2-Pyrrolidinone, 1-methyl-: Human health tier II assessment

22 November 2013

CAS Number: 872-50-4

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.

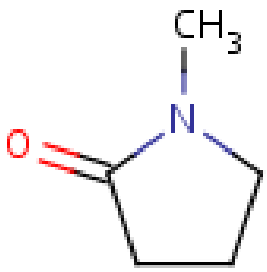
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	N-methyl-2-pyrrolidone N-methyl pyrrolidone 1-methylazacyclopentan-2-one methyl pyrrolidone NMP
Structural Formula	
Molecular Formula	C5H9NO
Molecular Weight (g/mol)	99.13
Appearance and Odour (where available)	A clear liquid with a mild amine odour.
SMILES	C1(=O)CCCN1C

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

The chemical has reported domestic use as a laundry spot remover.

The chemical has reported commercial use including in:

- graffiti removal products;
- paint strippers;
- industrial coatings (including as a co-solvent in water-dispersed polymers used in formulating water-based automotive re-finish paints);
- industrial degreasers;
- fixing solutions for colour copy machines;
- pipe cement;
- shoe re-colourant; and
- screen printing inks.

The chemical has reported site-limited use including:

- in the coatings and electronics industries;
- in adhesive manufacture, including PVC adhesives; and
- as a solvent in polyurethane processing.

The total volume introduced into Australia reported under previous mandatory and/or voluntary calls for information was between 100 and 1000 tonnes.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR), Galleria Chemica, Substances in Preparations in Nordic countries (SPIN) database, the European Commission Cosmetic Substances and Ingredients (CosIng) database, United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) directory and other data sources via the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use as a:

- solvent;
- fragrance; and
- surfactant.

The chemical has been reported as being used in a limited number (<30) of cosmetic products in the US (CIUCUS, 2011). The final concentration of 2-pyrrolidinone, 1-methyl- (NMP) in cosmetic products is not known (SCCS, 2011).

The chemical has reported domestic use including in:

- paints, varnishes and adhesive removers;
- cleaning products; and
- paints, varnishes and other surface coatings.

The chemical is reported to be present in a range of domestic products including home maintenance products such as paint and varnish removers up to a concentration of 100 % and cleaning products up to a concentration of 5 % (Household Products Database, US Department of Health and Human Services; HSDB).

The chemical has reported commercial use including in:

- welding and soldering agents;
- viscosity adjustors;
- lubricants;
- construction materials;
- cutting fluids; and
- reprographic agents.

The chemical has reported site-limited use including:

- as a laboratory chemical; and
- in heat transferring agents.

The following non-industrial uses have been identified internationally:

- used to enhance the absorption of topically applied drugs; and
- solvent in agricultural products.

Restrictions

Australian

This chemical is listed in the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) in Schedules 5 and 6.

- Schedule 6 except (a) when included in Schedule 5; or (b) in preparations containing 25 % or less of designated solvents.

Schedule 6 chemicals are labelled with 'Poison'. These are substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label.

- Schedule 5 (a) when packed in single use containers having a capacity of 2 mL or less; or (b) in preparations containing 50 % or less of N-methyl-2-pyrrolidone or preparations containing 50 per cent or less of a mixture of any two or more of N-methyl-2-pyrrolidone, N-(N-octyl)-2-pyrrolidone or N-(N-dodecyl)-2-pyrrolidone **except** in preparations containing 25 % or less of designated solvents.

Schedule 5 chemicals are labelled with 'Caution'. These are substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

A list of designated solvents is provided in the SUSMP.

International

European Union

Using CMR 1A or 1B substances in cosmetics is prohibited under Article 15(2) of the Cosmetics Regulation 1223/2009. Therefore the chemical is restricted in cosmetic products, irrespective of the concentration limit (EU Regulations, 2009).

The chemical is listed on the candidate list of substances of very high concern (SVHC) for Authorisation (ECHA, 2011).

The Netherlands has submitted an Annex XV report proposing to restrict manufacture and use of 1-methyl-2-pyrrolidone (N-methylpyrrolidone, NMP) (ECHA, 2013a).

In the report, it is proposed that 1-methyl-2-pyrrolidone shall not be manufactured and used by a professional or industrial worker, unless:

- the eight-hour time weighted average (TWA) exposure will remain below 5 mg/m³ and the 15 min peak exposure remains below 10 mg/m³; and
- dermal exposure is avoided by preventative measures.

