Piperazine salts: Human health tier II assessment

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Piperazine, dihydrochloride	142-64-3
Hexanedioic acid, compound with piperazine (1:1)	142-88-1
Piperazine, 2-hydroxy-1,2,3-propanetricarboxylate (3:2)	144-29-6
Piperazine, phosphate	1951-97-9
Piperazine, phosphate (1:1)	14538-56-8
Piperazine, phosphate (1:1), monohydrate	18534-18-4
Piperazine, 2-hydroxy-1,2,3-propanetricarboxylate (3:2), hydrate	41372-10-5

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

Grouping Rationale

Piperazine dihydrochloride and piperazine phosphate are both salts of piperazine (CAS No. 110-85-0), with a piperazine content of 50 % and 42 %, respectively (EU RAR, 2005). The hazard profiles of the two salts are considered similar to that of the parent base, piperazine, except they are reported to lack the corrosivity of the parent base. These two salts have similar uses and were assessed together in Tranche 9. Following the Tier II assessment, additional piperazine salts with similar uses were identified from the Australian Inventory of Chemicals Substances (AICS). This updated assessment includes new data for the following additional piperazine salts:

- piperazine phosphate (1:1) (CAS No. 14538-56-8) and its hydrate form (CAS No. 18534-18-4);
- piperazine adipate (CAS No. 142-88-1); and
- piperazine citrate (CAS No. 144-29-6) and its hydrate form (CAS No. 41372-10-5).

Import, Manufacture and Use

Australian

No current industrial use, import, or manufacturing information has been identified for any of the chemicals.

These salts identified below are used as active constituents of veterinary medicines (APVMA):

- piperazine dihydrochloride; and
- piperazine citrate.

These salts identified below are listed on the Australian Approved Names List for Therapeutic Substances and potentially used in prescription medicines and biological products:

- piperazine adipate;
- piperazine citrate; and
- piperazine phosphate monohydrate.

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 dihydrochloride and piperazine phosphate have reported commercial use including in rubber products.

Piperazine dihydrochloride and piperazine phosphate have reported site-limited use including in:

- the manufacturing of fibres; and
- polymers to manufacture plastics and resins.

All of the chemicals have reported non-industrial uses including:

- in insecticides;
- as intermediates in formulation of therapeutic drugs and veterinary products (e.g. antihistamines); and
- as active ingredients in therapeutic drugs and veterinary products (mainly antihelminthics).

Restrictions

Australian

The chemicals are not individually listed on the Poisons Standard (*Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP*).

However, as piperazine salts, they are covered under the entry for PIPERAZINE in Schedules 2 and 5 for non-industrial uses only (SUSMP, 2018).

Schedule 2 – Pharmacy Medicines

‘PIPERAZINE for human therapeutic use.’

Schedule 2 chemicals are labelled with 'Pharmacy medicines' and 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 labelled with 'Caution'. These are 'substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label'.

International

Piperazine dihydrochloride and piperazine phosphate are listed on the following:

Under Article 15 of the European Cosmetics Regulation, use of piperazine dihydrochloride and piperazine phosphate is prohibited in cosmetic products (CosIng; Galleria Chemica).

There are no restrictions on the other piperazine salts to date.

Existing Worker Health and Safety Controls

Hazard Classification

Piperazine dihydrochloride and piperazine phosphate are classified as hazardous with the following hazard categories and hazard statement for human health in the Hazardous Chemicals Information System (HCIS) (Safe Work Australia). This classification is based on the recommended amendment to the hazard classification in the HSIS (Hazardous Substance Information System–the Safe Work Australia online classification database at the time) from the IMAP assessment published in Tranche 9:

- Eye irritation – Category 2A; H319 (Causes serious eye irritation)
- Skin irritation – Category 2; H315 (Causes skin irritation)
- 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 through the oral route)
- Respiratory sensitisation – Category 1; H334 (May cause allergy or asthma symptoms or breathing difficulties if inhaled)
- Skin sensitisation – Category 1; H317 (May cause an allergic skin reaction)
- Reproductive toxicity – Category 2; H361fd (Suspected of damaging fertility. Suspected of damaging the unborn child)

The other piperazine salts in this assessment are currently not classified in the HCIS.

