Piperazine: Human health tier II assessment

08 March 2019

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Piperazine	110-85-0
Piperazine, hexahydrate	142-63-2

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

NICNAS has made every effort to assure the quality of information available in this report. However, before relying on it for a specific purpose, users should obtain advice relevant to their particular circumstances. This report has been prepared by NICNAS using a range of sources, including information from databases maintained by third parties, which include data supplied by industry. NICNAS has not verified and cannot guarantee the correctness of all information obtained from those databases. Reproduction or further distribution of this information may be subject to copyright protection. Use of this information without obtaining the permission from the owner(s) of the respective information might violate the rights of the owner. NICNAS does not take any responsibility whatsoever for any copyright or other infringements that may be caused by using this information.

ACRONYMS & ABBREVIATIONS

Grouping Rationale

Piperazine (anhydrous form; CAS No. 110-85-0) is also commercially available in hydrated form, piperazine hexahydrate (CAS No. 142-63-2). Both chemicals will be referred in this assessment as 'piperazine', unless otherwise specified.

Import, Manufacture and Use

Australian

No current industrial use, import, or manufacturing information has been identified for piperazine.

However the following non-industrial uses have been identified:

- in veterinary products (worm treatment) registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA);
- as a stabiliser in therapeutic products registered by the Therapeutic Goods Administration (TGA), but the amount used is 'not sufficient to exert a pharmacological action' (TGA); and
- as an absorbent for carbon dioxide in research (CSIRO).

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening Information Dataset Initial Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary; and eChemPortal:

OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

Piperazine has reported domestic use including in adhesives and binding agents.

Piperazine has reported commercial use including as a:

- hardener;
- scrubber (gas washing liquid); and
- corrosion inhibitor.

Piperazine has reported site-limited use including:

- as an intermediate in formulating industrial chemicals;
- as a process regulator; and
- in manufacturing food contact materials (coatings for polypropylene films that have contact with food at temperatures not exceeding the room temperature (US FDA)).

Piperazine has reported non-industrial use including:

- in insecticides;
- as an intermediate in formulating therapeutic drugs and veterinary products (e.g. antibiotics, analgesics, antihistamines);
- as an active ingredient in therapeutic drugs and veterinary products (mainly antihelminthics); and
- as a flavouring substance in food (Galleria Chemica).

The US FDA maximum recommended therapeutic dose (MRTD) for piperazine is 66.7 mg/kg bw/day (Galleria Chemica).

Restrictions

Australian

Piperazine is listed in Schedules 2 and 5 of the *Poisons Standard* (Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP) for non-industrial uses only (SUSMP, 2019).

Schedule 2 – Pharmacy Medicine

'PIPERAZINE for human therapeutic use.'

Schedule 2 chemicals are 'substances, the safe use of which may require advice from a pharmacist and should be available from a pharmacy or, from a licensed person'.

Schedule 5 – Caution

'PIPERAZINE for animal use.'

Schedule 5 chemicals 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'.

International

Piperazine is listed on the following (Galleria Chemica):

- Under Article 15 of the European Commission (EC) Regulation No. 1223/2009, use of the chemical is prohibited in cosmetic products (CosIng);
- US FDA Indirect Food Additives—'Substances for use as components of coatings— limitations: For use only in coatings for polypropylene films that contact food at temperatures not to exceed room temperature: Resinous and polymeric coatings for polyolefin films 21CFR 175-320, under the following entry: (i) resins and polymers: polyamide resins, as the basic resin, derived from: polyamide resins, as the basic resin, derived from: piperazine in an amount not to exceed 6.4 percent by weight of the polyamide resin'; and
- US FDA Indirect Food Additives: 'Adhesives and components of coatings—Substances for use only as components of adhesives—piperazine'.

Existing Worker Health and Safety Controls

Hazard Classification

Piperazine 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). This classification is based on the recommended amendments to the hazard classification in the HCIS (formerly known as HSIS) from the IMAP assessment published in Tranche 9:

- Skin corrosion – Category 1B; H314 (Causes severe skin burns and eye damage)
- Skin sensitisation – Category 1; H317 (May cause an allergic skin reaction)
- Respiratory sensitisation – Category 1; H334 (May cause allergy or asthma symptoms or breathing difficulties if inhaled)
- Specific target organ toxicity (single exposure) – Category 3; H335 (May cause respiratory irritation)
- Reproductive toxicity – Category 2; H361fd (Suspected of damaging fertility. Suspected of damaging the unborn child)
- Specific target organ toxicity (single exposure) – Category 1; H370 (Causes damage to organs if swallowed)
- Specific target organ toxicity (repeated exposure) – Category 2; H373 (May cause damage to organs through prolonged or repeated exposure if swallowed)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

- 0.1 mg/m^3 time weighted average (TWA) and 0.3 mg/m^3 short-term exposure limit (STEL) in most European countries including France, the UK, Germany, Spain, Bulgaria, Ireland and the Netherlands;
- 0.14 mg/m^3 TWA in the USA;
- 0.3 mg/m^3 TWA in Canada, Norway and Sweden; and

- 1 mg/m^3 STEL in Canada and Sweden.