In March 2013, a reclassification proposal for n-methyl pyrrolidnone (NMP) was submitted by the Netherlands. With this, the Netherlands proposes to lower the specific concentration limit for classification as reprotoxic category 1B from 5 % to 0.3 % which, under entry 30 of REACH Annex XVII, would lower the allowable level in consumer products. If adopted, this will effectively restrict the use of NMP in consumer applications. Using NMP at concentrations <0.3 % will have no functionality in present consumer applications (ECHA, 2013a).

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):

R61 Repr. Cat. 2 (Developmental toxicity)

Xi; R36/37/38 (Irritation)

The R61 classification currently has a specific concentration limit of ≥5 %.

Exposure Standards

Australian

The chemical has an exposure standard of 103 mg/m³ (25 ppm) TWA and 309 mg/m³ (75 ppm) short-term exposure limit (STEL). The exposure standard includes a notation that absorption through the skin may be a significant source of exposure (Safe Work Australia).

International

The following exposure standards are identified (Galleria Chemica):

- An exposure limit (TWA) of 4–400 mg/m³ (1–100 ppm) in different countries such as USA (Alaska, Hawaii), Canada (Yukon), Norway and Switzerland.

Health Hazard Information

The chemical 2-pyrrolidinone, 1-methyl-, is commonly abbreviated to NMP.

Toxicokinetics

The chemical is rapidly absorbed following inhalation (40–60 %), dermal (100 %) or oral (≤100 % depending on conditions) exposure in rats (OECD, 2009). Once absorbed, the chemical is widely distributed and eliminated by hydroxylation to polar compounds (see below for details on metabolites) and excreted in the urine (OECD, 2009; SCCS, 2011).

In rats, the main metabolite identified in urine was 5-hydroxy-N-methyl-2-pyrrolidone (5-HNMP) which amounted to 60 % after an oral dose, and 70–75 % after an intravenous dose (OECD, 2009). Furthermore, it has been reported that at lower doses NMP was completely metabolised, which suggests that at higher doses the metabolic pathways become saturated (OECD, 2009). The rate of dermal absorption was proportional to the concentration of NMP applied dermally to rats. Furthermore, it was shown that prolonged exposure to the chemical may increase permeability to NMP by up to seven-fold (OECD, 2009). Following dermal exposure to the chemical (300 mg) in human volunteers, approximately 70 % of the chemical was absorbed. The rate of skin penetration in human volunteers was 1–2 mg/cm²/hour which is described as being 2–3 times lower than in rats (OECD, 2009).

In humans, the chemical is also primarily metabolised to 5-HNMP, which is further metabolised to N-methylsuccinimide (MSI) and then to 2-hydroxy-N-methylsuccinimide (2-HMSI) (OECD, 2009). The relative proportions of the urinary metabolites following inhalation exposure for eight hours (0.01, 0.025 or 0.05 mg/L) were 2 % NMP, 60 % 5-HNMP, 0.1 % MSI and 37 % 2-HMSI (OECD, 2009). In addition, NMP is also metabolised through the cytochrome P450 (CYP450) enzyme CYP2E1 (OECD, 2009). Following oral administration of the chemical (100 mg) to human volunteers, 65 % of the total dose was recovered in the urine (2 % NMP, 67 % 5-HNMPm, 0.1 % MSI and 31 % 2-HMSI) (OECD, 2009).

Acute Toxicity

Oral

The chemical exhibits low acute toxicity in animal tests—the reported oral median lethal dose LD50 in Sprague Dawley (SD) rats is > 2000 mg/kg bw. Observed sub-lethal effects included ataxia and diuresis (OECD, 2009).

In a study conducted in SD rats, the LD50 was 4150 mg/kg bw. Studies conducted in mice gave an oral LD50 value of 7725 mg/kg bw.

Dermal

The chemical exhibits low acute toxicity in animal tests—the reported dermal LD50 in SD rats is > 2000 mg/kg bw (OECD, 2009).

Inhalation

Based on a study in rats conducted according to OECD Test Guideline (TG) 403, the chemical is considered to be of low acute toxicity following inhalation exposure to aerosols. No mortalities were observed at the highest dose tested (median lethal concentration (LC50) >5.1 mg/L). Observed sub-lethal effects included accelerated, irregular breathing; slightly reddish nasal

secretion and reduced pain sensitivity. There were no clinical findings noted from day four after exposure onwards (OECD, 2009).