Exposure Standards

Australian

Piperazine dihydrochloride has an exposure standard of 5 mg/m^3 time weighted average (TWA).

No exposure standards are available for the other chemicals.

International

The following exposure standards are identified for piperazine dihydrochloride (Galleria Chemica):

- 0.1 mg/m^3 TWA and 1 mg/m^3 short-term exposure limit (STEL) in United Kingdom, Ireland and Iceland;
- 5 mg/m^3 TWA in most countries including Canada, South Africa, Malaysia, Indonesia, Taiwan, Singapore and most of European countries (including France, Germany, Spain, Denmark, Greece);
- 10 mg/m^3 STEL in Canada and USA.

The chemical piperazine phosphate (CAS No. 1951-97-9) has no specific exposure standards but is listed in the entry "Piperazine and its salts, as piperazine" in some countries as follows:

- 0.1 mg/m^3 time weighted average (TWA) and 0.3 mg/m^3 short-term exposure limit (STEL) in Iceland; and
- 0.3 mg/m^3 time weighted average (TWA) and 1 mg/m^3 short-term exposure limit
- (STEL) in Canada and Sweden (Galleria Chemica).

Health Hazard Information

Piperazine is often available as salts for veterinary and/or medical purposes. Apart from classification for corrosivity/irritation specific to the parent base, hazard classifications for piperazine, piperazine dihydrochloride and piperazine phosphate are similar. The systemic toxicity of piperazine salts is considered to be associated with the parent compound. Therefore, the piperazine salts in this assessment are expected to have similar systemic toxicity as the parent compound. In the absence of hazard data for piperazine salts, data are read across from the parent compound.

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, piperazine (CAS No. 110-85-0) undergoes nitrosation to produce N-mononitrosopiperazine (NPZ) in a rapid reaction, and at a slower rate to produce the di-nitroso derivative N,N'-dinitrosopiperazine (DNP) (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 salts have low acute oral toxicity, with median lethal doses (LD50) typically above 5000 mg/kg bw in animal studies.

The following LD50 values are available:

- for piperazine dihydrochloride: 6200 mg/kg bw (4360 mg/kg bw as piperazine base) in mice (EMEA, 2002) and 4900 mg/kg bw in rats (RTECS; HSDB);
- for piperazine phosphate: 22350 mg/kg bw (9500 mg/kg bw as piperazine base) in mice (EMEA, 2002);
- for piperazine adipate: 7900 mg/kg bw in rats and 8000 mg/kg bw in mice (ChemIDPlus);
- for piperazine citrate: 11200 mg/kg bw in rats and 8500 mg/kg bw in mice (ChemIDPlus).

Dermal

No data are available for piperazine salts. Based on the available data for piperazine (CAS No. 110-85-0), piperazine salts are expected to have a low acute dermal toxicity.

In a study (comparable to OECD TG 402) with New Zealand White rabbits, an LD50 of 8300 mg/kg bw was established for piperazine (REACHa).

Piperazine dihydrochloride is not expected to be absorbed through the skin (HSDB).

Inhalation

No data are available for piperazine salts and only limited data are available for piperazine (CAS No. 110-85-0). The available information is insufficient to assess the acute inhalation toxicity of piperazine salts.

The following data are available for piperazine:

- median lethal concentration (LC50) greater than 1.61 mg/L/8-h (vapour) in rats (REACHa);
- an LC50 of 5400 mg/m^3/2-h (5.4 mg/L/2-h) in mice (form of exposure, i.e. vapour or aerosol, not available) (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 to piperazine in humans (EU RAR, 2005).