Health Hazard Information

Piperazine is also available in the form of piperazine salts for use in veterinary and medical purposes. Piperazine and piperazine salts have similar hazard classification in the HCIS, except that piperazine can also cause severe skin burns and eye damage (NICNAS). Therefore, in the absence of data on the systemic toxicity effects for piperazine, data available on piperazine salts are used in this assessment.

Toxicokinetics

Radiolabelled piperazine dihydrochloride (CAS No. 142-64-3) was administered to pigs as a single oral gavage dose of 300 mg/kg bw. Almost complete absorption occurred within the seven-day observation period. The administered radioactivity was eliminated in the urine (56 % with 46 % within the first 24 hours) and in the faeces (16 % with 8 % within the first 24 hours) within seven days. The major part of the excreted compound was identified as unchanged piperazine during the first 24 hours. The chemical was found in kidneys and liver, with the elimination rate quite slow for the liver (25 % remaining after seven days) compared with the kidneys (only 3 % remaining 12 hours after dosing). The proportion of metabolites in the urine increased from less than 20 % after 24 hours to 40–50 % after 168 hours, and in the kidneys from about 20 % at 12 hours to 80–90 % of the remaining activity at 96 hours post dosing (EU RAR, 2005).

The urinary excretion of piperazine was measured by a colourimetric method in ten healthy volunteers who received piperazine phosphate orally (Standen et al., 1955; Rogers, 1958). Excretion was highest between one and eight hours after administration, and virtually complete within 24 hours, with 30.5 % ± 4.27 of the administered dose being excreted. Results showed a wide variation in the rate of excretion between individuals, but no significant difference in the amount (%) excreted comparing different salts such as adipate and citrate (Standen et al., 1955).

A dog study showed that, in the presence of nitrite, the chemical undergoes nitrosation to produce N-mononitrosopiperazine (NPZ) in a rapid reaction, and at a slower rate to produce di-nitroso derivative N,N'-dinitrosopiperazine (DNP) (EU RAR, 2005).

In five human subjects, piperazine citrate excreted through urine was investigated by colourimetry. After oral administration of 3.5 g of the test substance, 60–75 % of the dose was excreted in the urine within 24 hours (EU RAR, 2005).

The metabolite NPZ was detected in small amounts in the gastrointestinal tract and urine of persons either exposed orally or by inhalation to the chemical (EU RAR, 2005).

Acute Toxicity

Oral

Piperazine has low acute oral toxicity.

In a study comparable to OECD Test Guideline (TG) 401, piperazine was administered to Sprague Dawley (SD) rats at 1000, 1210, 1780, 2610 or 3830 mg/kg bw. No mortalities were observed at the three low doses. The median lethal dose (LD50) was estimated to be 2600 mg/kg bw (EU RAR, 2005; REACHa). Reported signs of toxicity were dyspnoea (shortness of breath), apathy, abnormal position, staggering, tremor, scrubby coat, lacrimation, yellow-coloured urine and poor general condition (REACHa).

A similar study also indicated an LD50 of 2500 mg/kg bw in SD rats. Reported signs of toxicity included dyspnoea, apathy, saltation (abrupt movements) and convulsions (HSDB; REACHa).

Dermal

Piperazine has low acute dermal toxicity.

Piperazine was applied to the abraded skin of New Zealand White rabbits (comparable with OECD TG 402) at 7000, 9000 or 10000 mg/kg bw for 24 hours, after a preliminary test induced mortality in 3/10 rabbits at 8000 mg/kg bw. The dermal LD50 was estimated to be 8300 mg/kg bw. Reported signs of toxicity included cyanosis, diarrhoea, salivation, mild convulsions, bleeding from the mouth and nose, ataxia, loss of righting (orientation reflex), abnormal stance, catatonia (motor immobility), ptosis (drooping eyelid), and decreased activity (REACHa).

An LD50 of 4000 mg/kg bw in rabbits was found in several information sources, with no details provided (Clayton & Clayton, 1994; EU RAR, 2005; REACHb; RTECS).

Inhalation

Only limited data are available indicating a median lethal concentration (LC50) of >1.61 mg/L.

The EU RAR (2005) indicates 'no adequate data' for acute inhalation toxicity of piperazine.

In a study similar to OECD TG 403, rats exposed (whole body) to a single dose of the chemical (vapours) at 1.61 mg/L for eight hours exhibited only a slight mucosal irritation. There were no mortalities (REACHa). The LC50 is greater than 1.61 mg/L.

An LC50 of 5400 mg/m^3/2 hours (5.4 mg/L/2 hours) was reported for mice, but study details (form of exposure, i.e. vapour or aerosol) are not available to consider this value for hazard classification (RTECS).

Observation in humans

A 'probable oral lethal dose' of 5–15 g/kg for an adult human was suggested, illustrating the low toxicity of piperazine (HSDB).

Based on the occurrence of severe neurotoxic symptoms in several human case reports, a lowest observed adverse effect level (LOAEL) of 110 mg/kg was proposed for acute exposure in humans (EU RAR, 2005).

Corrosion / Irritation

Corrosivity

Piperazine is classified as hazardous with hazard category 'Skin corrosion – Category 1B' and hazard statement 'Causes severe skin burns and eye damage (H314)' in the HCIS (Safe Work Australia). The available data support this classification for both forms of piperazine (see **Recommendation** section).

