# Acetonitrile: Human health tier II assessment

**27 October 2017**

## CAS Number: 75-05-8



## 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.

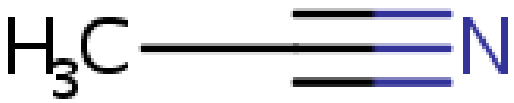
For more detail on this program please visit:www.nicnas.gov.au

**Disclaimer**



Acronyms & Abbreviations

## Chemical Identity

| | |
|---|---|
| Synonyms | methylcyanide<br>cyanomethane<br>ethylnitrile<br>methanecarbonitrile<br>methane carbonitrile |
| Structural Formula |  |
| Molecular Formula | C2H3N |
| Molecular Weight (g/mol) | 41.05 |
| Appearance and Odour (where available) | colourless liquid with a sweet ether-like odour |
| SMILES | C(C)#N |

# Import, Manufacture and Use

## Australian

The National Pollutant Inventory (NPI) holds data for all sources of the chemical in Australia.

The chemical has reported commercial uses, including in:

- the photographic industry;
- printing inks; and
- the textile industry.

The chemical has reported site-limited uses, including:

- as a solvent in the production of vitamin B, pharmaceuticals, perfumes, pesticides and plastics;
- as a solvent in lithium batteries;
- in the extraction and refining of copper; and
- in the extraction of fatty acids from oils.

## 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 United States (US) National Library of Medicine's Hazardous Substances Data Bank (HSDB); and the European Chemicals Bureau (ECB) EU Risk Assessment Report on Acetonitrile (ECB, 2002).

The chemical has reported commercial uses, including in:

- printing processes; and
- dyeing textiles.

The chemical has reported site-limited uses, including:

- as a solvent in the production of pharmaceuticals, perfumes, plastics and electrochemical cells;
- in photographic film manufacturing;
- as an intermediate in the synthesis of other chemicals; and
- as an extraction agent.

# Restrictions

## Australian

No known restrictions have been identified.

## International

The chemical is listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist').

# Existing Work Health and Safety Controls

## Hazard Classification

The chemical is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

Acute toxicity – category 4 – H332 (Harmful if inhaled)

Acute toxicity – category 4 – H312 (Harmful in contact with skin)

Acute toxicity – category 4 – H302 (Harmful if swallowed)

Eye irritation – category 2 – H319 (Causes serious eye irritation)

## Exposure Standards

### Australian

The chemical has an exposure standard of 67 mg/m$^3$ (40 ppm) time weighted average (TWA) and 101 mg/m$^3$ (60 ppm) short-term exposure limit (STEL) (Safe Work Australia).

### International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 34–70 mg/m$^3$ (20–40 ppm) TWA and 101–105 mg/m$^3$ (60–70 ppm) short-term exposure limit (STEL) in different countries such as Canada (Alberta, Quebec, Saskatchewan), Denmark, Egypt, Estonia, Greece, Hungary, Iceland, Latvia, Malta, Poland, Singapore, South Africa, Spain and the United States of America.

# Health Hazard Information

## Toxicokinetics

Based on the studies available, acetonitrile is readily absorbed following skin contact and by ingestion and inhalation. Once administered, acetonitrile is rapidly distributed throughout the body. Data from a human with lethal acetonitrile poisoning indicated that after five days the highest concentration of acetonitrile was in the kidneys, liver and spleen, while concentrations in the heart and lungs were much lower (MAK, 2012).

Acetonitrile is predominantly excreted in the form of its metabolites. The first step in the metabolism process is the oxidation of acetonitrile to glycolonitrile which then decomposes into hydrogen cyanide. The toxic effects of acetonitrile are the result of its metabolism into hydrogen cyanide. The severity and speed of the onset of cyanide poisoning is dependent on the dose and the administration route (MAK, 2012).

Hydrogen cyanide is further metabolised by the enzyme, rhodanese, which converts hydrogen cyanide into thiocyanate which is then excreted in urine. A small amount of hydrogen cyanide can also be eliminated via the lungs (MAK, 2012).