Observation in humans

Workers exposed to the chemical at concentrations up to 280 mg/m³ reported severe eye irritation and headaches. There were no reported symptoms relating to respiratory irritation or neurological impairment in six volunteers exposed to up to 50 mg/m³ in an eight hour study (SCCS, 2011).

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in HSIS (Safe Work Australia). The available data support this classification.

In a three month inhalation study, male and female Wistar rats exposed to concentrations of 0, 0.5, 1.0 or 3.0 mg/L for six hours a day, five times a week developed respiratory tract irritation (described in **Repeat dose toxicity *Inhalation***) at a concentration of =1.0 mg/L. The no observed adverse effect concentration (NOAEC) for local irritation was 0.5 mg/L (OECD, 2009).

Skin Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). While the available data do not support this classification, in the absence of more comprehensive information, there is insufficient evidence to support a recommendation to amend this classification. The chemical is reported in animal studies to slightly irritate skin, particularly following repeated exposure. The human findings on skin irritation support the animal (albino rabbits) studies, which reported swelling and wrinkling of the skin after repeated exposure (OECD, 2009).

Application of undiluted chemical (0.5 mL) to the shaved backs of rabbits for 24 hours under occlusive conditions produced slight erythema. This was reversible after 72 hours (OECD, 2009).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). While the available data do not support this classification, in the absence of more comprehensive information, there is insufficient evidence to support a recommendation to amend this classification.

In an eye irritation study in New Zealand White rabbits, the chemical (0.1 mL undiluted) was found to be highly irritating causing conjunctivitis, corneal opacity and iritis. Effects were reversible within the observation period (OECD, 2009).

Observation in humans

Skin irritation was reported in workers after occupational exposure to NMP using a paper cloth to wipe the chemical surplus from plastic pieces that had been dipped in the solvent (OECD, 2009). Adverse effects reported included swelling and wrinkling of the skin where workers were exposed.

Six male volunteers exposed to 10, 25 or 50 mg/m³ (eye irritation study) of the chemical for eight hours on a single day did not report any discomfort in the eyes. In contrast, repeated occupational exposure to the chemical is reported to cause eye irritation, although exposure concentrations were not accurately measured (OECD, 2009).

With respect to respiratory effects, six male volunteers exposed to the chemical (10, 25 or 50 mg/m³) did not report any changes in pulmonary function nor irritating effects (OECD, 2009).

Sensitisation

Skin Sensitisation

There is no evidence of sensitisation from the limited animal and human data available (REACH). The chemical does not contain any structural alert for skin sensitisation (OECD Toolbox).

Observation in humans

In a repeated human patch test, 15 exposures for 24 hours caused minor to moderate transient dermal irritations in 50 human subjects. No signs of contact sensitisation were observed (REACH).

Repeated Dose Toxicity

Oral

Considering the no observed adverse effect levels (NOAELs) available from 28 and 90 day studies in rats and mice (169–820 mg/kg bw/d), and based on the treatment-related effects reported in various repeated dose toxicity studies, the chemical is not considered to cause serious damage to health from repeated oral exposure.

In a repeated dose study, five male and female SD rats were exposed to dietary concentrations of the chemical (149/161, 429/493, 1234/1548, 2019/2269 mg/kg bw/day males/females) for 28 days. Adverse effects including reduced body weight, reduced food consumption and changes in clinical chemistry were observed in males at ≥1234 mg/kg bw/day and in females at 2269 mg/kg bw/day. The NOAEL was 429 mg/kg bw/day in males and 1548 mg/kg bw/day in females (OECD, 2009).

In a similar study conducted in B6C3F$_1$ mice, the chemical was orally administrated (277, 619 or 1931 mg/kg bw/day) for 28 days or three months. Resultant adverse effects included swelling of the renal tubular epithelia (=1931 mg/kg bw/day in males and 619 mg/kg bw/day in females). One male in the high dose group (1931 mg/kg bw/day) died prematurely as a result of renal toxicity. The NOAEL was 820 mg/kg bw/day for both sexes in animals exposed for 28 days, and 562 and 676 mg/kg bw/day in males and females exposed for 90 days respectively (OECD, 2009).

Dermal

Based on the limited data available, the chemical is not considered to cause serious damage to health from repeated dermal exposure.

