Piperidine: Human health tier II assessment

05 February 2016

CAS Number: 110-89-4

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

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

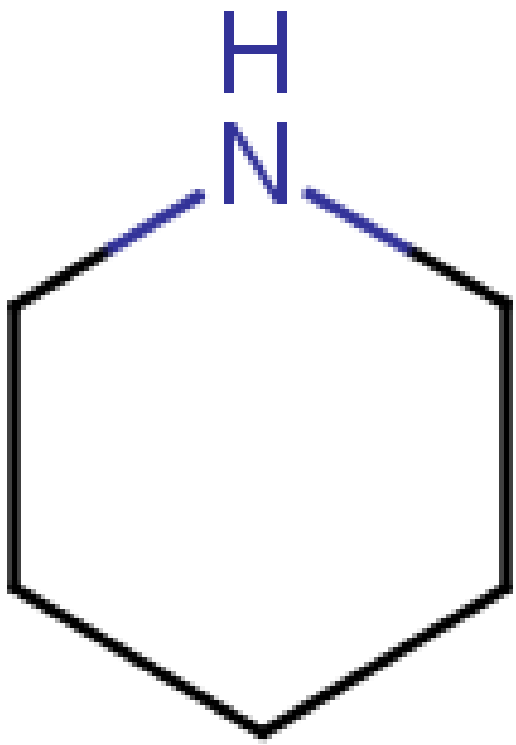
For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	cyclopentimine pentamethyleneimine pyridine, hexahydro-
Structural Formula	

	
Molecular Formula	C5H11N
Molecular Weight (g/mol)	85.15
Appearance and Odour (where available)	Clear, colourless liquid with amine-like odour
SMILES	C1CCCCN1

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through European Union Registration, Evaluation Authorisation and Restriction of Chemicals (EU REACH) dossiers; Substances and Preparations in Nordic Countries (SPIN) database and Galleria

Chemica.

The chemical has reported domestic and/or cosmetic uses as a fragrance compound (frangrance, perfume, deodouriser).

The chemical has reported commercial uses as:

- a solvent;
- an ingredient in fuels and oils; and
- a curing agent for rubber and epoxy resins.

The chemical has reported site-limited uses as:

- an intermediate in manufacture of other substances;
- a catalyst for condensation reactions; and
- a complexing agent.

Restrictions

Australian

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

- Customs (Prohibited Exports) Regulations 1958 - Schedule 9 Precursor substances - Part 2 (piperidine, neat and in mixtures at a concentration of at least 90%);
- Queensland Drugs Misuse Act 1986 - Drugs Misuse Regulation 1987 - Schedule 6: Controlled substances;
- Victoria Drugs, Poisons and Controlled Substances (Precursor Chemicals) Regulations 2007 - Schedule 1 - Precursor Chemicals and Quantities;
- Victoria Drugs, Poisons and Controlled Substances Act 1981 - Schedule 11 - Part 1 (Piperidine derivatives including allylprodine, meprodine, phenoperidine and prodine);
- Crimes (Traffic in Narcotic Drugs and Psychotropic Substances) Act - Schedule 1 - United Nations Convention Against Illicit Traffic In Narcotic Drugs And Psychotropic Substances - Table II;
- Illicit Drug Precursors/Reagents - Category II; and
- Implementation of model schedules for Commonwealth serious drug offences - Attachment 2.5: The Model Schedules - List of Controlled Precursors. The implementation is achieved through the Organised Crime Strategic Framework by targeting the primary markets of organised crime – the importation, domestic production and distribution of illicit drugs.

International

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

- China List of Dual-Use Items and Technologies Subject to Export License Administration - Section 2 and 7: Precursor chemicals 1;
- Canada Controlled Drugs and Substances Act Schedule VI (Peperidine and its salts);
- EU Commission Regulation 1277/2005 Implementing Drug Precursors Export Requirements - Annex IV - Category 2;

- EU Council Regulation (EC) No 111/2005 laying down rules for the monitoring of trade between the Community and third countries in drug precursors - Scheduled Substances Category 2;
- European Union (EU) Drug Precursors - Scheduled Substances Annex I Category 2;
- United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances - Table II (Piperidine and its salts);
- United Nations List of Precursors and Chemicals Frequently used in the Illicit Manufacture of Narcotic Drugs and Psychotropic Substances Under International Control (Red List) - Table II; and
- United States (US) Drug Enforcement Administration (DEA) List I and II Regulated Chemicals.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- T; R23/24 (acute toxicity)
- C; R34 (corrosivity)

Exposure Standards

Australian

The chemical has an exposure standard of 1 ppm or 3.5 mg/m^3 time weighted average (TWA), with a notation indicating that absorption through the skin may be a significant source of exposure (Safework Australia).