Pharmacokinetic studies have examined the time course of acetonitrile metabolising to cyanide. The results showed that the maximum serum levels of acetonitrile occurred after 7.5 hours; while after 72 hours it was barely detectable. Blood cyanide levels peaked at comparable levels after 7.5 hours and declined after 72 hours almost to base levels (ECB, 2002).

## Acute Toxicity

### Oral

The chemical is classified as hazardous with hazard category ‘Acute Toxicity Category 4’ and hazard statement ‘Harmful if swallowed’ (H302) in the HCIS (Safe Work Australia). Sufficient human data (see **Acute Toxicity: Observation in Humans** section) are available to indicate that the current classification is appropriate.

The following oral median lethal dose (LD50) values were available (ECB, 2002; HSDB; REACH):

- 140 mg/kg bw in male guinea pigs (strain not specified);
- 269 mg/kg bw in male ddY mice;
- 617 mg/kg bw in Crl:CD-1 (ICR) BR mice (similar to the Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 401);
- 158 mg/kg bw in 14-day-old Sprague Dawley (SD) rats;
- 175–200 mg/kg bw in rats (sex and strain not specified);
- >200–2000 mg/kg bw in Wistar rats;
- 1327 mg/kg bw in male Wistar or Nelson albino rats;
- 3081–3476 mg/kg bw in adult SD rats;
- 3800 mg/kg bw in Sherman rats;
- 6500 mg/kg bw in male ChR-CD rats; and
- 6762 mg/kg bw in female Wistar or Nelson albino rats.

Reported signs of the chemcial toxicity include tremors, prostration, decreased activity, laboured breathing, convulsions, gasping and increased salivation (REACH).

### Dermal

The chemical is classified as hazardous with the hazard category ‘Acute Toxicity Category 4’ and hazard statement ‘Harmful in contact with skin’ (H312) in the HCIS (Safe Work Australia). Sufficient human data (see **Acute Toxicity: Observation in Humans** section) are available to indicate that the current classification is warranted.

The following dermal LD50 values were available (ECB, 2002; HSDB; REACH):

- 395 mg/kg bw in male rabbits (strain not specified) using a 75 % (v/v) acetonitrile solution;

- 988 mg/kg bw in male rabbits (strain not specified) using an undiluted acetonitrile solution;
- >2000 mg/kg in New Zealand White (NZW) rabbits (similar to OECD TG 402); and
- 3950 mg/kg bw in rabbits (sex and strain not specified).

### Inhalation

The chemical is classified as hazardous with the hazard category 'Acute Toxicity Category 4' and hazard statement 'Harmful if inhaled' (H332) in the HCIS (Safe Work Australia). Sufficient human data (see **Acute Toxicity: Observation in Humans** section) are available to indicate that the current classification is warranted.

The following LC50 values were available for the chemical vapour (ECB, 2002; HSDB; REACH):

- 4525 mg/m$^3$/1 hr (equivalent to 2.3 mg/L for a four hour exposure) in male Crl:CD-1 (ICR) BR mice;
- 6026 mg/m$^3$/4 hrs (equivalent to 6.0 mg/L) in Crl:CD-1 (ICR) BR mice (similar to OECD TG 403);
- 4751 mg/m$^3$/4 hrs (equivalent to 4.8 mg/L) in male rabbits (strain not specified);
- 9495 mg/m$^3$/4 hrs (equivalent to 9.5 mg/L) in guinea pigs (strain not specified);
- 12685 mg/m$^3$/8 hrs (equivalent to at least 25.4 mg/L for a four hour exposure) in male Nelson rats;
- 20890 mg/m$^3$/8 hrs (equivalent to at least 41.8 mg/L for a four hour exposure) in female Nelson rats;
- 26880 mg/m$^3$/4 hrs (equivalent to 26.9 mg/L) in Nelson rats;
- 28710 mg/m$^3$/4 hrs (equivalent to 28.7 mg/L) in male ChR-CD rats;
- 33495 mg/m$^3$/4 hrs (equivalent to 33.5 mg/L) in male SD rats; and
- >13432–26864 mg/m$^3$/4 hrs (equivalent to 13.4–26.9 mg/L) in male dogs

Reported signs of toxicity include tremors, abnormal gait, decreased activity, limb splaying, laboured breathing, convulsions and gasping. Prostration and convulsions occurred prior to death. Lung haemorrhage and congestion was reported in animals that survived, as well as animals that died (ECB, 2002; REACH).

