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

28 June 2013

CAS Number: 127-19-5

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.

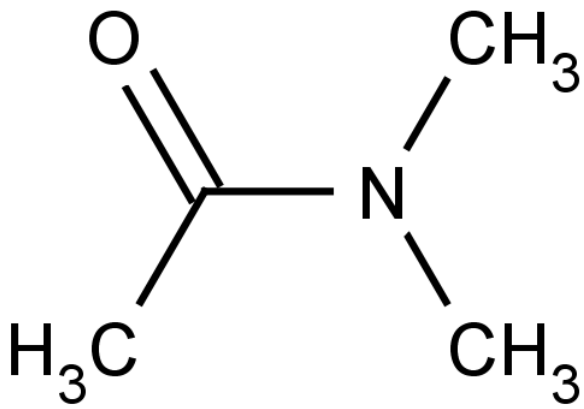
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Dimethylacetamide N,N-dimethylacetamide Acetic acid, dimethylamide Acetyldimethylamine DMAC
Structural Formula	
Molecular Formula	C4H9NO
Molecular Weight (g/mol)	87.12
Appearance and Odour (where available)	Colourless liquid with ammonia or fish like odour
SMILES	C(C)(=O)N(C)C

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacture information has been identified.

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 Dataset Initial 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 Cosmetic Ingredients (INCI) directory; and eChemPortal: the US Environmental Protection Agency (EPA) Aggregated Computational Toxicology Resource (ACToR); and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

It should be noted that the chemical may occur as a residual solvent in cosmetic products or in various textiles (domestic and commercial), although it is not specifically used in formulations. It is reported to be present at concentrations < 0.01 %.

The chemical has reported site-limited use including as a solvent for:

- organic reactions (reaction medium, catalyst, crystallisation and purification);
- industrial applications such as manufacture of plastics, resins, gums, synthetic fibres and electrolytes;
- production of X-ray and photographic products (10–20 %);
- cosmetic and pharmaceutical intermediates (10–20 %);
- aramid fibres (10–20 %);
- polyimide films and polymers (< 10 %);
- resin and polymers (< 10 %);
- liquid treatment fibres (< 10 %); and
- production of photo resistant stripping chemicals.

The following non-industrial uses have been identified internationally (EMA, 1999):

- as a drug vehicle in pharmaceuticals; and
- an anti tumour agent.

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 5: 'in preparations containing 20 per cent or less of dimethylacetamide.'

Schedule 6: 'except when included in Schedule 5.'

International

The chemical is prohibited in the final formulation of cosmetic products under a number of international directives (Galleria Chemica). These include listings in:

- Annex II of the EU Cosmetic Ingredients Directive (Ref No: 747) (CosIng);
- Annex II of the Association of Southeast Asian Nations (ASEAN) Cosmetic Directive; and
- Schedule 4 (Table 1) of the New Zealand Cosmetic Products Group Standard.

The chemical is also restricted under the EU Dangerous Substances Directory 67/548/EEC (Annex I) and EU regulation 1272/2008 on the classification, packaging and labelling of chemicals and their mixtures (Annex VI, Table 3.1). The chemical may not be used in substances and preparations placed on the market for sale to the general public at individual concentrations ≥ 5 %.

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):

T; R61 Repr. Cat 2. (reproductive toxicity)

Xn; R20/R21 (acute toxicity)

Notices: Sk (absorption through the skin may be a significant source of exposure).

Exposure Standards

Australian

The chemical has an exposure standard of 36 mg/m³ (10 ppm) time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica; OECD, 2001):

An exposure limit (OEL, TWA, STEL or PEL) of 35–72 mg/m³ (10–20 ppm) in different countries such as USA (California, Hawaii, Washington), Canada (Alberta, British Columbia, Quebec, Saskatchewan, Yukon), Norway and Switzerland.

Health Hazard Information

Toxicokinetics

The chemical can be absorbed by oral, inhalation or dermal routes of exposure (OECD, 2001).

Human data on the toxicokinetics (absorption, metabolism, distribution and excretion) of the chemical is available. The urine of five workers (three females and two males) was monitored daily (five days/week) for one month. Daily exposures were calculated as an 8-h TWA (0.5–2 ppm) for the subjects' normal working conditions. Exposure could occur through either

inhalation and/or dermal contact. It was found that for each 1 ppm of the chemical in air, 10 mg/L of the metabolite *N*−methylacetamide (NMAC) was found in the urine (OECD, 2001; REACH).