In a dermal repeated dose study in male albino rabbits, dermal exposure to doses of 413, 826 or 1653 mg/kg bw/day for four weeks resulted in mild local skin irritation at ≥413 mg/kg bw/day. At the highest dose administered (1653 mg/kg bw/day) 1/4 rabbits with abraded skin were reported dead after one week of treatment. No further signs of systemic toxicity were noted in clinical, haematological or histopathological examinations. The NOAEL for systemic toxicity was reported as 826 mg/kg bw/day (OECD, 2009).

Inhalation

In a 90-day repeated dose inhalation toxicity study in male and female Wistar rats, the no observed adverse effect concentration (NOAEC) for the chemical was reported to be 0.5 mg/L. Effects observed at higher concentrations (=1.0 mg/L) included a

retardation in body weight gain, changes in red blood cell parameters, an increase in polymorphonuclear neutrophils and a decrease in lymphocytes. All other findings reduced during recovery (OECD, 2009).

In a subchronic three month study, male and female Wistar rats were exposed to 0.5, 1 or 3 mg/L of the chemical for six hours a day, five days a week by inhalation. A separate group of rats was also allowed a four-week recovery period after three months of exposure. Adverse effects reported after three months of exposure included nasal irritation and crust formation (≥1.0 mg/L), retardation in male body weight gain (3.0 mg/L), changes in red cell parameters, an increase in polymorphonuclear neutrophils and a decrease in lymphocytes. After recovery, male rats showed a significantly reduced body weight gain and cellular depletion in the testes. The NOAEC for both systemic toxicity and local irritation was defined as 0.5 mg/L (OECD, 2009).

Genotoxicity

Based on the available in vitro and in vivo genotoxicity studies the chemical is not considered to be genotoxic.

The chemical tested negative in several in vitro tests (bacterial and mammalian cell gene mutation assays and unscheduled DNA synthesis), with or without metabolic activation (OECD, 2009; REACH).

In vivo, the chemical showed no mutagenicity, as assessed through the mouse micronucleus test and Chinese hamster cytogenic assay. Results indicated that the chemical is not clastogenic and does not poison spindles in vivo, hence the chemical does not have a profile indicative of genotoxicity (OECD, 2009).

Carcinogenicity

There is no evidence of carcinogenicity in two-year studies conducted in rats exposed orally (highest dose 678 mg/kg bw/day) and by inhalation (highest dose 400 mg/m³). (OECD, 2009; REACH). There is evidence of liver tumours in mice, although this finding was concluded to be species ($B6C3F_1$) dependent.

In a two-year inhalation study, male and female CD rats were exposed to 0.04 or 0.4 mg/L of the chemical for six hours a day for five days a week. There was no treatment-related effect on survival rates in male or female rats. Male rats exposed to 0.4 mg/L showed a significant 6 % decrease in body weight. There were no treatment-related benign or malignant tumours in male or female rats (OECD, 2009).

In a two-year oral exposure study, male and female SD rats were exposed to 66/88, 207/283 or 678/939 mg/kg bw/day (males/females). Treatment at any dose did not affect survival rates in female rats. Male rats exposed to 678 mg/kg bw/day had a lower survival rate; however, this was determined not to be treatment related and was attributed to ageing male rats. Body weight was significantly decreased, accompanied with reduced body weight gain at the highest dose administered (678/939 mg/kg bw/day). Male rats administered 678 mg/kg bw/day showed treatment-related macroscopic findings including an increased incidence of large kidneys, chronic nephropathy, fluid in the pleural cavity and small testes (OECD, 2009).

In a two-year study conducted in $B6C3F_1$ mice, male and female mice were orally exposed to the chemical (89/115, 173/221, 1089/1399 mg/kg bw/day, males/females). There were no treatment-related effects on the survival rate in male or female mice. Male mice exposed to the highest dose (1080 mg/kg bw/day) had an increased incidence of liver carcinomas. At lower doses (173 mg/kg bw/day), liver weights were increased in males and 3/50 male animals had centrilobular liver cell hypertrophy (OECD, 2009).

Reproductive and Developmental Toxicity

The chemical is currently classified as hazardous as a Category 2 reproductive toxin with the risk phrase ‘May cause harm to the unborn child’ (T; R61) in HSIS (Safe Work Australia). Developmental effects, including post implantation loss, foetal malformations and pup mortality, have been observed in rats, rabbits and mice following oral and/or dermal exposure. As the developmental effects reported are not considered secondary to maternal toxicity, the available data support the existing classification. The lowest reported LOAEL was 250 mg/kg bw/day (oral administration in rats) (OECD, 2009; SCCS, 2011).