### Observation in humans

In humans, case studies reporting death following a single exposure to the chemical are limited.

In toddlers, an estimated oral dose of 1000–2000 mg acetonitrile/kg bw caused death in a 16-month-old male, weighing 11.8 kg, following ingestion of 15–30 mL of a nail polish remover product containing the chemical. Ingestion by an older toddler (3-year-old, sex not specified, weighing 17.2 kg) of 15–30 mL of a nail tip and glue remover product containing the chemical resulted in a similar estimated dose of the chemical (800–1700 mg acetonitrile/kg bw), but did not cause death; gastric lavage was performed as part of this child's treatment. Ingestion by a 2-year-old female weighing 15.8 kg of 5–10 mL of a nail glue containing the chemical at 84 % and resulting in an estimated dose of 250–500 mg/kg bw, did not lead to death (ECB, 2002).

In adults, ingestion of an estimated oral dose of 570 mg acetonitrile/kg bw by a 26-year-old male in a suicide attempt caused severe health effects (i.e. respiratory insufficiency, metabolic acidosis, cardiac arrest and coma) but did not result in death. In another suicide case study, ingestion of the chemical at an estimated dose of 64 mg/kg bw (followed by ingestion of 1 mL ammonium) by a 30-year-old male did not lead to death. However, death was reported in a 22-year-old female, 30 hours after ingesting an unspecified amount of the chemical combined with acetone, and in a couple (one male and one female) after accidental ingestion of the chemical (dose not available) (ECB, 2002).

Accidental dermal and inhalation exposure to the chemical by a toddler (2-year-old male, weighing 12 kg), following spillage on his bed of 30 mL of a nail remover product containing the chemical at 98–100 %, resulted in lethargy and vomiting, but not death (ECB, 2002).

Two mortalities have been reported in male workers following inhalation exposure to the chemical over two days—in one case after painting of a chemical plant storage tank with acetonitrile-containing paint and thinner, and in another case after cleaning a photographic laboratory floor with acetonitrile and boiling water. Mortality was preceded by nausea, vomiting, convulsions and coma in both cases. High levels of cyanide were also measured in blood and urine (NTP, 1996; ECB, 2002).

In an inhalation study, three adult male volunteers were exposed to the chemical at 40, 80 or 160 ppm (67, 134 and 269 mg/m$^3$) for four hours on separate occasions spaced 7–9 days apart. Chest and bronchial tightness, as well as facial flushing were reported in some volunteers, but there were no significant changes in blood cyanide or urinary thiocyanate levels (NTP, 1996; US EPA, 1999; ECB, 2002).

## Corrosion / Irritation

### Respiratory Irritation

Based on the available data, the chemical is considered to cause some respiratory irritation in animals and humans (see **Observations in humans** below).

In a developmental toxicity study, pregnant Syrian golden hamsters (n = 6–12/dose) were exposed (whole body) to the chemical vapour at 0, 3022, 6380, 8395 or 13432 mg/m$^3$ for 60 minutes on GD 8 and euthanised on GD 14. There were deaths in dams exposed at 6380 mg/m$^3$ (1/6), 8395 mg/m$^3$ (1/6) and 13432 mg/m$^3$ (3/12). Signs of respiratory irritation preceded death and included nose irritation, excess salivation, breathing difficulties and gasping (US EPA, 1999; ECB, 2002; REACH).

Respiratory irritation was also reported in rats exposed to the chemical vapour at ≥3104 mg/m$^3$ for six hours per day, five days per week, for one month (NTP, 1996; REACH).

### Skin Irritation

Based on the available data, the chemical is not considered to cause skin irritation.