Piperazine is a strong basic amine (EU RAR, 2005). A 10 % aqueous solution has a pH of 10.8–11.8 (HSDB); therefore, the chemical is expected to be corrosive.

Piperazine at 50 % (in water) was applied to the shaved skin of Vienna White rabbits (OECD TG 404) for four hours as semi-occlusive patches. Mean scores for oedema and erythema were 1.33 and 3.88 respectively; these were not fully reversible after 72 hours post exposure. Additional findings were necrosis (24 hours after exposure) turning into deep necrosis (involving all layers of the skin) after 72 hours. Piperazine at 50 % was corrosive to the skin (EU RAR, 2005; REACHa).

In another study, New Zealand White rabbits were exposed to 0.5 mL of piperazine (melted) as occlusive patches, for three minutes or one hour. Moderate to severe erythema (score = 3) was observed one hour after one rabbit was exposed for three minutes. Desquamation was also observed in one animal. Desquamation, scab formation, full thickness necrosis or alopecia were recorded in four animals exposed for one hour, indicating that the chemical was corrosive (REACHa).

Irreversible damage to corneal tissue (necrosis) was observed when a 5 % solution of piperazine was applied to the eyes of rabbits for up to 24 hours. The chemical was graded 9 on a scale ranging from 1 to 10, with necrosis covering 60–90 % of the

cornea (EU RAR, 2005). However, these results were obtained from a study conducted in 1946, which was not compliant with the current OECD Test Guidelines.

Observation in humans

Eight volunteers were exposed to two samples of piperazine hexahydrate as dermal patches containing 25 g/100 mL water (equivalent to 11 % piperazine) for up to 48 hours. Both samples were dermal irritants, with one sample causing severe erythema and oedema. The experiment was repeated with seven volunteers and led to similar results (McCullagh, 1968).

Sensitisation

Respiratory Sensitisation

Piperazine is classified as hazardous with hazard category 'Respiratory sensitisation – Category 1' and hazard statement 'May cause allergy or asthma symptoms or breathing difficulties if inhaled (H334)' in the HCIS (Safe Work Australia). No animal data are available, but the available human data support this classification for both forms of piperazine (see **Observation in humans** section).

Skin Sensitisation

Piperazine is classified as hazardous with hazard category 'Skin sensitisation – Category 1' and hazard statement 'May cause an allergic skin reaction (H317)' in the HCIS (Safe Work Australia). The available human data support this classification for both forms of piperazine (see **Recommendation** section).

In a Magnusson and Kligman guinea pig maximisation test, Dunkin-Hartley guinea pigs were administered intradermal injections of piperazine at 5 % according to the protocol. Seven days later, guinea pigs were exposed to a 50 % solution of piperazine (epicutaneous induction) for 48 hours and challenged after 14 days, epicutaneously with a 25 % concentration. Piperazine was a mild sensitiser with 5 % of the animals (n = 19) exhibiting a positive allergic response, including at least well-defined erythema (Leung & Auletta, 1997; REACHa).

Piperazine was tested in a local lymph node assay (LLNA) on Balb/c mice at concentrations of 5, 10 or 20 % (w/v) in a mixture of water, acetone and olive oil for three days. The chemical induced only a weak positive response at 10 % concentration, measured by ^{3}H-thymidine incorporation in the lymph nodes and cytokine production, indicating an allergic response, but failed to induce the production of other allergen markers (EU RAR, 2005).

Observation in humans

A number of human case reports support the existing classifications (EU RAR, 2005).

Respiratory sensitisation

Respiratory sensitisation was demonstrated in reports of occupational asthma in workers exposed to piperazine. A survey was conducted among 130 Swedish workers involved in manufacturing piperazine and some of its salts. Asthma associated with occupational exposure was identified in 15 current employees and 18 former employees. Most (29/33) of these cases of asthma were directly related to piperazine exposure. Symptoms associated with asthma were recurrent dyspnoea with wheezing and coughing. None of the subjects had a history of asthma before their employment (Hagmar et al.,1982; EU RAR, 2005).

A study on more than 600 Swedish workers (employed between 1942 and 1979) showed a strong relationship between exposure to piperazine and asthma symptoms. In the most exposed group (number not indicated), about a third of the workers had experienced symptoms of asthma, and every fourth worker had chronic bronchitis (Hagmar et al., 1984; EU RAR, 2005).

A case of respiratory allergy was reported for a 60-year-old Australian after he was exposed to piperazine while mixing 26 batches of sheep drench between March and June 1964. The man had no history of allergic reactions, but during the exposure to piperazine he developed serious allergic symptoms described as 'severe cough with white frothy sputum and a severe wheezing dyspnoea'. He also had rhinorrhoea (free discharge of a thin nasal mucus) and excessive lachrymation (tear formation). Symptoms disappeared after he ceased work, but came back as soon as he came in contact with the chemical again (McCullagh, 1968).

Respiratory sensitisation was observed in two workers exposed to a mixture of piperazine dihydrochloride and lactose dust (250 g chemical per kg of lactose). The adverse effect was reported to be delayed (3–4 h) asthmatic reaction in both workers (Pepys et al., 1972).