International

The chemical has the following exposure limits identified (Galleria Chemica):

- New Zealand Workplace Exposure Standards (WES) of 1 ppm or 3.5 mg/m^3 TWA, with a skin absorption notation;
- United Kingdom (UK) Workplace Exposure Limits (WELS) of 1 ppm or 3.5 mg/m^3 TWA, with a skin absorption notation; and
- Canada (British Columbia) Occupational Exposure Limit of 1 ppm TWA.

Health Hazard Information

Piperidine contains an amine functional group that is expected to act as a Lewis base (electron paired donor). Therefore, the chemical is expected to have the typical reactions of secondary amine compounds which could cause corrosivity effects.

Toxicokinetics

Piperidine is well absorbed by inhalation, and through the gastrointestinal tract and the skin. Absorption of piperidine through the skin was sufficient to cause death in laboratory animals (REACH; Clayton & Clayton, 1994).

Piperidine was found in the urine of animals (cattle, horse, pig, cat and rabbit) and humans. It has been postulated that cadaverine (pentamethylenediamine), which is formed naturally from the amino acid lysine, is cyclised to form piperidine (REACH; Clayton & Clayton, 1994).

In humans, piperidine derived from cadaverine and lysine is excreted at 3 to 20 mg/day. Oral administration of cadaverine in rabbits caused a sevenfold increase in the excretion of piperidine compared with untreated animals. The majority of piperidine injected to chicken and rabbits was excreted unchanged (REACH; Clayton & Clayton, 1994).

Acute Toxicity

Oral

The chemical has moderate acute oral toxicity based on results from several animal tests, warranting hazard classification. The median lethal doses (LD50) in rats ranged from 133 to 740 mg/kg bw (REACH; US EPA, 2003; Clayton & Clayton, 1994). Observed sublethal effects included decreased motor activity, tremors, blanching, piloerection, lethargy and respiratory effects.

In rats of unspecified strain, LD50 values of 133 and 447 mg/kg bw were reported. Rats treated with 100 mg/kg bw of the chemical also showed weakness, respiratory distress and convulsions (Clayton & Clayton, 1994).

Sprague Dawley (SD) rats orally administered the chemical at doses of 5, 50, 500 and 2000 mg/kg bw showed decreased motor activity, respiratory effects, tremors, blanching, piloerection, ataxia and salivation during the 14-day observation period. Stomach and intestinal haemorrhage with ulcers were noted at necropsy. The LD50 was determined to be 337 mg/kg bw in this study (US EPA, 2003; Clayton & Clayton, 1994).

In a range finding study, SD rats were administered a single dose of the chemical by oral intubation at doses of 300, 550 and 800 mg/kg bw and observed for 14 days. Clinical signs observed at the highest dose included: catalepsy (seizure with a loss of sensation and consciousness accompanied by rigidity of the body), tremors and lethargy. Gross necropsy findings included haemorrhaging in the stomach and small intestines. The LD50 was determined to be approximately 740 mg/kg bw (REACH; US EPA, 2003).

Dermal

The chemical is classified as hazardous with the risk phrase 'Toxic in contact with skin' (T; R24) in HSIS (Safe Work Australia). The available data support this classification.

In a dermal study, the chemical was applied to the shaved trunk of four male rabbits. The application site was covered by an impervious plastic film for 24 hours and the rabbits were observed for 14 days. A dermal LD50 of 0.32 mL/kg (calculated to be approximately 275 mg/kg bw) was reported (US EPA, 2003; REACH).

In another study, the chemical was dermally applied to the shaved trunk (occlusive) of albino rabbits (6/dose) at doses of 500, 1000 or 2000 mg/kg bw, for 24 hours. Observations were conducted during and after administration. Lethargy and weight loss were observed in all animals. Severe burns at the site of application were also reported. The LD50 was determined to be <2000 mg/kg bw (REACH).

Inhalation

The chemical is classified as hazardous with the risk phrase 'Toxic by inhalation' (T; R23) in HSIS (Safe Work Australia). The available data are insufficient to support or amend the existing classification.

A median lethal concentration (LC50) of >2000 ppm in rats (n = 6; unspecified strain) was reported following inhalation exposure for four hours at 2000 ppm (US EPA, 2003).

In an acute inhalation (similar to OECD Test Guideline (TG) 403), SD rats (10/sex/dose) were exposed (whole body) to vapours of the chemical at concentrations ranging from 1 to 7 mg/L for four hours. An inhalation LC50 of 4.8 mg/L was reported (REACH).