In an acute dermal irritation/corrosion study (similar to OECD TG 404), NZW rabbits (n = 6 males) were exposed (semi-occlusive) to 0.5 mL of the chemical on intact shaved skin for four hours and examined up to 72 hours later. No signs of irritation were reported (ECB, 2002; REACH).

In another skin irritation study, white rabbits (strain, sex and number not specified) were exposed (occlusive) to the undiluted chemical via saturated cotton pads for either 15 minutes or 20 hours. The site of application was rinsed after the 15 minutes treatment, but not rinsed after the 20 hours treatment. Observations were made immediately after the pad was removed, and at 1, 3 and 8 days. It was reported that there were no skin reactions (ECB, 2002; REACH).

In a non-guideline study, one albino rabbit was exposed to 0.01 mL of the undiluted chemical on shaved belly skin and observations were made after 24 hours. It was reported that the skin irritating potential of acetonitrile was similar to that of acetone (ECB, 2002; REACH).

### Eye Irritation

The chemical is classified as hazardous with hazard category 2 and hazard statement ‘Causes serious eye irritation’ (H319) in the HCIS (Safe Work Australia). The available data support an amendment to this classification (see **Recommendation** section) as guideline studies indicate that exposure to the chemical results in irreversible effects on the eye.

In an acute eye irritation study (similar to OECD TG 405), NZW rabbits (n = 6 males) were exposed to 0.1 mL of the chemical in the conjunctival sac of one eye. The exposed eyes were held closed for one second and then released; the eyes were not rinsed. Eyes were observed at one hour, and one, two, three, four, seven, 14 and 21 days after dosing. Signs of irritation were present in all animals from the one hour observation and included corneal opacity, diffuse red conjunctivae, slight iris injection, swelling, partial lid eversion and considerable discharge. Corneal opacity was reversed in three rabbits by day 14, but was still present in three rabbits at day 21; these rabbits also had corneal vascularisation. Conjunctival redness and discharge was reversed in two rabbits by day 14, but was still present in four rabbits at day 21. Iritis was reversed by 14 days in all rabbits. There were no other signs of ill health or toxicity observed during the study (ECB, 2002; REACH).

In other eye irritation studies, one drop of the undiluted chemical was administered in one eye of five rabbits and after 24 hours the effects were scored 5 on a scale of 1–10 (where a score ≥5 represents severe damage). Using a different scoring system, an irritation score of 3/6 was reported following exposure to one drop of the chemical in the conjunctival sacs of rabbits and monitoring up to eight days. Oedema and slight necrosis were also reported (ECB, 2002; REACH).

In a developmental toxicity study, pregnant Syrian golden hamsters (n = 6–12/dose) were exposed (whole body) to the chemical vapour at 0, 3022, 6380, 8395 or 13432 mg/m$^3$ for 60 minutes on gestation day (GD) 8 and euthanised on GD 14. Eye (and nose) irritation was reported in 4/12 animals exposed at 13432 mg/m$^3$. In all animals exposed at 8395 mg/m$^3$, 'irritation' was reported (no details available) (US EPA, 1999; ECB, 2002; REACH).

Ocular irritation was also reported in rats exposed to the chemical vapour at ≥3104 mg/m$^3$ for six hours per day, five days per week, for one month (NTP, 1996: REACH).

### Observation in humans

In 15 workers exposed to the chemical in an industrial setting reported nose, throat, and skin irritation (NTP, 1996; ECB, 2002).

## Sensitisation

### Skin Sensitisation

Based on the available data, the chemical is not considered to cause skin sensitisation.

In a skin sensitisation study (OECD TG 406) using the Buehler method, Hartley guinea pigs (n = 10/sex) were exposed (occlusive) to 0.3 mL of the undiluted chemical for approximately six hours, once weekly for three weeks for the induction phase. Animals were challenged two weeks after the last exposure, on a different skin site, using 0.3 mL of the chemical for six hours, and observations made up to 48 hours later. The incidence and severity of the responses in the test group (3/20) was comparable to that of the negative control (exposed to distilled water) group (2/10) (ECB, 2002; REACH).