A 42-year old woman developed occupational asthma after being exposed to piperazine citrate via inhalation. Coughing was initially reported, followed by chest tightness, shortness of breath and wheezing as well as nasal stuffiness, watery nose, and nasal and ocular itching. Symptoms were assessed as mild and intermittent. Chronic asthma was reported to have occured following exposure to piperazine citrate. A skin prick test confirmed that piperazine citrate had caused the allergic reaction (Quirce et al., 2006).

Skin sensitisation

Many cases of allergic dermatitis caused by piperazine in therapeutic products have been reported. Signs of allergy included urticarial erythematous swellings, oedema and pruritic rash following dermal contact or ingestion (EU RAR, 2005).

Four men with clinical evidence of sensitivity (eczema, erythema and oedema) were exposed to patches moistened with aqueous solutions containing piperazine hexahydrate at 1 and 0.1 g/100 mL. All four men showed exacerbation of their symptoms (McCullagh, 1968).

A woman developed urticaria and generalised erythema after being treated with various piperazine derivatives, including piperazine phosphate (MAK, 2012).

Repeated Dose Toxicity

Oral

Based on the available human data, piperazine is expected to cause serious damage to health following repeated oral exposure. Therefore a hazard classification is recommended for both forms of piperazine (see **Recommendation** section).

EU RAR (2005) reported a LOAEL around 30 mg/kg bw/day for repeated exposure to piperazine in healthy humans (see **Observation in humans** section).

In a 90-day study, groups of rats (n = 10/sex/dose) were administered the chemical at 0, 1000, 3000 or 10000 ppm (corresponding to 0, 50, 150 and 500 mg/kg bw/day, respectively) or piperazine dihydrochloride at 0, 1830, 5500 or 18300 ppm (corresponding to 0, 45, 140 and 450 mg/kg bw/day of piperazine, respectively) in the diet. While piperazine dihydrochloride did not induce any adverse effects up to the highest dose tested, the administration of piperazine induced adverse effects at 3000 and 10000 ppm. These included degenerative changes in the liver (with diffuse swelling and focal necrosis) along with fibrotic and degenerative changes in the kidneys, but the effects were milder at 3000 ppm. A no observed adverse effect level (NOAEL) of 50 mg/kg bw/day was determined for the chemical. However, the validity of this study was stated as questionable (EU RAR, 2005).

In a 90-day feeding study (following US FDA standards and good laboratory practice (GLP) compliant), Sprague Dawley (SD) rats (n = 20/sex/dose) were administered piperazine dihydrochloride at 0, 400, 1200 or 2394 mg/kg bw/day. Apart from a dose-related decrease in body weight gain, no adverse effects were observed during the study. A NOAEL of 1200 mg/kg bw/day was determined, corresponding with a NOAEL of 627 mg/kg bw/day for piperazine (REACHa).

In a 13-week study, beagle dogs (n = 8/dose) were administered piperazine dihydrochloride at 0, 92, 369 or 1476.8 ppm in the diet (corresponding to piperazine at 1.5, 6 or 25 mg/kg bw/day). Except for mild hepatic effects (details not available), no other compound-related systemic toxicity was observed. A NOAEL of 25 mg/kg bw/day for the chemical (50 mg/kg bw/day for

piperazine dihydrochloride) was proposed by the EU Committee for Veterinary Medicinal Products (CVMP) (EU RAR, 2005; REACHa).

Dermal

No animal data are available.

Inhalation

No animal data are available.

Observation in humans

EU RAR (2005) reported a LOAEL around 30 mg/kg bw/day for repeated exposure to piperazine in healthy humans, based on neurotoxic effects during a 3–7 day treatment period. However, as there were no data on doses lower than 30 mg/kg bw/day (therapeutic dose as an antihelminthic drug), this value was not regarded as a true LOAEL.

Repeated inhalation exposure to piperazine can induce chronic bronchitis in humans (details of doses not available) (EU RAR, 2005).

Genotoxicity

Based on the negative in vitro results for a number of salts of piperazine, it is considered that piperazine is not mutagenic. Only in vitro data are available on piperazine and one of the in vitro assays showed positive results for gene mutation, with metabolic activation. Available epidemiological data also indicate mixed results. The positive results for genotoxicity could have occurred due to formation of the metabolite, N-nitroso-piperazines (NPZ).

EU RAR (2005) concluded: 'Studies conducted in vitro, as well as in vivo indicate that piperazine does not induce point mutations or chromosome aberrations', and '... however, NPZ that can be formed by nitrosation of piperazine in vivo demonstrate clear genotoxic properties (in vivo DNA strand breaks and mutations)'.

Piperazine gave negative results in several in vitro studies including:

- a bacterial reverse mutation test (similar to OECD TG 471) using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 at doses 33–2167 µg/plate, with or without metabolic activation (Haworth et al., 1983);
- another Ames test (similar to OECD TG 471) using *S. typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 at doses up to 10000 µg/plate, with or without metabolic activation (REACHa); and
- a mammalian cell transformation assay (following EU Method B.21) using BALB/3T3 mouse cells at doses 1–300 µg/mL (no data on metabolic activation) (REACHa).