Multigenerational studies:

In a two-generation study performed according to OECD TG 416, SD and Wistar rat strains were exposed to 50, 160 or 500 mg/kg bw/day in diet for 10 weeks before mating; during mating and gestation; in the rest period between pregnancies; and during lactation. As severe pup mortality was observed at the 500 mg/kg bw/day dose in the first generation (F1) in both rat strains, this dose was reduced to 350 mg/kg bw/day. The chemical did not affect reproductive performance or fertility in the F0 or F1 parental animals in both strains. Signs of developmental toxicity occurred at 350/500 mg/kg bw/day in the form of increased pup mortality and reduced body weight gain. The NOAEL for systemic (parental) and developmental toxicity was defined as 160 mg/kg bw/day (OECD, 2009).

In a two-generation study, SD rats were exposed to vapour concentration of the chemical (0.04, 0.21, 0.479 mg/L) for six hours a day for 14 weeks (during premating, mating, gestation and lactation). Ten males and 20 males were also mated with unexposed animals to identify sex-specific effects. There were no effects on reproductive organs, reproductive performance or fertility; therefore, the NOAEC for reproductive toxicity was defined as 0.479 mg/L (OECD, 2009).

Inhalation exposure

In an inhalation exposure study, SD rats were exposed to the chemical (0.124, 0.247 or 0.494 mg/L) during gestation days 6–20 for six hours a day. Exposure to 0.247 and 0.494 mg/L resulted in a decrease in body weight and food consumption. At the highest dose administered (0.494 mg/L), maternal toxicity and reduced foetal body weights were observed (OECD, 2009).

Reproductive toxicity, characterised by slight testicular atrophy, was seen in male rats exposed to 0.1 or 0.5 mg/L of the chemical for six hours a day for four weeks, although this was reversible within 14 days. At the highest dose (1 mg/L) used in this study, severe testicular atrophy was observed in 3/15 rats (OECD, 2009). A further study reported significantly reduced body weight and body weight gain and depletion of cells in the testes at the highest exposure concentration (3.0 mg/L).

Dermal exposure:

In a dermal exposure study, SD rats were exposed to the chemical (75, 237 or 750 mg/kg bw/day) for eight hours a day on gestation days 6–15. Maternal toxicity occurred at the highest dose (750 mg/kg bw/day) and was highlighted through a 28 % decrease in body weight. Developmental toxicity was observed at 750 mg/kg bw/day and consisted of fewer live foetuses, increased resorption rate, reduced foetal weight and indications of retarded skeletal development (fusion of skull bones and surplus or cleft ribs) (OECD, 2009).

In a further study conducted in Himalayan rabbits, exposure to a 40 % aqueous solution of NMP (100, 300 or 1000 mg/kg bw/day) under semiocclusive conditions for six hours a day (days 7–19 of pregnancy) did not result in any reproductive toxicity (NOAEL was defined as 1000 mg/kg bw/day). A common developmental variation in this strain of rabbits (additional ribs) was increased in the group administered the highest dose (1000 mg/kg bw/day) (OECD, 2009).

Oral exposure:

In an oral exposure study carried out according to OECD TG 414, SD rats were exposed to the chemical (125, 250, 500 or 750 mg/kg bw/day) during gestational days 6–20. Exposure to the chemical resulted in significant maternal weight decrease and reduced food consumption at 500 mg/kg bw/day. An increase in post implantation loss and the number of resorptions was noted at 500 mg/kg bw/day. Foetal malformations (external, skeletal and soft tissue) were also increased at 500 mg/kg bw/day. At 250 mg/kg bw/day, developmental toxicity was characterised by reduced foetal body weight. The NOAEL for developmental characterisation was defined as 125 mg/kg bw/day (OECD, 2009).

Reproductive toxicity (decreased testes weights, small testes, testicular lesions and degeneration of the seminiferous epithelium) was reported in male SD rats orally administered the maximum study dose of 2066 mg/kg bw/day for 28 days. In New Zealand White rabbits, the NOAEL for maternal toxicity was 55 mg/kg bw/day while the NOAEL for developmental toxicity was 175 mg/kg bw/day (OECD, 2009).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (developmental toxicity) and skin, eye and respiratory irritation.