Corrosion / Irritation

Skin Irritation

While the parent base piperazine is corrosive to the skin and eyes, piperazine salts are expected to be at most irritating to the skin (EU RAR, 2005). Piperazine dihydrochloride and piperazine phosphate are classified as hazardous with hazard category

'Skin irritation – Category 2' and hazard statement 'Causes skin irritation (H315) in the HCIS. No test data are available but quantitative structure activity relationship (QSAR) data based on the Danish EPA model predicted piperazine phosphate as an irritant to the skin (REACHb). This information supports the retention of the existing classification for piperazine phosphate.

The other piperazine salts are not classified, but QSAR predictions (REACH) reported that:

- piperazine adipate was expected to be slightly irritating to the skin; and
- piperazine citrate was expected to be highly irritating to the skin.

Based on the existing classification for piperazine dihydrochloride and piperazine phosphate and available data on piperazine adipate and piperazine citrate, it is recommended that the existing HCIS classification be extended to cover other piperazine salts in this assessment.

Eye Irritation

While the parent base piperazine is corrosive to the skin and eyes, piperazine salts are expected to be at most irritating to the eyes (EU RAR, 2005). Piperazine dihydrochloride and piperazine phosphate are classified as hazardous with hazard category 'Eye irritation – Category 2A' and hazard statement 'Causes serious eye irritation' (H319) in the HCIS.

Piperazine dihydrochloride was reported to cause reversible eye effects ('marked pain and moderate eye irritation') within two days of administration in animals (species not stated). No corneal injury was recorded (HSDB). This information supports the retention of the existing classification.

QSAR predictions (REACH) reported that piperazine citrate was expected to be irritating to the eyes.

Based on the existing classification for piperazine dihydrochloride and piperazine phosphate and data on piperazine citrate, it is recommended that the existing HCIS classification be extended to cover other piperazine salts in this assessment.

Sensitisation

Respiratory Sensitisation

Piperazine dihydrochloride and piperazine phosphate are 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. No animal data are available but the available human data support this classification (see **Observation in Humans**).

Results are available from QSAR modelling predicting piperazine phosphate as a respiratory sensitiser (REACHb).

Based on the existing classification for piperazine dihydrochloride and piperazine phosphate, it is recommended that the existing HCIS classification be extended to cover other piperazine salts in this assessment.

Skin Sensitisation

Piperazine dihydrochloride and piperazine phosphate are classified as hazardous with hazard category 'Skin sensitisation – Category 1' and hazard statement 'May cause an allergic skin reaction' (H317) in the HCIS. No animal data are available but the available human data support this classification (see **Observation in Humans**).

Based on the existing classification for piperazine dihydrochloride and piperazine phosphate, it is recommended that the existing HCIS classification be extended to cover other piperazine salts in this assessment.

Observation in humans

In contrast to the animal data, a number of human case reports support the existing classifications (EU RAR, 2005).

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

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 (CAS No. 142-63-2) at 1 and 0.1 g/100 mL. All four men showed exacerbation of their symptoms (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).

Respiratory sensitisation was demonstrated by 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 (EU RAR, 2005; Hagmar et al.,1982).

A study on more than 600 Swedish workers (employed between 1942 and 1979) showed a strong relationship between the 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 (EU RAR, 2005; Hagmar et al., 1984).

A case of respiratory allergy was reported for a 60-year old Australian after he was exposed to piperazine, when 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 piperazine again (McCullagh, 1968).

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 was the chemical causing the allergic reaction (Quirce et al., 2006).

Repeated Dose Toxicity

Oral

Based on the available human data on piperazine (CAS No. 110-85-0), piperazine salts are expected to cause serious damage to health following repeated oral exposure. Therefore, hazard classification is recommended for all piperazine salts in this assessment.

EU RAR (2005) reported a lowest observed adverse effect level (LOAEL) around 30 mg/kg bw/day for repeated exposure to the chemical in healthy humans (see **Observation in humans**).