One in vitro mammalian cell gene mutation assay (OECD TG 476) with piperazine using mouse lymphoma cells L5178Y, gave positive results, with metabolic activation, at 125–500 µg/mL (REACHa).

No in vivo genotoxicity studies are available on piperazine.

The salt piperazinium dihydrogen phosphate (CAS No. 14538-56-8), was found negative in an in vivo micronucleus test in CD-1 mice that received a single oral dose of the salt at 5000 mg/kg bw (EU RAR, 2005; REACHa).

Piperazine dihydrochloride (CAS No. 142-64-3) was found negative in a host-mediated *S. typhimurium* (TA 1950) mouse assay in which NMRI mice were administered gavage doses of the salt at 1450–2900 µmol/kg bw. However when co-administered with nitrite, the test substance induced some mutagenic response from 145 µmol/kg bw (lowest effective dose) (Braun et al., 1977).

A cohort study in workers exposed mainly to piperazine indicated a significant, but modest, increase in the incidence of micronuclei in cultured peripheral lymphocytes compared with control subjects (Hogstedt et al., 1988). However, other studies in workers exposed to mixtures of chemicals including piperazine showed no difference in the incidence of micronuclei and chromosome aberrations in lymphocytes between exposed workers and unexposed control subjects (Hagmar et al., 1988; Pero et al., 1988).

Carcinogenicity

The limited information available indicates that piperazine is not expected to have carcinogenic properties on its own. However, the nitrosated chemical NPZ (a minor metabolite, according to EU RAR, 2005) has shown some carcinogenic potential in mice.

EU RAR (2005) stated that, 'Although there are no solid indications of a carcinogenic effect of piperazine, either in animal studies, or from the investigation in humans, the supporting database is insufficient to permit definite conclusions. However, in view of lack of genotoxic action, it appears unlikely that piperazine poses a carcinogenic risk.'

Swiss mice (n = 20/sex/dose) were administered piperazine in the feed at 6.25 mg/kg (equivalent to 938 mg/kg bw/day), alone or together with sodium nitrite (at 1000 mg/L drinking water) or sodium nitrite alone, for 28 weeks with observation for a further 12 weeks before being euthanised. Dinitrosopiperazine (DNPZ) (40 mg/L drinking water) was used as positive control. The chemical alone or sodium nitrite alone produced no effect, but administering piperazine with sodium nitrite induced significant increase in the percentage of adenoma-bearing mice (64 %) and lung adenoma per mouse (1.8 ± 2.2). The study authors suggested that in vivo nitrosation of piperazine to mononitrosopiperazine (NPZ) could be responsible for the carcinogenic effects (Greenblatt et al., 1971; EU RAR, 2005).

Similar results were observed in strain A mice treated with piperazine at 0.69–18.75 g/kg in food and sodium nitrite in drinking water for 20–25 weeks. The chemical alone did not induce any effects, whereas the combination with sodium nitrite significantly increased lung adenoma (Greenblatt et al., 1973; EU RAR, 2005).

Reproductive and Developmental Toxicity

Piperazine is classified as hazardous with hazard category 'Reproductive toxicity – Category 2' and hazard statement 'Suspected of damaging fertility. Suspected of damaging the unborn child (H361fd)' in the HCIS (Safe Work Australia). The available data on piperazine dihydrochloride (CAS No. 142-64-3) and piperazine phosphate (CAS No. 14538-56-8) support these classifications for both forms of piperazine (see **Recommendation** section).

A human case report indicates a mother exposed to two, 7-day oral courses of piperazine adipate (at 2100 mg/day or 38 mg/kg/day assuming a body weight of 55 kg, during gestation days (GD) 41–47 and 55–61) gave birth to a girl with malformed hands and feet. The parents had two healthy children previously (EU RAR, 2005). However, the EU RAR (2005) concluded that 'it is difficult to evaluate the possible relationship with the piperazine treatment from this only case'.

In a two-generation animal study (OECD TG 416), SD rats were treated with 0, 5000, 12000 or 25000 ppm of piperazine dihydrochloride in the diet (equivalent to 0, 125, 300 and 625 mg/kg bw/day piperazine base) throughout maturation, mating, gestation and lactation phases for two successive generations. There was clear evidence of toxicity at the highest dose in both generations indicated by reduced body weight gain, reduced number of pregnancies (significant only in F1) and reduced litter size. Developmental effects were also noted including delayed sexual maturation in F1 animals (age at vaginal opening in females and preputial separation in males), but this could be related to the decreased body weight. Reduced body weights and food consumption were noted at 300 mg/kg bw/day, along with reduced litter size in both generations, reduced implantation sites in F1 and delayed sexual maturation in F1. No treatment-related effects were reported at 125 mg/kg bw/day. A NOAEL of 125 and a LOAEL of 300 mg/kg bw/day for maternal toxicity were established (EU RAR, 2005; REACHa).

In a developmental toxicity study (non-guideline), Charles River CD(SD)BR female rats were treated orally with 250, 1000 or 5000 mg/kg bw/day piperazine phosphate (presumably CAS No. 14538-56-8) equivalent to 105, 420 and 2100 mg/kg bw/day piperazine base during GD 6–15. Signs of maternal toxicity included excessive salivation, lethargy, reduced food consumption and body weight gain at the highest dose. No teratogenic effect was reported, but foetal weights were reduced (EU RAR, 2005; REACHa).