Public Risk Characterisation

The general public may be exposed to the chemical through dermal and/or inhalation routes when using domestic products containing the chemical. Although use in cosmetic products in Australia is not known, the chemical is reported to be used in cosmetic products overseas at unknown concentrations (SCCS, 2011; CIUCUS, 2011). The chemical is expected to be readily absorbed through the skin.

The chemical is currently listed on schedules 5 and 6 of the SUSMP. At concentrations greater than 25 % (or lower in the presence of other specified solvents), a number of warning statements and first aid instructions apply.

However, the opinion of the Scientific Committee on Consumer Safety (SCCS) on NMP concludes that the current 5 % concentration cut-off in cosmetic products in the European Union (EU) is not safe for consumers (SCCS, 2011).

Data available in the form of risk characterisation ratios (RCRs) obtained from the Annex XV restriction report for NMP, indicate that the chemical may pose a risk for certain industrial uses (see **Occupational risk characterisation**). A number of the processes considered in this risk assessment such as application by roller and brush and spraying are considered applicable for potential domestic uses of the chemical identified such as paint, varnish removers and cleaning products. Although the frequency of exposure may differ between work and home, using risk management measures such as use of personal protective equipment is less likely in a domestic setting. Therefore the chemical may pose an unreasonable risk from domestic use (ECHA, 2013a).

Therefore, in the absence of any further regulatory controls, the characterised critical health effects (developmental effects) have the potential to pose an unreasonable risk for the identified uses.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may 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 health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure to the chemical are implemented. Pregnant workers are considered to be of greatest risk considering the developmental effects observed. 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 appropriate controls.

Data available in the form of risk characterisation ratios (RCRs) obtained from the annex XV restriction report of NMP indicate that the chemical may pose a risk in certain industrial processes (ECHA, 2013a).

The toxicity values used for the derived no effect level (DNEL) for pregnant workers were 247 mg/m^3 (NOAEC—reduced foetal body weight in rats) and 237 mg/kg bw/d (NOAEL—reduced live foetuses and foetal body weight in rats) for the inhalation and dermal routes, respectively. The DNELs derived for pregnant workers were 5 mg/m^3 and 2.4 mg/kg bw/d for the inhalation and dermal route, respectively. Based on the data available the DNELs are considered appropriate. The risk characterisation took into account known risk management measures. By combining derived no-effect levels (DNELs) with the exposure estimates, risk characterisation ratios (RCRs) were obtained. The RCRs were >1 in most cases for workers and pregnant workers, indicating that there is a risk (ECHA, 2013a). Current practices for the uses of this chemical are not known in Australia.

Based on the available data, the hazard classification in HSIS is considered appropriate. However, the specific concentration limit for the developmental toxicity classification may not be appropriate. Based on the chemical's potency, in Europe, the Netherlands has submitted a harmonised classification and labelling proposal to remove specific concentration limits (ECHA, 2013b).

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemical in cosmetics and/or domestic products be managed through changes to poisons scheduling.

Safe Work Australia should consider whether current controls, including the specific concentration limit for developmental toxicity, are adequate to minimise the risk to workers. The outcome of the proposal currently being considered in Europe may inform this process. A Tier III assessment may be necessary to provide further information as to whether the current exposure controls are appropriate to offer adequate protection to workers and members of the public using the chemical in domestic products.

Regulatory Control

Public Health

Given the risk characterisation, it is recommended that the concentration of the chemical in cosmetics/personal care products and domestic products be restricted. The toxicity profile at concentrations reported to be in use indicate that this chemical be considered for listing in Schedule 6, which is consistent with the Scheduling Policy Framework guidelines.

Consideration should be given to the following:

- the chemical is expected to be readily absorbed through the skin;
- the SCCS opinion on the chemical which concluded that the margin of safety for dermal exposure is too low to be considered safe in consumer cosmetic products at the current maximum concentration of 5 %;
- the chemical is prohibited for use in cosmetics overseas and use in domestic products is being reviewed (see **International restrictions)**;
- data indicate domestic uses such as paint, varnish removers and cleaning products may pose an unreasonable risk to the public.

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 hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
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)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May cause harm to the unborn child (T; R61)*	May damage fertility or the unborn child - Cat. 1B (H360D)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

* Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from 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 which may 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 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 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 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 22 November 2013

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