group) received 0 or 4.3 mM (435 mg/L) solutions of the chemical in the drinking water for six weeks (total administered doses were not reported). The treated females exhibited signs of hind limb weakness by the end of the study period. Clinical signs such as bodyweight, food and water consumption were unaffected in all animals. There was only a slight decrease in fertility observed when treated males were mated with control females. The offspring had no changes in bodyweight or behaviour up to four weeks after birth. The main signs of toxicity were related to treated males, as there were significant decreases in the relative weights of testes, and a reduction, but not statistically significant, in seminal vesicle weights. The epididymal sperm count was significantly reduced and there was also an increase in head and tail abnormalities in sperm. Overall, this study showed clear effects on epididymal sperm count following exposure of males to 4.3 mM for six weeks. Testicular histopathology was not reported. Fertility effects on females were not reported (US EPA, 2002).

In a non-guideline fertility study, male ddY mice (5–7 animals/group) were administered the chemical via oral gavage, at doses of 0 or 292 mg/kg bw, twice weekly, for eight weeks. Relative testicular weights were reduced in the higher dose group (55 % of control value). Decreases in the number of spermatids and spermatocytes were observed in the epithelial lining when compared to controls, as well as a reduction in spermatozoa and the presence of multinucleated giant cells. Sertoli cells, interstitial cells and the epididymis were unaffected. No further histopathological investigations were performed, and no information on clinical signs of toxicity was provided (US EPA, 2002).

In a 13-week oral repeated dose toxicity study, administration of the chemical to rats and mice (10 animals/sex/dose for each species) by gavage at doses of 0, 12.5, 25, 50, 100 or 200 mg/kg bw/day did not affect any reproductive parameters in male and female rats or female mice; however, treatment-related effects (neurotoxicity) were observed at doses as low as 12.5 mg/kg bw/day for male rats, and 25 mg/kg bw/day for female rats and mice. In the same study, a dose-dependent decrease in relative right testis weight was observed in male mice that received 12.5 mg/kg bw/day or more. No other treatment-related effects were observed at the lowest dose, and no testicular histopathology effects were reported. Neurological effects, such as decreased forelimb grip strength, were observed in male mice starting at 25 mg/kg bw/day and became more severe at higher doses. The LOAEL for reproductive toxicity in male mice was 12.5 mg/kg bw/day, based on testicular effects. The LOAEL for parental (male mice) toxicity was 25 mg/kg bw/day, based on neurotoxic effects (NTP, 1989).

In a continuous breeding study using CD-1 mice, NMA at 0, 60, 180 or 360 ppm in drinking water (equivalent to doses of 0, 13, 37 and 68 mg/kg bw/day and 0, 17, 47 and 101 mg/kg bw/day for males and females, respectively) was administered to parental animals and offspring. A dose-related increase in early resorptions was observed at all concentration levels. A decrease in testes weight was also observed in the absence of systemic toxicity or structural tissue changes to the testes or epididymis; however, testicular spermatid measures were affected by exposure to NMA (increase and decrease in testicular spermatid heads at the highest dose in parental animals and offspring, respectively). Epididymal sperm concentrations were decreased in both generations of NMA-exposed mice, although the magnitude of these changes were reported to be small and were observed only at the highest dose (68 mg/kg bw/day). Although there were measurable adverse effects on the male reproductive system following NMA exposure, the degree of cellular damage was determined to be insufficient to account for the observed decreases in fertility, which was attributed to a dominant lethal effect in parental males. Neurotoxic effects, measured by the reduction in hind limb grip strength with aging, was evident at all concentrations except the lowest dose tested in both male and female animals. Offspring also displayed dominant lethal effects and slightly greater systemic toxic effects than the parental animals (Chapin et al., 1995).

Other Health Effects

Neurotoxicity

Evidence of neurotoxicity has been observed in acute and repeated dose toxicity studies in both animals and humans. These effects have been considered in the hazard classification of the chemical for acute and repeated dose toxicity endpoints (see **Recommendation** section). The effects observed in animal studies following single oral and dermal exposures to high concentrations of the chemical included ataxia, tremors, limb paralysis, delayed coordination and convulsions. Repeated exposures to low concentrations of the chemical have also caused signs of severe neurotoxicity in mice.