In a 90-day study, groups of rats (n=10/sex/dose) were administered piperazine (CAS No. 110-85-0) at 1000, 3000 or 10000 ppm (corresponding to 50, 150 and 500 mg/kg bw/day, respectively) or piperazine dihydrochloride (CAS No. 142-64-3) at 1830, 5500 or 18300 ppm (corresponding to 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 some 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 piperazine. 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 400, 1200 or 2394 mg/kg bw/day of piperazine dihydrochloride (CAS No. 142-64-3). Apart from 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 (REACHa).

In a 13-week study, beagle dogs (n=8/dose) were administered piperazine dihydrochloride in the diet at 92, 369 or 1476.8 ppm. Except for mild hepatic effects (details not available), no compound-related systemic toxicity was observed. A NOAEL of 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 data are available.

Inhalation

No data are available.

Observation in humans

EU RAR (2005) reported a LOAEL around 30 mg/kg bw/day for piperazine in healthy humans, based on neurotoxic effects during a 3–7 day treatment period. However, as there was 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 data available for piperazine dihydrochloride, piperazine phosphate and parent compound piperazine, piperazine salts are not expected to have genotoxic potential.

Piperazine dihydrochloride was found negative in a host mediated *Salmonella 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 (to form nitrosopiperazine), the test substance induced some mutagenic response from 145 µmol/kg bw (Braun et al., 1977).

Piperazine phosphate gave mostly negative results in the following in vitro assays:

- a bacterial gene mutation test (OECD TG 471) using *S. typhimurium* strains TA 97, TA 98, TA 100 and TA 1535 at 8 to 5000 µg/plate (EU RAR, 2005);
- a mammalian cell gene mutation test on L5178Y mouse lymphoma cells, from doses of 200 to 400 µg/L, with or without metabolic activation (EU RAR, 2005; REACHb);
- a mouse lymphoma fluctuation assay which gave a weak positive response at 400 µg/L, with metabolic activation; but it was within the historical control range and had no reproducibility (EU RAR, 2005);
- a chromosome aberration test on Chinese hamster ovary (CHO) cells at 1.7 to 110 mg/mL, with or without metabolic activation (EU RAR, 2005; REACHb).

In an in vivo micronucleus test, a mixture of piperazinium dihydrogen phosphate and piperazine phosphate at 1:1 (CAS No. 14538-56-8) gave negative results in CD-1 mice which received a single oral dose of the mixture at 5000 mg/kg bw (EU RAR,

2005; REACHa).

For piperazine, 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, nitroso-piperazines (NPZ) that can be formed by nitrosation of piperazine *in vivo* demonstrate clear genotoxic properties (*in vivo* DNA strand breaks and mutations)'.

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 and Pero et al., 1988).

Carcinogenicity

No data are available for the chemicals. Based on the the limited information available for piperazine (CAS No. 110-85-0), piperazine salts are not expected to have carcinogenic properties on their own. Only the nitrosated piperazine 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 and observed for a further 12 weeks before being euthanised. Dinitrosopiperazine (DNPZ) (40 mg/L drinking water) was used as positive control. Piperazine alone or sodium nitrite alone produced no effect but administering them together 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 may be responsible for the carcinogenic effects (Greenblatt et al., 1971).

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. Piperazine alone did not induce any effects whereas the combination with sodium nitrite significantly increased lung adenoma (Greenblatt et al., 1973 cited in EU RAR, 2005).

Reproductive and Developmental Toxicity

Piperazine dihydrochloride and piperazine phosphate are 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. The available data on the chemicals support these classifications. The other piperazine salts in this assessment are expected to have the same toxicity and are recommended for classification.