## Repeated Dose Toxicity

### Oral

No data are available.

### Dermal

In a non-guideline study, rabbits (n = 3, sex and strain not specified) were exposed to 2 mL of the undiluted chemical to each ear (total of 4 mL) for 24 hours, four times over 10 days. Body weights decreased over the 10 days, but recovered over a three week

period after exposure ceased. Light purple skin discolouration was reported at the site of application, but there were no signs of systemic toxicity or changes in urinary parameters (REACH).

### Inhalation

Based on the available data, the chemical is not considered to cause serious health effects from repeated inhalation exposure, except at high doses.

In a repeated dose inhalation toxicity study, Fischer (F344/N) rats (n = 10/sex/dose) were exposed (whole body) to acetonitrile vapour at 0, 100, 200, 400, 800 and 1600 ppm (0, 168, 335, 670, 1340 or 2681 mg/m$^3$) for six hours per day, five days per week for 13 weeks. Mortality was reported in six male and three female rats exposed at 1600 ppm and one male exposed at 800 ppm. Hypoactivity and ruffled fur were observed in males (≥800 ppm) and females (1600 ppm) in the first week of the study. In rats exposed at the highest concentration, body weight gain and terminal body weight were significantly lower than the control group in both sexes. Clinical findings in the males (1600 ppm) which died in the first week of the study were ataxia, abnormal posture and clonic convulsions. In animals that died, lung lesions consisting of congestion, oedema, and alveolar haemorrhage were reported in males exposed at ≥800 ppm and females exposed at 800 ppm; various lesions such as brain haemorrhage, cellular depletion of the bone marrow and thymus atrophy were noted in both sexes; and lymphoid depletion of the spleen and depletion of the corpora lutea in the ovary were noted in females exclusively. In rats exposed at ≥800 ppm, the absolute and relative thymus weights were lower than the control groups. At 1600 ppm, female rats had significantly greater absolute and relative heart, kidney and liver weights compared with the control group; and decreased triiodothyronine ($T_3$) concentration (without changes in thyroxine ($T_4$) and thyroid stimulating hormone (TSH) concentrations). Decreases in the haemoglobin concentration, the red blood cell count and haematocrit were reported in males exposed at 1600 ppm and females exposed at ≥800 ppm. Based on these results, the no observed adverse effect concentration (NOAEC) for the chemical is 670 mg/m$^3$ and the lowest observed adverse effect concentration (LOAEC) is 1340 mg/m$^3$ (NTP, 1996; ECB, 2002; REACH).

In a repeated dose inhalation toxicity study, B6C3F1 mice (n = 10/sex/dose) were exposed (whole body) to acetonitrile vapour at 0, 100, 200, 400, 800 and 1600 ppm (0, 168, 335, 670, 1340 or 2681 mg/m$^3$) for six hours per day, five days per week for 13 weeks. There were mortalities in mice exposed at concentrations ≥400 ppm—one female at 400 ppm, one male and four females at 800 ppm and all mice at the highest dose. Terminal body weights of rats in groups exposed to the chemical were not significantly different compared with controls, except in males exposed at 800 ppm which had a reduced body weight. In both sexes at doses ≥800 ppm, hypoactivity and rigid posture were recorded in the first week of the study. In males exposed at ≥200 ppm and in females exposed at 800 ppm, absolute liver weights were greater than that of the controls, while relative liver weights were greater in all exposed male groups and in females exposed at ≥400 ppm. Non-neoplastic forestomach lesions and epithelial hyperplasia were reported in females (≥200 ppm) and males (≥400 ppm). In one female at 200 ppm, and one male and five females at 1600 ppm, focal ulcers associated with areas of epithelial hyperplasia were reported. In mice exposed at 400 and 800 ppm there was an increase in hepatocellular cytoplasmic vacuolation. In mice that died during the study, lymphoid depletion and lymphocytosis in the thymus and spleen were reported. Based on these results, the NOAEC for the chemical was reported to be 168 mg/m$^3$ for females and 335 mg/m$^3$ for males (NTP, 1996; ECB, 2002; REACH).