In another developmental toxicity study from the same author (GLP compliant), groups of 16 New Zealand White female rabbits were orally administered piperazine phosphate (CAS No. 14538-56-8) suspended in 1 % w/v methyl cellulose at 0, 100, 225 or 500 mg/kg bw/day from GD 6–18 of gestation (equivalent to 0, 42, 94 and 210 mg/kg bw/day piperazine base). Animals were euthanised on day 28. Signs of maternal toxicity at the highest dose included neurotoxicity (excessive salivation and nervousness), anorexia, reduced food intake (by 85 % during days 6–14), reduced faeces production and body weight, abortion (in one female) and intestinal abnormalities (in two females killed in extremis). A LOAEL of 94 mg/kg bw/day for maternal toxicity was determined based on transiently reduced body weight gain, food consumption (-39 %) and faeces production. Teratogenic effects included a high rate of post-implantation loss (100 % resorption in four litters), reduced foetal weight, slight retardation in ossification, major abnormalities in 23 % of foetuses (cleft palate, umbilical hernia) and increased incidence of poorly ossified hindlimbs, all at the highest dose. The study suggested that teratogenic effects could be secondary to maternal toxicity, due to reduced food intake (EU RAR, 2005; REACHa).

Based on the available information, the EU RAR (2005) suggested piperazine be classified for reproductive and developmental toxicity.

Other Health Effects

Neurotoxicity

The available human data indicate piperazine causes serious damage to health following a single oral exposure (acute LOAEL = 110 mg/kg bw for neurotoxicity). Therefore, a hazard classification is recommended for both forms of piperazine.

Based on the occurrence of severe neurotoxic symptoms following exposure to high doses of piperazine in several human case reports, a LOAEL of 110 mg/kg was proposed for acute exposure in humans (EU RAR, 2005).

There were case reports from Europe, in the USA, the Middle East and South-East Asia that piperazine induced neurotoxicity in humans with a few daily doses. Due to these case reports, the pharmaceutical use of the chemical was withdrawn in Sweden and some other countries. These effects were not observed in rats or mice, but were observed in other mammalian species (EU RAR, 2005).

There were 36 human cases reported with varying degrees of neurotoxicological symptoms following administration of piperazine, totalling around 200 mg/kg bw, administered within 5–7 days. Electroencephalogram (EEG) changes were noted in 37 % of 89 children exposed to piperazine at 90–130 mg/kg bw (two doses in one day). Reported neurotoxic effects included muscular weakness, unsteadiness, lack of coordination, hypotonia, diminished tendon reflexes, tremor, spasms, mental confusion and hallucinations after administration of piperazine as an antihelminthic drug in adults and children at 100 mg/kg bw and 50–65 mg/kg bw, respectively (EU RAR, 2005). The mechanism of action of piperazine is unknown in mammals, but could be due to gamma-amino butyric acid (GABA) receptor agonism (EU RAR, 2005).

A 12-year old girl showed signs of neurotoxicity after a single oral dose of 24 mg/kg bw of piperazine citrate. Symptoms included hypotonia, diminution of muscle power and tendon reflexes, and these disappeared within 24 hours (EU RAR, 2005).

Following ingestion of 500 mg piperazine citrate, three times a day for two days for a threadworm infestation, a four-year old girl showed toxic neurological signs (inability to stand up, repeated jerks of head and limbs), that disappeared after 24 hours. Toxic effects were attributed to a chemical overdose. It is also reported that 'a higher incidence of abnormal electroencephalograms (EEG) occurred in children on therapeutic doses of piperazine hexahydrate, compared with the less soluble piperazine tartrate', implying that the incidence of neurotoxicity is related to the solubility of the piperazine compound (i.e. less soluble piperazine compounds have a lower incidence of neurotoxicity) (Savage, 1967).

Piperazine has reported neurotoxic side effects in animals treated with antihelminthic formulations (recommended dose in cats and dogs is 45–65 mg/kg bw). Neurological effects in dogs included acute distress, ataxia, head and neck stretched out, front legs pulled back along the chest wall, and hind legs stretched outwards. Felidae species (cats, tigers, lions) appeared to be more sensitive to piperazine and have showed effects including lethargy, tonic seizures and lack of muscular coordination with ataxia (EU RAR, 2005).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic acute and long-term effects (neurotoxicity, reproductive and developmental toxicity); and
- local effects (corrosivity, skin and respiratory sensitisation).

Public Risk Characterisation

Piperazine is listed on Schedules 2 and 5 of the SUSMP for non-industrial uses. Currently there are no restrictions in using piperazine in domestic products in Australia.

Information on Australian use of the chemical has not been made available. International information is considered representative for Australian use and indicate domestic use as adhesive and binding agents (see **Import, manufacture and use** section). Considering this use, it is unlikely that the public will be exposed to piperazine at high concentrations. Hence, the public risk is not considered to be unreasonable. However, if it were to be used in domestic products at high concentrations, it could pose an unreasonable risk to the public given the critical health effects of piperazine.