A human case report indicates that 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, 250, 600 and 1250 mg/kg bw/day) throughout maturation, mating, gestation and lactation phases for two successive generations. There was a 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 and include delayed sexual maturation in F1 animals (age at vaginal opening in females and preputial separation in males), but this may be related to the decreased body weight. Reduced body weights and food consumption were noted at 600 mg/kg bw/day, along with reduced litter size in both generations, reduction of implantation sites in F1 and delayed sexual maturation in F1. No treatment-related effects were reported at 250 mg/kg bw/day. A NOAEL of 250 and a LOAEL of 600 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 (CAS No. 14538-56-8) 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. 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 225 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 high rate of post-implantation loss (100 % resorption in four litters), reduced foetal weight, slight retardation in ossification, major abnormalities in 23 % foetuses (cleft palate, umbilical hernia) and increased incidence of poorly ossified hindlimbs, all at the highest dose. The study suggested that teratogenic effects may be secondary to maternal toxicity, due to reduced food intake (EU RAR, 2005; REACHa).

Other Health Effects

Neurotoxicity

The available human data indicate that piperazine and its salts may cause serious damage to health following a single oral exposure (acute LOAEL = 110 mg/kg for neurotoxicity). Therefore, hazard classification is recommended for all the chemicals in this assessment.

Based on the occurrence of severe neurotoxic symptoms following exposure to high doses of piperazine base (CAS No. 110-85-0) in several human case reports, a LOAEL of 110 mg/kg was proposed for acute exposure in humans (EU RAR, 2005).

The administration of piperazine and some of its salts, as anthelmintic drugs, have caused neurotoxic effects in humans. There were case reports from Europe, in 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 piperazine 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 (as two doses in one day). Reported neurotoxic effects include 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 base (as 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 4-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 caused 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. These effects were usually observed following a single high dose or mutiple doses of piperazine (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 (skin and respiratory sensitisation, skin and eye irritation).

Public Risk Characterisation

The chemicals are listed on Schedules 2 and 5 of the SUSMP for non-industrial uses. No industrial uses are identified in Australia and currently there are no restrictions in using these chemical in domestic products in Australia.

Given the industrial uses identified overseas, it is unlikely that the public will be exposed to these chemicals through domestic uses.

Occupational Risk Characterisation

Given the critical health effects, the chemicals may pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal and ocular exposure to the chemicals are implemented. The chemicals 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 in HCIS (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

Public Health

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

No domestic use of the chemicals is expected.

Work Health and Safety

Based on the recommended amendment to the hazard classification from the IMAP assessment published in Tranche 9, piperazine dihydrochloride and piperazine phosphate are currently classified in HCIS (see Existing Work Health and Safety Controls). Note that this updated assessment report does not change the current classifications for these two chemicals.

However, this updated assessment report recommends the following chemicals for classification and labelling aligned with the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards:

- Piperazine phosphate (1:1) (CAS No. 14538-56-8) and its hydrate form (CAS No. 18534-18-4)
- Piperazine adipate (CAS No. 142-88-1)
- Piperazine citrate (CAS No. 144-29-6) and its hydrate form (CAS No. 41372-10-5)

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 serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315)
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 consumers

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

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular and inhalation exposure to the chemicals 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 hazardous chemicals depend on the physical form and the manner in which the chemicals are 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 chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemicals 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 chemicals.

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 chemicals 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 chemicals has not been undertaken as part of this assessment.