In two year carcinogenicity studies in F344/N rats and B6C3F1 mice (see **Carcinogenicity** section), it was reported that the chemical had no significant systemic effects following repeated dose inhalation exposure. In the F334/N rats, no mortality was reported and there was no effect on body weight gain or on terminal body weights in treated compared with control rats. A statistically significant increase in liver basophilic foci was reported in rats exposed at ≥335 mg/m$^3$ compared with controls. In the B6C3F1 mice, the survival rates of male and female mice exposed at ≤100 ppm were similar to that of the controls; in male mice exposed at 200 ppm, survival was significantly greater than that of the controls. Exposure to the chemical had no effect on body weight gain or on terminal body weight of the male and female mice, and no significant haematological or clinical effects were reported (NTP, 1996; ECB, 2002; REACH).

## Genotoxicity

Based on the weight of evidence from available studies, the chemical is not considered to be genotoxic.

The following in vitro test results were available (NTP, 1996; ECB, 2002; REACH):

- negative results for point mutation or recombination, but positive results for aneuploidy, in yeast cytogenetic assays in *Saccharomyces cerevisiae* strain D61.M exposed to the chemical at up to 4.76 %, without metabolic activation;
- negative results in several bacterial reverse mutation assays in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535 or TA1537 and *Escherichia coli* strains WP2uvrA and Wp2uvrA/pKM101 exposed to the chemical at up to 10000 µg/plate, with or without metabolic activation;
- negative results in mammalian cell gene mutation assays using Chinese hamster ovary (CHO) cells exposed to the chemical at up to 30 mg/mL or mouse lymphoma L5178Y cells exposed to the chemical at 50 µL/mL, with or without metabolic activation;
- negative results in a chromosome aberration assay in CHO cells without metabolic activation and equivocal results with metabolic activation, using the chemical at up to 5000 µg/mL;
- overall equivocal (weakly positive without metabolic activation, negative with metabolic activation) results in a sister chromatid exchange (SCE) assay in CHO cells exposed to the chemical at up to 5000 µg/mL; and
- positive results in an in vitro comet (DNA damage) assay in HepG2 cells and peripheral human lymphocytes exposed to the chemical at up to 500 µM, without metabolic activation.

In vivo tests were mostly negative (NTP, 1996; ECB, 2002; REACH):

- negative results in a mammalian erythrocyte micronucleus test (OECD TG 474) in peripheral blood and bone marrow from NMRI mice exposed to the chemical once by intraperitoneal (i.p.) injection at up to 125 mg/kg bw;
- negative results in a micronucleus assay using peripheral blood samples from female B6C3F1 mice exposed (whole body) to the chemical for six hours per day, five days per week at up to 800 ppm for 13 weeks, but positive results in males exposed at 400 ppm under the same study conditions; and
- positive results in germ line aneuploidy studies in female *Drosophila melanogaster* fed an aqueous solution containing the chemical at up to 50000 ppm as larvae or adults, or exposed (whole body) to the chemical vapour once at 131 ppm for 70 minutes.

## Carcinogenicity

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

The National Toxicology Program (NTP) concluded that 'there was *equivocal evidence of carcinogenic activity* in male F344/N rats based on marginally increased incidences of hepatocellular adenoma and carcinoma' and that '[t]here was *no evidence of carcinogenic activity* of acetonitrile in female F344/N rats … [and] male or female B6C3F1 mice' (NTP, 1996).

In a two year carcinogenicity study, F344/N rats (n = 56/sex/dose) were exposed (whole body) to the chemical vapour at 0, 100, 200 or 400 ppm (0, 168, 335 or 672 mg/m$^3$) for six hours per day, five days per week for 103 weeks. There were no significant effects on survival or terminal body weight in exposed rats compared with control. In rats exposed at 400 ppm, there was an increased incidence of liver adenomas and carcinomas in males; however, these results were not significant as they sit on the outer limit of historical controls (NTP, 1996; ECB, 2002; REACH).