Occupational Risk Characterisation

Given the critical health effects, piperazine may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure to piperazine are implemented. Piperazine 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.

The data available support an amendment to the hazard classification of piperazine hexahydrate in the HCIS (see **Recommendation** section).

NICNAS Recommendation

Assessment of piperazine is considered to be sufficient, provided that the recommended amendment to the classification of piperazine hexahydrate 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. No further assessment is required, unless any domestic uses of piperazine with potential high level public exposure in Australia are identified.

Regulatory Control

Public Health

At present, therapeutic products containing piperazine for human use, and products containing piperazine for animal use fall within Schedules 2 and 5 of the SUSMP, respectively.

Work Health and Safety

Based on the recommended amendment to the hazard classification from the IMAP assessment published in Tranche 9, anhydrous piperazine is currently classified in the HCIS (see Existing Work Health and Safety Controls). Note that this updated assessment report does not change the current hazard classification for anhydrous piperazine (CAS No 110-85-0).

However, it is recommended that the current hazard classification for anhydrous piperazine (CAS No 110-85-0) be extended to piperazine hydrate (CAS No 142-63-2) for classification and labelling aligned with the globally Harmonised System of chemicals and Labelling of Chemicals (GHS) as below. This assessment 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]
Irritation / Corrosivity	Not Applicable	Causes severe skin burns and eye damage - Cat. 1B (H314)
Sensitisation	Not Applicable	May cause allergy or asthma symptoms or breathing difficulties if inhaled - Cat. 1 (H334) May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Not Applicable	May cause damage to organs through prolonged or repeated exposure through the oral route - Cat. 2 (H373)
Reproductive and Developmental Toxicity	Not Applicable	Suspected of damaging fertility or the unborn child - Cat. 2 (H361fd)
Other Health Effects	Not Applicable	Causes damage to organs if swallowed - Specific target organ tox, single exp Cat. 1 (H370)

[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 piperazine 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 piperazine from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to piperazine 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 piperazine.

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 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 piperazine has not been undertaken as part of this assessment.

References

Aggregated Computational Toxicology Resource (ACToR). Accessed at **http://actor.epa.gov/actor/faces/ACToRHome.jsp**

Australian Pesticides and Veterinary Medicines Authority (APVMA). Available at **http://www.apvma.gov.au/**

Braun R, Schöneich J and Ziebarth D, 1977. In Vivo Formation of N-Nitroso Compounds and Detection of Their Mutagenic Activity in the Host-mediated Assay.Cancer Res 1977;37:4572-4579.

Clayton GD and Clayton FE (eds.) 1994. Patty's Industrial Hygiene and Toxicology: Volume II Part E: Toxicology. 4th ed. New York: John Wiley Sons, 1994., p. 3315-3319

Commonwealth Scientific and Industrial Research Organisation (CSIRO), 2013. Concentrated Piperazine based Post-Combustion-Capture for Australian coal-fired power plants Summary Report. September 2013. Available at **http://decarboni.se/sites/default/files/publications/120061/concentrated-piperazine-based-pcc-australian-coal-fired-p**ower-plants.pdf

European Union Risk Assessment Report (EU RAR) 2005. Piperazine CAS No.: 110-85-0 EINECS No.: 203-808-3 Risk Assessment Final Report, 2005. Accessed at **http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/piperazinereport324.pdf**

Galleria Chemica. Accessed at **http://jr.chemwatch.net/galleria/**

Greenblatt M and Mirvish S, 1973. Dose-Response Studies With Concurrent Administration of Piperazine and Sodium Nitrite to Strain A Mice. J Nat Cancer Inst 50(1): 119-124, 1973

Greenblatt M, Mirvish S and So BT, 1971. Nitrosamine Studies: Induction of Lung Adenomas by Concurrent Administration of Sodium Nitrite and Secondary Amines in Swiss Mice. J Nat Cancer Inst 46: 1029-1034, 1971

Hagmar L, Bellander T, Englander V, Ranstam J, Attewell R and Skerfving S, 1986. Mortality and cancer morbidity among workers in a chemical factory. Scand J Work En viron Health 12 (1986) 545-551.

Hagmar L, Bellander T, Hogstedt B, Hallberg T, Attewell R, Raihle G, Au WW, Legator MS, Mitelman F and Skerfving S, 1988. Biological effects in a chemical factory with mutagenic exposure. I. Cytogenetic and haematological parameters. Int Arch Occup Environ Health. 1988;60(6):437-44.

Haworth S, Lawlor T, Mortelmans K, Speck W and Zeiger E, 1983. Salmonella Mutagenicity Test Results for 250 Chemicals. Environmental Mutagenesis Supplement 1 :3-142 (1983)

Hazardous Substances Data Bank (HSDB). Accessed at **http://toxnet.nlm.nih.gov**

Hogstedt B, Bratt I, Holmen A, Hagmar L and Skerfving S, 1988. Frequency and size distribution of micronuclei in lymphocytes stimulated with phytohemagglutinin and pokeweed mitogen in workers exposed to piperazine. Hereditas 109: 139-142 (1988)

Leung HW and Auletta CS, 1997. Evaluation of Skin Sensitization and Cross-Reaction of Nine Alkyleneamines in the Guinea Pig Maximization Test. J Toxico Cut Ocular Toxicol, 16(3), 189-195 (1997).