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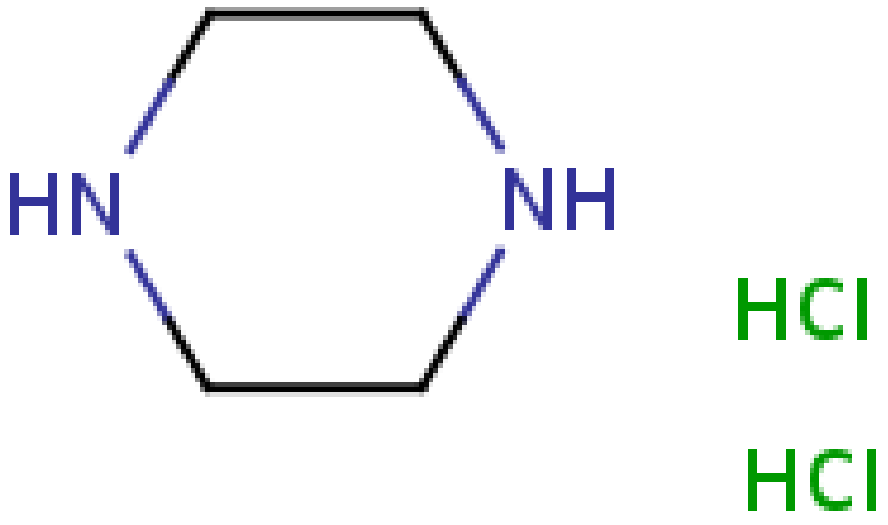
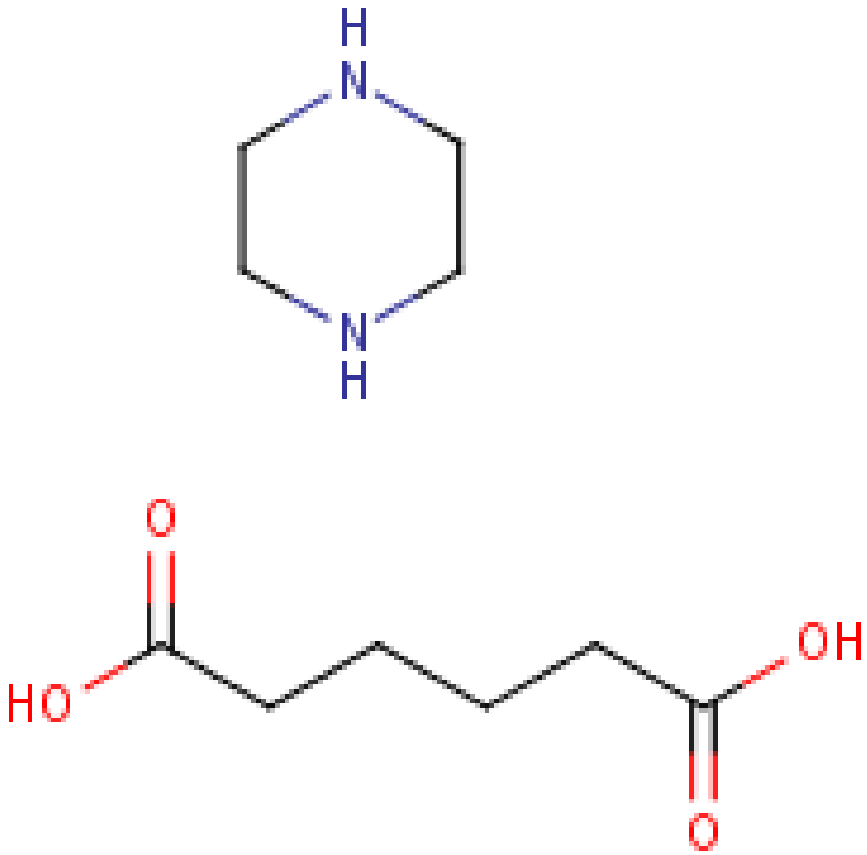
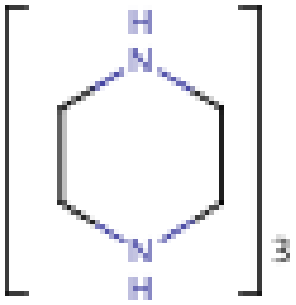
Last Update 26 October 2018