Similarly, metabolism and excretion of the chemical was tested in 12 men exposed to the chemical for two 4-h intervals with a ≥ 96 h interval between exposures, via dermal or inhalation routes. The vapour was significantly absorbed through the skin (40.4 % of total uptake) and via inhalation at 6.1 ppm. The chemical was metabolised to NMAC and excreted via the urine (nine and 5.6 hour half life for dermal and inhalation routes, respectively) (OECD, 2001).

A number of studies that examine the toxicokinetics of the chemical in rats more extensively are also available. These studies show that the chemical is absorbed via oral, dermal and inhalation routes. The chemical is then sequentially demethylated at the nitrogen to NMAC and acetamide.

N-hydroxymethylacetamide is another metabolite that can be produced. These are then eliminated via the urine (OECD, 2001). In addition to urinary excretion, the chemical and its metabolites were also found in faeces, in exhaled air (including as carbon dioxide), and retained in fat and muscle tissues (OECD, 2001).

Acute Toxicity

Oral

The chemical is reported to have low acute toxicity via the oral route (median lethal dose (LD50) >2000 mg/kg bw in rats and mice). An LD50 for beagle dogs was established as <2000 mg/kg bw (limited number of animals tested). Considering the limitations of this study (limited, variable numbers in treatment groups), it cannot be relied upon to warrant a hazard classification.

Oral gavage studies with rats (delivering the chemical at concentrations of 20–50 % in water or 20 % in corn oil; similar to OECD TG 401), report LD50s ranging from 4800–5830 mg/kg bw (REACH). At lower doses, clinical toxicity signs included diarrhoea, prostration, staining and sensitivity to noise. At higher doses, clinical toxicity signs included convulsions, stomach bleeding, bloody tears, laboured breathing and death.

Oral gavage studies with mice (delivering the chemical at concentrations of 20–50 % in water; similar to OECD TG 401), report LD50s from 4610–6020 mg/kg bw (REACH). In one of these studies, clinical toxicity signs included apathy and laboured breathing, and mortality at high doses, sometimes within hours of dose delivery.

An oral gavage study with rabbits, similar to OECD TG 401, established an LD50 of 2820 mg/kg bw (REACH).

An oral gavage study with beagle dogs, similar to OECD TG 401, reports a lowest lethal dose of 470 mg/kg bw (REACH) with 0/2; 1/4; 2/2 and 1/2 mortalities at doses of 235, 470, 940 and 1900 mg/kg bw respectively. It is noted that the surviving dog at the highest dose vomited after receiving the dose. Clinical signs of toxicity included refusing food (≥470 mg/kg bw), nosebleeds (≥470 mg/kg bw), extensor spasms (stiff, spasmodic extensions of the legs) (≥940 mg/kg bw) and death.

Dermal

The chemical is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in HSIS (Safe Work Australia). The data available for guinea pigs support this classification.

The LD50 was 940 mg/kg bw in guinea pigs, although the LD50s for rats, mice and rabbits were >2000 mg/kg bw (OECD, 2001).

In rats, mice and rabbits, LD50s of greater than 2000 mg/kg bw have been reported (OECD, 2001; REACH). The LD50 for pregnant female rats was 7500 mg/kg bw (24-h exposure on gestation day 11). The LD50 for pregnant female rabbits was 5000 mg/kg bw (24-h exposure on gestation day 15). Clinical toxicity signs were not reported (OECD, 2001; REACH). The LD50 for mice was 9600 mg/kg bw (OECD, 2001).

The LD50 for male New Zealand white rabbits was 2100 mg/kg bw in a study similar to OECD TG 402 (REACH). Sublethal effects were observed as a result of a 24-h exposure to the chemical at concentrations of 1180–4700 mg/kg bw. These included erythema, necrosis and desquamation (shedding of skin) at the treatment site. At necropsy of animals that died as a result of exposure, blood was observed in the lungs and peritoneum. Changes to the kidney were also observed (REACH).