Repeated oral administration of the chemical, together with simultaneous dietary and i.p. exposure, resulted in peripheral neuropathy in rats (see **Repeat Dose Toxicity: Oral** section). Rats administered the chemical have also been shown to develop increased susceptibility to neurotoxic effects from acrylamide (less acrylamide is required to produce the same toxic effects). The neuropathy produced by the chemical was indistinguishable from that produced by acrylamide and, after returning to a normal diet, the rats slowly recovered. The chemical was found to be 30 % as potent a neurotoxin as acrylamide (Edwards, 1975).

Observation in humans:

Mild effects on the PNS were observed in 25 tunnel workers exposed to acrylamide and NMA during grouting operations. Reported symptoms included tingling or numbness in the hands or feet, pain in the hands and cramping in the legs. The exposed workers reported an increased prevalence of symptoms during grouting work compared to the examination period four and 16 months later. Apart from a possible delayed axonal effect on sensory

fibres in the sural nerve, the effects seemed largely to have been reversible within a 16-month period post-exposure. Mild effects on the visual system were also reported (NIOH, 2002; Kjuus et al., 2004).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is neurotoxicity following acute and chronic exposure to the chemical. Other potential health effects include systemic long term effects (carcinogenicity, mutagenicity and impaired fertility) and local effects (eye/skin/respiratory irritation). The chemical may also cause skin sensitisation.

Public Risk Characterisation

Although use in consumer products in Australia is not known, the chemical has reported domestic use overseas. In these instances, the general public could be exposed through the dermal or inhalation routes. In the absence of regulatory controls, the characterised critical health effects have the potential to pose an unreasonable risk under the identified uses. Additional risk management could be required should information become available to indicate that the chemical is used in domestic products in Australia.

While use of the chemical in the manufacture of textiles or as a durable press agent in Australia is currently unknown, overseas information indicates that the chemical can be used in clothing, with concomitant release of low levels of formaldehyde observed under certain conditions. In these instances, dermal exposure to residual formaldehyde may occur, increasing the public risk of skin sensitisation. In relation to this, in 2007 the Australian Competition and Consumer Commission (ACCC) investigated the residual formaldehyde content of a broad range of clothing purchased in the Australian market, and "no formaldehyde was detected in any of the garments submitted". In addition to actively monitoring the safety concerns arising from the presence of formaldehyde in consumer products, the ACCC has provided interim, non-regulatory reference limits for levels of formaldehyde in various garment and fabric products (ACCC) that are considered sufficient to mitigate the risk posed by the release of formaldehyde from the chemical.

Occupational Risk Characterisation

The use of NMA-containing grouts is currently unknown in Australia. During product formulation (such as in grouting operations), dermal, ocular and inhalation exposure 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.

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

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

NICNAS Recommendation

Concerns have been raised regarding occupational health from the use of NMA-containing grouts in construction work. In the Priority Existing Chemical report for acrylamide (NICNAS, 2002), use of acrylamide (including NMA) grouts in Australia was not identified; therefore, recommendations to control this use are not necessary at this time. However, should NMA-based grouts be introduced or used in Australia in the future, further risk management measures may be required.

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

The chemicals fall within the scope of the listing of ‘formaldehyde’ in Schedule 6 and Schedule 10 of the SUSMP. Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2016).

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	Irritating to eyes (Xi; R36) Irritating to skin (Xi; R38) Irritating to respiratory system (Xi; R37)	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Harmful: danger of serious damage to health by prolonged exposure in contact with skin (Xn; R48/21) Harmful: danger of serious damage to health by prolonged exposure if swallowed (Xn; R48/22)	May cause damage to organs through prolonged or repeated exposure through the dermal route - Cat. 2 (H373) May cause damage to organs through prolonged or repeated exposure through the oral route - Cat. 2 (H373)
Genotoxicity	Muta. Cat 2 - May cause heritable genetic damage (T; R46)	May cause genetic defects - Cat. 1B (H340)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)	Suspected of causing cancer - Cat. 2 (H351)
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, 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;
- 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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Last update 01 July 2016

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