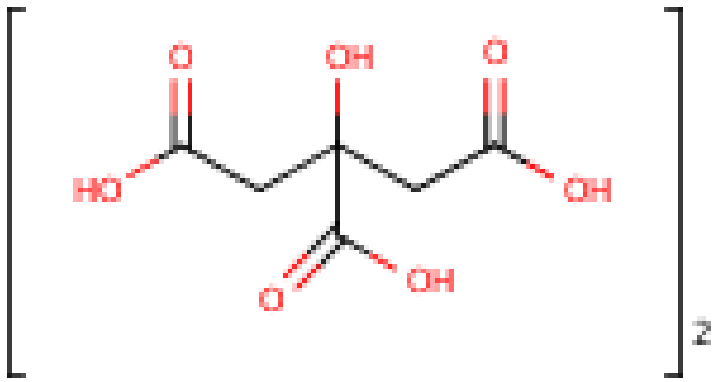
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Piperazine, dihydrochloride** piperazine hydrochloride dihydrochloride salt of diethylenediamine
CAS Number	142-64-3
Structural Formula	
Molecular Formula	C4H10N2.2ClH
Molecular Weight	159.05

Chemical Name in the Inventory and Synonyms	**Hexanedioic acid, compound with piperazine (1:1)** piperazine adipate
CAS Number	142-88-1
Structural Formula	
Molecular Formula	C6H10O4.C4H10N2
Molecular Weight	232.28

Chemical Name in the Inventory and Synonyms	**Piperazine, 2-hydroxy-1,2,3-propanetricarboxylate (3:2)** piperazine citrate (3:2) tripiperazine dicitrate piperazine citrate anhydrous
CAS Number	144-29-6
Structural Formula	





Molecular Formula	C6H8O7.3/2C4H10N2
Molecular Weight	642.65

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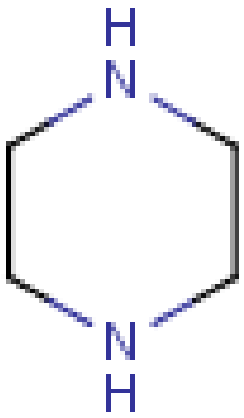
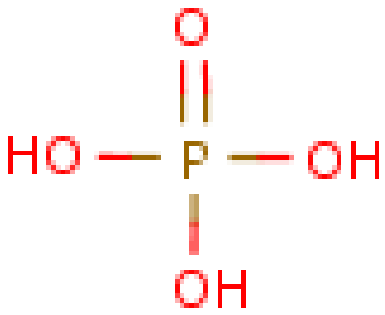
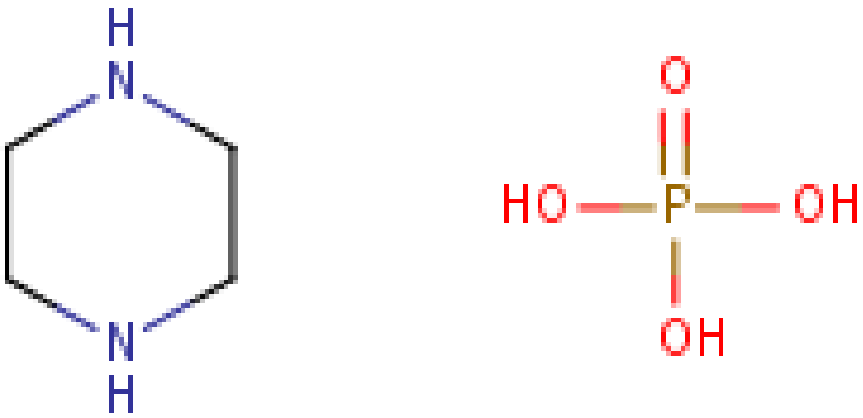
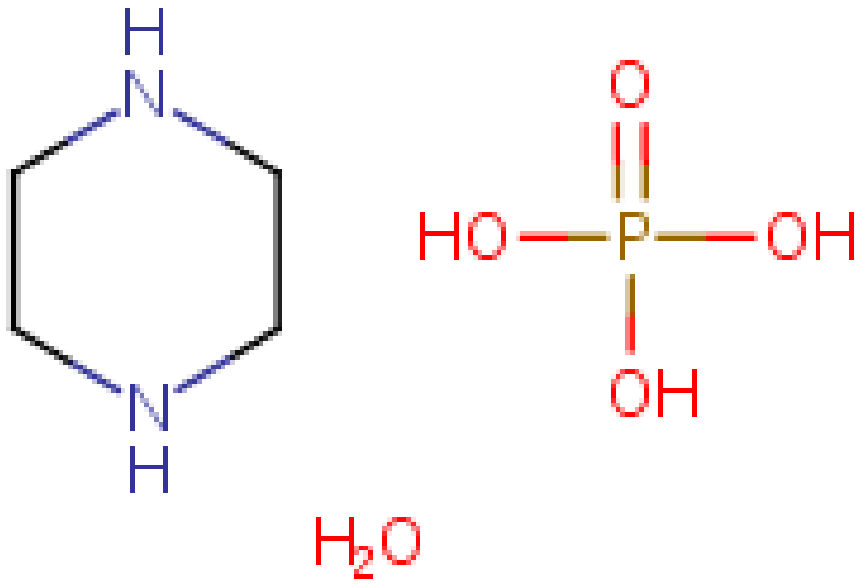
CAS Number	1951-97-9
Structural Formula	