Inhalation

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

In an inhalation study, rats (eight per dose) were exposed to vapour of the chemical for one hour at doses of 3.4, 5.8 and 8.8 mg/L. The median lethal concentrations (LC50s) were 8.8 mg/L in females (4/8 died at the highest dose) and >8.8 mg/L in males (no mortalities). The only reported clinical sign of toxicity (besides mortality) in females was hyperactivity (OECD, 2001; REACH).

A study exposing 10 mice to vapour of the chemical at 1.47 mg/L for 3.5 hours resulted in 4/10 mortalities. In two of the mice that died, the lungs were congested, and degeneration of the liver and renal tubules was observed. No LC50 was calculated (OECD, 2001).

In an acute inhalation toxicity test (OECD TG 403), rats were exposed to vapour of the chemical for four hours at 10.7 or 32.0 mg/L. There were 2/6 and 6/6 mortalities at the lower and higher doses respectively. The LC50 was 10.7–32 mg/L (REACH).

In two other acute inhalation studies (8 h exposure) with vapour of the chemical (OECD TG 403), no rat mortalities were observed at 5.2 or 7.16 mg/L (REACH).

Observation in humans

In a clinical case study based on a single accidental exposure via both inhalation and dermal contact, severe health effects were reported.

A 32 year old male was accidentally exposed to a 65 % solution of the chemical at work. The solution also contained 0.5 % 1,2-ethanediamine (CAS No: 107-15-3), which is a known corrosive, and 34.5 % polyurethane. Following inhalation of the chemical fumes, he was overcome and fell into the solution for 90 minutes. In addition to skin and eye irritation effects, he suffered from confusion, hallucinations, and developed hepatitis, coagulopathy (poor blood clotting) and rhabdomyolysis (skeletal muscle tissue breakdown) as a result of chemical exposure. He fully recovered and was discharged from hospital after 13 days (REACH).

Corrosion / Irritation

Skin Irritation

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

In a study similar to OECD TG 404, the chemical (99.9 %) was tested under occlusion on the skin of two rabbits for 20 hours. The mean (24, 72 and 96 h) erythema score was 1. No oedema was observed. Any redness was reversible.

In a US DOT skin corrosion test on rabbits (n = 6), a 50 % solution of the chemical showed no corrosive effects on the skin following four hours of exposure. This study was supported by another test on rabbits (n = 2/dose) given 100, 250 or 500 mg/kg bw doses, where no irritation was observed even at the highest dose (OECD, 2001; REACH).

Eye Irritation

Based on the limited data available, the chemical is not considered to cause eye irritation at a level that warrants a hazard classification.

The chemical was reported to slightly irritate the eyes when tested using a study similar to OECD TG 405. Two rabbits were exposed to the chemical (~0.05 mL, 99.9 % purity, no washing) in one eye each. The average scores for the cornea, iris, redness of conjunctivae and chemosis were 1.33, 0.17, 2 and 1 respectively. In one rabbit, the effects were fully reversible within 72 h. In the other rabbit, improvements were noted, but mild effects were still observed at 72 hours (scores of 1 for cornea, redness and chemosis) (OECD, 2001; REACH).

In another study (non guideline), 0.1 mL of the chemical was applied to one eye in each of two rabbits. One rabbit appeared to be in severe pain so the chemical was washed out after one minute. The effects were not scored, but in the washed eye, effects included injury to the cornea, iritis, chemosis and redness of the conjunctivae. In the unwashed eye, the effects were less severe, but moderate corneal damage was still noted. The effects lessened over time and were fully reversible in 14 days (REACH).

Observation in humans

As discussed in the acute toxicity section, a clinical case study is available for a 32 year old male who was accidentally exposed to a chemical mixture including 65 % of this chemical, 0.5 % 1,2-ethanediamine (which is a known corrosive), and 34.5 % polyurethane. Amongst other effects, the man suffered from skin burns where the solution touched his skin, cellulitis (severe inflammation of the skin and inflammation of the connective tissue), oesophagitis (inflammation of the oesophagus) and irritation to the eye. However, given the nature of the chemical mixture, it is difficult to draw conclusions about the irritant effects of this specific chemical (REACH).

Sensitisation

Skin Sensitisation

The chemical was not considered to be a skin sensitiser.