In a two year carcinogenicity study, B6C3F1 mice (n = 60/sex/dose) were exposed (whole body) to the chemical vapour at 0, 50, 100 or 200 ppm (0, 84, 168, or 335 mg/m$^3$) for six hours per day, five days per week for 103 weeks. Mortality was similar in all groups, except for male mice exposed at 200 ppm where survival was significantly greater than the controls. Mean body weights and organs weights were similar in all groups, and there were no signs of systemic toxicity. In males only, there was a significantly increased incidence of liver adenoma or carcinoma in rats exposed at 100 ppm and a significantly increased incidence of alveolar/bronchiolar adenoma or carcinoma in mice exposed at 200 ppm; these were within the range of historical controls. There was a dose-related increase in the incidence of non-neoplastic forestomach epithelium squamous cell hyperplasia in exposed mice, which was statistically significant in males exposed at 200 ppm and in females exposed at ≥100ppm; the highest incidence in this study equalled the highest incidence in historical controls (NTP, 1996; ECB, 2002; REACH).

## Reproductive and Developmental Toxicity

Based on the available data information, the chemical does not show specific reproductive or developmental toxicity. Any developmental effects were only observed secondary to maternal toxicity.

In a reproductive study, F344/N rats and B6C3F1 mice (n = 10/sex/dose) were exposed to the chemical via inhalation at concentrations of 100, 200 and 400 ppm (168, 336 and 672 mg/m³) for 13 weeks. Results from the study include no changes in the absolute or relative weight of the right cauda or right testes and no effect on sperm motility. In a second study, SD rats (n = 10/sex/dose) exposed to 1200 ppm (2015 mg/m³) for six hours/day for 42 days (males) and up to 41 days (females), resulted in a lower fertility rate compared to controls and a change in oestrous cycles for some of the animals. At the highest concentration mortality also occurred (NTP, 1996; ECB, 2002).

In a developmental toxicity study, pregnant SD rats (n = 20/dose) were exposed to the chemical at approximately 0, 900, 1200, 1500 and 1800 ppm (0, 1511, 2015, 2518 and 3023 mg/$m^3$) for six hours per day on GD 6–20 and euthanised on GD 21. Maternal lethality (8/20) and a decrease in maternal body weight gain during GD 6–21 was reported in rats exposed at 1800 ppm; at concentrations ≥1500 ppm the maternal absolute weight gain in exposed animals was approximately 60 % of the control group. Pregnancy rate was not significantly altered by exposure to the chemical; however, an increase in the mean percentage of non-surviving implants and early embryonic reabsorptions were reported at 1800 ppm. There were no significant effects on the average number of implantation sites, foetal sex ratios or foetal weights and no significant changes in the incidences of visceral or skeletal variations. The NOAEC for maternal toxicity was reported to be 2015 mg/$m^3$, and 2518 mg/$m^3$ for developmental toxicity (IRIS, 1999; ECB, 2002).

In a second developmental toxicity study, SD rats (n = 10 non pregnant females, and 33 mated females) were exposed to 0, 100, 400 or 1200 ppm (0, 168, 672 or 2015 mg/m³) for six hours/day seven days/week for 14 days (GD 6–19 for pregnant animals). Mortality occurred in the highest exposure groups (2/33 pregnant; 1/10 non pregnant). No treatment related effects on body weight, pup weight, pup deformity, or litter size were observed in any exposure group. The only statistically significant effect occurred at the lowest dose range where there was an increase in the incidence of supernumerary ribs in the offspring. This did not have a dose-response relationship as there was no variation in the other exposure groups compared to controls (ECB, 2002).