	 
Molecular Formula	C4H10N2.xH3O4P
Molecular Weight	184.13

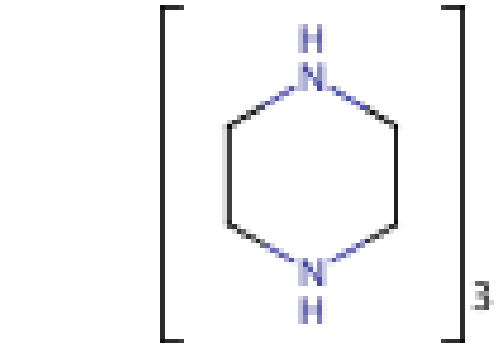
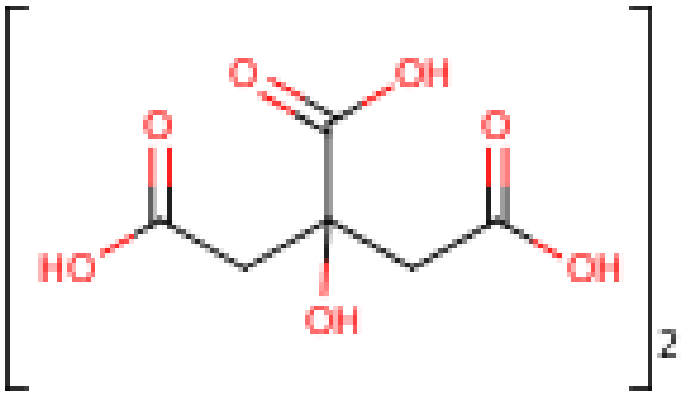
Chemical Name in the Inventory and Synonyms	**Piperazine, phosphate (1:1)** piperazinium dihydrogen phosphate
CAS Number	14538-56-8
Structural Formula	

	
Molecular Formula	C4H10N2.H3O4P
Molecular Weight	184.13

Chemical Name in the Inventory and Synonyms	**Piperazine, phosphate (1:1), monohydrate** piperazine phosphate
CAS Number	18534-18-4
Structural Formula	

	
Molecular Formula	C4H10N2.H3O4P.H2O
Molecular Weight	202.15

Chemical Name in the Inventory and Synonyms	**Piperazine, 2-hydroxy-1,2,3-propanetricarboxylate (3:2), hydrate** piperazine citrate hydrated piperazine citrate (3:2) hydrate piperazine citrate
CAS Number	41372-10-5
Structural Formula	

	  
Molecular Formula	C6H8O7.3/2C4H10N2.xH2O
Molecular Weight	660.67

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