During the induction phase of a non-guideline skin sensitisation study, 10 guinea pigs were exposed to the chemical using either intradermal injections (0.1 % solution, n = 5) or direct application to abraded skin (50 % solution, n = 5). Six doses were applied over a period of 14 days. Three guinea pigs died as a result of dysentery (one in the injection group, two in the direct application group). On day 29, all seven remaining animals were challenged with a 50 % solution on intact skin, then four animals were challenged with a intradermal solution (0.1 %) and three animals with direct application to abraded skin (50 % solution). Irritant effects were observed after one hour in 7/7; 3/3 and 3/4 animals challenged on intact skin, abraded skin and intradermally respectively. The irritation effects disappeared within 48 hours of the challenge. No allergic skin reactions were reported (REACH).

Repeated Dose Toxicity

Oral

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

Rats (Long Evans) were exposed to the chemical in drinking water for 24 months. The no observed adverse effect levels (NOAELs) were established as 100 and 300 mg/kg bw/day in male and female rats, respectively. These NOAELs were based on reduced body weight and liver cell degeneration at 300 and 1000 mg/kg bw/day in males and females, respectively. However, histopathological observations, where liver cell degeneration was observed, were only conducted for controls and at the highest dose (1000 mg/kg bw/day); therefore, the reported NOAELs may have overlooked histopathological effects at lower doses. Clinical signs of toxicity at the highest dose included hair loss (alopecia) in both sexes, and staining around the anus and genitalia in female rats (REACH).

The lowest observed effect level (LOEL) was established as 290 mg/kg bw/day in a 28-day rat study. Atrophy (wasting of the tissue) of the uterus in female rats and a decrease in the absolute weight of the heart in males occurred at this lowest dose tested (290 mg/kg bw/day). At the two highest doses of 1170 and 2350 mg/kg bw/day, significant decreases in food consumption and body weight, and ruffled coats were also observed. At the highest dose, rats also experienced tremors and died (9/10 and 7/10 mortalities in male and female rats, respectively) (REACH).

In a 90-day study (non-guideline) conducted with a single dose group of mice treated at 50 mg/kg bw/day, this dose was stated as the LOEL. Clinical signs of toxicity, including slight leucocytosis, slight anaemia and reduced food consumption were reported. The toxicological relevance of the observations are questionable due to incomplete histopathology (Government of Canada, 2009; REACH).

Dermal

Dermal absorption of the chemical is acknowledged as a significant source of systemic exposure in the HSIS (with the 'Sk' notice referring to 'absorption through the skin may be a significant source of exposure'). Although the chemical is not considered to cause serious damage to health through repeated dermal exposure in animals, human epidemiological/occupational data indicate adverse effects to the liver with repeated dermal exposure. Therefore, a hazard classification is warranted.

In two repeat-dose dermal toxicity studies (28 days and 56 days; 10 males and 20 females per dose in each test) the NOELs were 500 and 1000 mg/kg bw/day for male and female rats, respectively. These NOELs were based on significantly reduced body weight gain in males at 1000 mg/kg bw/day, and no effects observed at the highest dose tested in females (REACH).

A repeat-dose dermal toxicity study in dogs (5 h/day, 5 d/week, for six weeks to six months; two dogs per dose) reported a NOAEL of 94 mg/kg bw/day. This was based on the presence of ulcers, a decrease in body weight gain, and an increase in alkaline phosphatase activity at a concentration of 300 mg/kg bw/day, when compared with controls. Two dogs exposed to 940 mg/kg bw/day had to be euthanised at six weeks. At the highest dose of 2760 mg/kg bw/day, one dog died after 15 days and another had to be euthanised on day 16. In these two dogs, anorexia, depression, lethargy, twitching, abdominal tenderness, diarrhoea and jaundice were observed. The clear presence of jaundice suggests severe impacts on the liver. Local effects of mild to moderate skin irritation were also observed at the treatment site (REACH).

There are some adverse liver effects seen in human epidemiological/occupational health studies with dermal exposure (see **Observations in humans**).

Inhalation

Based on the data available from repeat-dose inhalation toxicity studies with rats and mice, and also based on the epidemiological/occupational exposure studies, repeated exposure to the chemical may cause serious damage to health.