McCullagh SF, 1968. Allergenicity of Piperazine: A Study in Environmental Aetiology. Brit.Jf. industr. Med., 1968, 25, 319.

Pepys J, Pickering CAC and Loudon HWG 1972. Asthma due to inhaled chemical agents–piperazine dihydrochloride. Clinical& Experimental Allergy Vol 2.2 pp 189–196.

Pero R, Hagmar L, Seidegard J, Bellander T, Attewell R and Skerfving S, 1988. Biological effects in a chemical factory with mutagenic exposure. II. Analysis of unscheduled DNA synthesis and adenosine diphosphate ribosyl transferase, epoxide hydrolase, and glutathione transferase in resting mononuclear leukocytes. Int Arch Occup Environ Health. 1988;60(6):445-51.

Quirce S, Pelta R and Sastre J 2006. Occupational asthma due to piperazine citrate. J Investig Allergol Clin Immunol. 2006;16(2):138-9.

Registration, Evaluation and Authorisation of Chemicals (REACH a) Dossier. Piperazine (CAS No. 110-85-0). Accessed at **http://echa.europa.eu/information-on-chemicals/registered-substances**.

Registration, Evaluation and Authorisation of Chemicals (REACH b) Dossier. Piperazine, compound with phosphoric acid (CAS No. 1951-97-9). Accessed at **http://echa.europa.eu/information-on-chemicals/registered-substances**.

Registry of Toxic Effects of Chemical Substances (RTECS). Accessed at **http://www.cdc.gov/niosh/rtecs/**

Savage DCL, 1967. Neurotoxic effects of piperazine. Br Med J. Jun 24, 1967; 2(5555): 840–841.

Substances and Preparations in Nordic countries (SPIN) database. Accessed November 2018 at **http://www.spin2000.net/spinmyphp/**

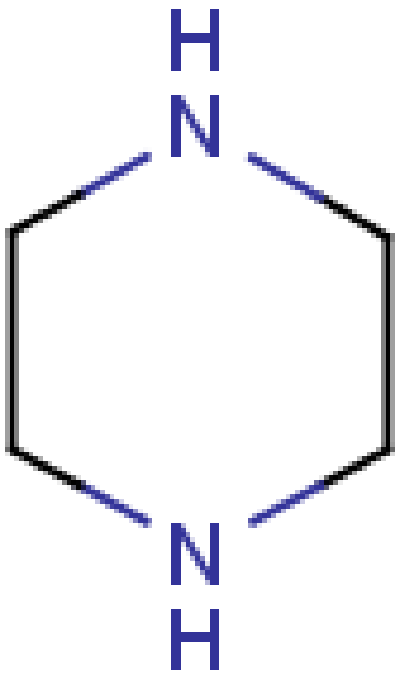
The Poisons Standard February 2019. The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) No. 23. Accessed February 2019 at **https://www.tga.gov.au/publication/poisons-standard-susmp**

Therapeutic Goods Administration (TGA). Available at **http://www.tga.gov.au/**

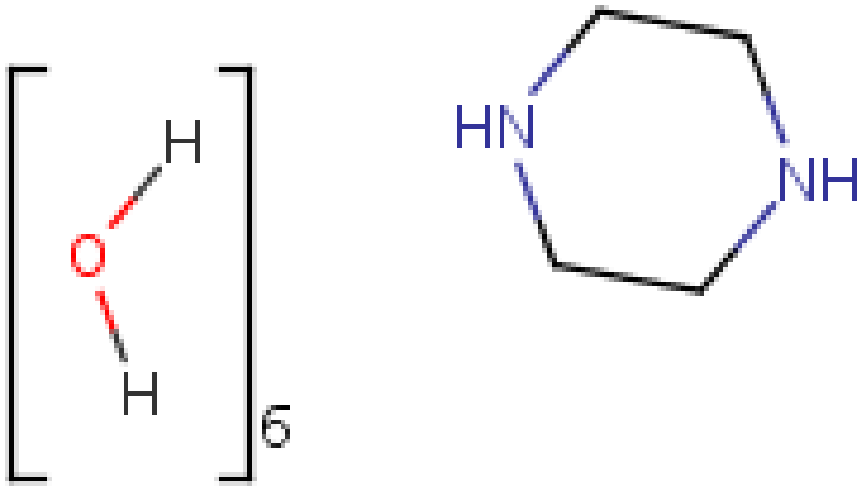
US Food and Drug Administration (FDA). The List of Indirect Additives Used in Food Contact Substances. Available at **http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/IndirectAdditives/default.htm**

Last Update 08 March 2019

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Piperazine** 1,4-diazacyclohexane 1,4-diethylenediamine diethyleneimine hexahydro-1,4-diazine hexahydropyrazine
CAS Number	110-85-0
Structural Formula	
Molecular Formula	C4H10N2
Molecular Weight	86.14

Chemical Name in the Inventory and Synonyms	**Piperazine, hexahydrate**
CAS Number	142-63-2

Structural Formula	
Molecular Formula	C4H10N2.6H2O
Molecular Weight	194.22

Share this page