Pregnant NZW rabbits (n = 25/dose) were administered the chemical by oral gavage at 0, 2, 15 or 30 mg/kg on GD 6–18. Mortality was reported in 5/25 dams exposed at the highest dose. Maternal body weight gain was reduced during the exposure period in rabbits exposed at ≥15 mg/kg bw, but returned to normal for the remaining gestation period. No effects were observed in the rabbits exposed at the lowest dose. Pregnancy rate, implantation rate, mean foetal body weight and sex ratio were not significantly affected. In dams exposed at the highest dose, there was a significant decrease in the average number of live foetuses and a non-significant increase in resorptions. It was reported that there were no gross external, soft tissue, skeletal or developmental malformations in foetuses related to the administration of the chemical. The maternal no observed adverse effect level (NOAEL) was reported to be 15 mg/kg bw/day and the developmental NOAEL 30 mg/kg bw/day (IRIS, 1999; ECB, 2002).

In a reproductive toxicity study, pregnant golden hamsters were exposed to the chemical at 0 (n = 10), 1800 (n = 6), 3800 (n = 6), 5000 (n = 6) or 8000 ppm (n = 12) (0, 3023, 6380, 8395 or 13432 mg/$m^3$) for one hour on GD 8. Maternal deaths occurred in hamsters exposed at concentrations ≥3800 ppm (1/6, 1/6 and 3/12 for 3800, 5000 and 8000 ppm concentrations, respectively). At concentrations ≥5000 ppm there was an increase in the incidence of foetal abnormalities such as resorption and malformations that were not seen in the animal control group or lower dose animal groups. Malformations included exencephaly (where the brain develops outside of the skull), encephelocoele (sac like protrusions that appear from openings in the skull), rib fusions and at the highest concentration one foetus had ectopia cordis (the heart is located partially or totally outside of the thorax). At the highest concentration mean animal foetal weights were significantly reduced (ECB, 2002).

In a reproductive toxicity study, pregnant golden hamsters were administered the chemical via gavage at doses of 0, 100, 200, 300 or 400 mg/kg on GD 8. Maternal mortality occurred at 300 mg/kg (1/6) and 400 mg/kg (4/12). There was a significant increase in resorptions in the 200 and 400 mg/kg dose groups. The incidence of foetal deformities significantly increased at doses =300 mg/kg. Two litters in the 100 mg/kg dose group also contained malformed foetuses compared to the control group which had none. Skeletal deformities included rib fusions and severe spinal development disorders (ECB, 2002).

In a reproductive toxicity study, pregnant Long-Evan rats were administered the chemical by intubation at concentrations of 0, 50, 150, 300 and 600 mg/kg on GD 7–21. Maternal death occurred at concentrations ≥300 mg/kg. In the surviving animals there

was no effect on the litter size, pup viability and birth weight (IRIS, 1999).

In a reproductive toxicity study, pregnant CD-1 rats received the chemical by gavage on GD 6–15 doses of 125, 190 and 275 mg/kg. Maternal mortality was observed at the highest dose (2/25). Maternal reduced weight gain (2/25) was also observed. No other maternal effects were noted in any of the other animal dose groups. At the highest dose there was an increase in toxic effects on the embryo as noted by the increase in resorptions and postimplantation losses compared to historic controls (ECB, 2002).

# Risk Characterisation

## Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from oral, dermal and inhalation exposure). The chemical can also cause eye irritation.

## Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. No evidence of the presence of the chemical in consumer products was found in available North American databases (Household Products Database and Environmental Working Group Cosmetic Database), indicating that the chemical is not likely to be widely used for domestic or cosmetic uses. Hence, the public risk from this chemical is not considered to be unreasonable.

## Occupational Risk Characterisation

Given the critical systemic acute health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, 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 supports an amendment to the hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

# NICNAS Recommendation

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

## Regulatory Control

### Work Health and Safety

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

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

| Hazard | Approved Criteria (HSIS)[a] | GHS Classification (HCIS)[b] |
|---|---|---|
| Acute Toxicity | Not Applicable | Harmful if swallowed - Cat. 4 (H302)* Harmful in contact with skin - Cat. 4 (H312)* Harmful if inhaled - Cat. 4 (H332)* |
| Irritation / Corrosivity | Not Applicable | Causes serious eye damage - Cat. 1 (H318) |

[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;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

***Obligations under workplace health and safety legislation***

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and

- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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