In a 24-month repeat dose inhalation toxicity study in rats, and an 18-month study in mice (6 h/day, 5 d/week exposures), the no observed adverse effect concentrations (NOAECs) were established as 25 ppm vapour (90 mg/m³ or 0.09 mg/L) for male and female rats and male mice, and 101 ppm vapour (360 mg/m³ or 0.36 mg/L) for female mice (REACH). The lowest observed adverse effect concentrations (LOAECs) were:

- 101 ppm for male rats, based on increased incidence of hepatic cystic degeneration with dose-response behaviour, and hepatic peliosis (random, blood-filled cavities in the liver).
- 101 ppm for female rats: based on increased serum concentrations of both cholesterol and glucose; signficantly higher relative liver weight; and increased pigmentation of Kupffer cells.
- 101 ppm for male mice: based on increased pigmentation of Kuppfer cells;
- 350 ppm (1260 mg/m³ or 1.26 mg/L) for female mice: based on increases in the absolute and relative liver and kidney weights.

In 14-day repeat dose inhalation studies (6 h/day, 5 d/week exposures), the NOEC was 300 ppm (1067 mg/m³) for male rats, based on a significant decrease in body weight and some testicular changes at 500 ppm (1800 mg/m³). Similarly, the NOEC was

300 ppm (1067 mg/m³) for male mice, with effects on the testes observed at 500 ppm (1800 mg/m³), including decreased testes weight, lowered sperm count, some degeneration of the seminiferous tubules. A similar testing regime, focusing on haematological and pathological changes, established a NOEC of 100 ppm (356 mg/m³) for male mice. Clinical signs of toxicity at 310 ppm (1104 mg/m³) included lethargy, laboured and irregular breathing and effects on the testes. Mortalities occurred at higher doses (490 ppm and 700 ppm) (REACH).

There are some adverse liver effects seen in humans following inhalation, in epidemiological or occupational health studies (see Observations in humans).

Observation in humans

A number of epidemiological/occupational health studies of workers have been undertaken to examine the effects from exposure to the chemical. In these studies, the impact of long-term, low level exposure to the chemical through combined inhalation and dermal exposure was assessed. The main organ targeted in these studies is the liver. In addition, a number of clinical case studies, based on accidental, repeated exposures, show that the chemical can cause hepatitis. Results from a clinical trial (using the chemical as an anti-tumour agent in cancer patients) show that continued exposure to the chemical can also cause extreme disorientation, lethargy and hallucinogenic effects. A hazard classification is warranted based on the observations in humans.

One occupational health study (between January 2001 and July 2004) examined the incidence of hepatic injuries in 1045 workers from two factories that were producing polyurethane fibres for spandex, using the chemical as a solvent (Jung et al. 2007). *N*-methylacetamide (NMAC) in the urine was used as a marker for exposure to the chemical. Changes in the serum biochemistry, including enzyme activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyltransferase (GGT), were used as markers for liver damage. Hepatic injuries were seen in 38 workers. The median urinary concentration of NMAC was 25.1 mg/g creatinine in the workers experiencing effects on the liver (range 4.6–196.5 mg/g creatinine). In other workers, the median urinary concentration of NMAC was 11.8 mg/g creatinine (range 0.1–133.9 mg/g creatinine). In a number of cases where workers were no longer exposed to the chemical, ALT levels declined. Exposure levels were not quantified, and so the relationship between dose and response was not clear (REACH).

Another occupational health study examined the impact of the chemical on 440 workers new to the industry, between January 2002 and July 2004 (Lee et al. 2008). Workers were from 19 different departments, with exposure to the chemical varying based on different tasks conducted in those departments. Twenty-eight cases of hepatic injury occurred (based on measurements of serum biomarkers like ALT, AST and GGT). In the eight departments where injury occurred, the median urinary NMAC concentration was 19.6 mg/g creatinine. In the 11 other departments, the median urinary NMAC concentration was 5.2 mg/g creatinine. The incidence of hepatic injury was seven times higher in workers with urinary NMAC concentrations > 20 mg/L than in the workers with urinary NMAC concentrations < 20 mg/L.

A separate one-year study on male workers exposed to the chemical at a factory, did not find increased incidence of hepatic injuries compared to a control group (Spies et al. 1995). Exposure was monitored using passive samplers and by measuring NMAC concentrations in the urine. Impacts on the liver were assessed via serum biochemistry markers (AST, ALT, GGT, alkaline phosphatase activity and total bilirubin). The high exposure group (98 samples/21 people) and unspecified exposure group (295 samples/106 people) had mean NMAC concentrations of 26.7 ± 2.7 mg/g creatinine, and 13.5 ± 2.3 mg/g creatinine, in urine respectively. Workers were put into the high exposure group if any one of their urine samples exceeded a trigger value of 60 mg NMAC/g creatinine. Total bilirubin concentrations were significantly lower in the high exposure group compared with the unspecified exposure group and the control group (217 people). Gamma glutamyltransferase was significantly lower in the high exposure group compared with the control group. No other differences in the serum biomarkers were observed in exposed workers compared to workers in the control group (REACH).

A number of clinical case studies are also available reporting on repeated exposure (REACH). At an acrylic fibre plant in two separate incidents, two female workers (aged 25 and 39) were accidentally exposed to the chemical when it splashed above the glove line repeatedly during work processes. As a result, both women reported having very dark urine, developed jaundice and were assessed as developing hepatitis.

In a study where volunteer cancer patients (n = 13) were exposed to the chemical (as an anti-tumour agent) at doses of 200, 300 or 400 mg/kg bw/day for five days (exposure route not reported, but probably oral or intravenously), the highest dose resulted in depression, lethargy, confusion, disorientation and hallucinations. These results were accompanied by changes in electroencephalography (EEG) readings (REACH).

In a volunteer study, eight male workers were deliberately exposed to the chemical as a vapour for 6 h/day (two 3-h doses with a one hour break) for five days at a concentration of 10.3 ppm (36 mg/m³). No clinical signs of toxicity were observed based on behaviour, urine and blood analyses, or various clinical chemistry parameters (REACH).

Genotoxicity

Based on the data available, the chemical is not considered genotoxic.

The chemical produced negative results in several in vitro gene mutation and clastogenicity tests (bacterial reverse mutation assays with *Salmonella typhimurium*; DNA damage and repair assay with human embryonic intestinal cells) and in some in vivo tests (rodent dominant lethal tests with mice and rats, mammalian bone marrow chromosome aberration assays with rats and a gene mutation sex-linked recessive lethal test with *Drosophila melanogaster*) (OECD, 2001; REACH).

The chemical produced positive results in an in vitro sister chromatid exchange assay with Chinese hamster ovary cells (OECD, 2001).

An epidemiological study examining the cytogenetics of lymphocytes in workers exposed to the chemical in industry, did not find significant differences in chromosomal aberrations for exposed workers (n = 20) compared with control, non-exposed workers (n = 16). The values for chromosomal aberrations were 4.9 ± 0.5 % and 3.7 ± 0.4 %, respectively ($p > 0.05$) (Katosova and Pavlenko, 1985). However, the size of the group is small for an occupational health/epidemiological study (REACH).

Carcinogenicity

Based on the data available, the chemical is not considered carcinogenic.

The chemical was not carcinogenic in rats (two-year study) and mice (18-month study) when exposed to the chemical as a vapour in whole body exposures (6 h/day, 5 d/week) at concentrations up to and including the highest dose of 1.26 mg/L (350 ppm). In addition, the chemical was not carcinogenic in rats at concentrations up to and including the highest dose of 1000 mg/kg bw/day by oral exposure in drinking water (two-year study).

Dermal application of the chemical did not result in carcinogenicity in hamsters (concentration not specified, applied three times a week for six weeks). The chemical actually lowered the incidence of tumours in hamsters that had resulted from other chemicals (OECD, 2001; REACH).

Reproductive and Developmental Toxicity

The chemical is classified as a substance toxic to reproduction (Category 2) with the risk phrase ‘May cause harm to the unborn child’ (T; R61) in HSIS (Safe Work Australia). This classification is supported, given the malformations observed in foetuses and young animals in rabbit developmental studies, at doses with no maternal toxicity. The chemical is not considered to affect fertility.

Results of two reproductive toxicity studies showed no adverse effects on fertility in rats, at doses up to 400 ppm (OECD, 2001). In a reproductive study (OECD TG 415), 10 male and 20 female rats were exposed to the chemical via whole body exposure for 6 h/day, 5 d/week for 10 weeks (prebreeding) and 7 d/week for 7–8 weeks (breeding, gestation and lactation periods). The NOAEC for parental toxicity was 100 ppm (360 mg/m³), based on decreased body weight in males and increased relative liver weights in both males and females at doses of 300 ppm (1080 mg/m³). No effects were noted on reproductive indices for the parent generation. The NOAEC for pups was also 100 ppm (360 mg/m³) based on decreased body weights at the highest dose (300 ppm; 1080 mg/m³) (REACH).

A large number of developmental toxicity studies have been conducted using this chemical on rats and rabbits. In a prenatal developmental toxicity study (OECD TG 414), pregnant rats were exposed to the chemical vapour at 0, 30, 100 or 300 ppm for 6 h/day on gestation days 6–15. The NOAECs for both maternal toxicity and developmental toxicity were 100 ppm (360 mg/m³). The pregnant rats had a significant decrease in body weight gain at 300 ppm. Foetal toxicity was observed by significantly lower body weights at 300 ppm. No adverse effects on reproductive parameters were reported (OECD, 2001; REACH).

In an oral gavage study (OECD TG 414–prenatal development toxicity study), the chemical was administered to pregnant rabbits (New Zealand White) on gestation days 6–18 at 0, 94, 280 or 850 mg/kg bw/day. A NOAEL for maternal toxicity was 280 mg/kg bw/day, as all dams died at the highest dose. Apart from reduced food consumption, no clear maternal toxicity effects were reported at 94 and 280 mg/kg bw/day. The NOAEL for developmental toxicity was 94 mg/kg bw/day, based on increased post implantation loss, reduced foetal weight, increased variations, increased rate of malformations at 280 mg/kg bw/day (four cleft palates in 3/10 litters, one fused ribcage and microphthalmia (eye defect)), without any maternal toxicity (OECD, 2001; REACH).

Pregnant rabbits were exposed to the chemical vapour for 6 h/day on gestation days 7–19 at 0, 0.2, 0.7, or 2 mg/L. No maternal toxicity was observed at any dose level. At 2 mg/L, reduced foetal and placental weight and increased skeletal variations of ribs, sternum and vertebral column were observed. The NOAEC for developmental toxicity was 0.7 mg/L (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include acute toxicity by the dermal and inhalation routes of exposure, developmental toxicity and harmful effects following repeated dermal or inhalation exposure.

Epidemiological studies and clinical case studies have raised concerns about potential liver injury in workers exposed to the chemical.

Public Risk Characterisation

Although use in cosmetic/domestic products in Australia is not known, the chemical is reported to be present as a residual solvent in cosmetic/domestic products overseas at concentrations up to 0.01 %.

Unless otherwise specified, if the concentration of a scheduled chemical is below 0.001 % in a formulation, it is exempt from Scheduling. Thus, as a residual solvent in cosmetic products at concentrations lower than 0.001 %, no action may be required. However, at concentrations above this threshold, up to and including 20 % in formulation, the chemical is listed on the SUSMP in Schedule 5. At concentrations greater than 20 %, the chemical falls in Schedule 6.

Chemicals listed in Schedule 6 require a number of warning statements, first aid instructions and safety directions on the label. Schedule 5 chemicals require appropriate packaging with simple warnings and safety directions on the label. These control measures are considered adequate to minimise the risk to public health from any cosmetic/domestic use of the chemical. Therefore the risk to public health is not considered to be unreasonable.

Occupational Risk Characterisation

Given the critical health effects, the risk to workers from this chemical is considered high unless adequate control measures to minimise occupational exposure to the chemical are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business, or an employee at a workplace, has adequate information to determine appropriate controls.

NICNAS Recommendation

The chemical is sufficiently assessed and risk managed providing the recommendation for classification and labelling is followed.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP).

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful in contact with skin (Xn; R21)* Harmful by inhalation (Xn; R20)*	Harmful in contact with skin - Cat. 4 (H312) Harmful if inhaled - Cat. 4 (H332)
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 through inhalation (Xn; R48/20)	May cause damage to organs through prolonged or repeated exposure through inhalation and dermal routes - Cat. 2 (H373)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May cause harm to the unborn child (T; R61)*	May damage the unborn child - Cat. 1B (H360D)

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

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

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

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

Advice for industry

Control measures

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

- 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 be solely 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 hazardous 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 physical hazards of the chemical has not been undertaken as part of this assessment.

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