Corrosion / Irritation

Corrosivity

The chemical is classified as hazardous with the risk phrase 'Causes burns' (C; R34) in HSIS (Safe Work Australia). Studies were performed in accordance with OECD Test Guideline (TG) 404. The results showed that the chemical was corrosive to rabbit skin after three minutes exposure. The available data are sufficient to amend the existing classification.

Skin

In a skin irritation study (similar to OECD TG 404), 0.5 mL of undiluted chemical was applied on the shaved back of Vienna white rabbits (1/sex) under occlusive conditions. Exposure times were 3 min, 1 hour and 4 hours, and observations were conducted 24 and 48 hours, and 8 days after application. Necrosis (hard and leathery skin, extending beyond the application site at 4-hour exposure) and oedema were observed at all exposure times. Histopathological observations were consistent with the necrosis. Effects were not reversible within 8 days (REACH).

Similar irritation effects (severe erythema and necrosis) were reported in other dermal irritation studies conducted in rabbits (albino rabbits, New Zealand white) under occlusive or non-occlusive conditions (REACH).

The chemical was also reported to be severely irritating to the skin of rats and mice (Clayton and Clayton, 1994).

Eyes

In an eye irritation study (similar to OECD TG 405), 0.1 mL of the undiluted chemical was instilled into the left eye of rabbits (three animals; unspecified strain) and the untreated right eye acted as the control. The eyes were observed for ocular reactions at 1, 4, 24, 48, 72, 96 hours, and 7, 14 and 21 days after application. Irreversible eye damage was observed in animals (REACH).

Irrevesible eye damage (including necrosis and permanent corneal damage) was reported in various eye irritation studies conducted in rabbits (REACH; Clayton and Clayton, 1994).

Sensitisation

Skin Sensitisation

The chemical was not considered to be a skin sensitiser.

In a Buehler test (similar to OECD TG 406), the chemical (25%) was directly applied to the shaved skin of Hartley (unspecified strain) guinea pigs for six hours, once per week for three consecutive weeks under occlusive conditions (induction phase). Two weeks after the induction phase, the chemical (25%) was applied to shaved untreated skin of the guinea pigs (challenge phase) for 6 hours and skin reactions were scored 24 hours following exposure. No reactions indicating skin sensitisation were reported in the study (REACH).

Repeated Dose Toxicity

Oral

Limited data are available due to the corrosive nature of the chemical. The available data are insufficient to support a hazard classification.

In a repeated dose study (non-guideline), rats (n = 6; unspecified strain) were dosed by gavage with the chemical at 90 mg/kg bw/day, five days/week for two weeks. Death of one animal and temporary loss of weight were reported. Histopathological examinations revealed necrosis of the liver and kidney changes (presence of hyaline casts) (REACH).

Dermal

No data are available due to the corrosive nature of the chemical.

Inhalation

Repeated exposure to the chemical via inhalation route in a non-guideline study resulted in changes in the liver, lung and kidneys. These observations were not consistent with the minor systemic effects observed from an inhalation study conducted in accordance with the OECD TG, which is considered most reliable. Based on the available information, no hazard classification for repeat dose inhalation toxicity is recommended.

In a repeated dose toxicity studies (non-guideline), rats (20/dose) and rabbits (six/dose) were exposed (whole body) to vapours of the chemical at concentrations of 0.002 mg/L (2 mg/m^3) and 0.01 mg/L (10 mg/m^3), four hours/day, five days/week for four months, and a recovery period of one month. At 10 mg/m^3, body weights were reduced, and impaired kidney function was reported. Histopathological observations included: scars in the myocardium with random necrotic areas; random thickening of the alveolar walls of the lungs; protein dystrophy in the liver; hyaline droplet degeneration in the kidneys; dead germinal epithelium and appearance of giant cells in the testes; and fewer lymphoid elements in the stroma of the spleen. Similar effects but to a lesser degree were observed at 2 mg/m^3. The effects were fully reversible. A lowest observed adverse effect concentration (LOAEC) of 10 mg/L was reported from the study (US EPA, 2003; REACH).

In a guideline study conducted in accordance with the OECD TG 412, Wistar rats (10/sex/dose and 5/sex/dose in the recovery group) were treated by whole body exposure to chemical vapour at concentrations of 5 ppm, 20 ppm and 100 ppm, six hours/day, five days/week for 28 days. At 100 ppm, slight decrease in body weight gain in males and increase in the relative liver weights of the females were observed. Reddish crusts around the nose (bloody nasal discharge) were also reported at the highest dose. A LOAEC of 100 ppm (approximately 350 mg/m^3) for local effects was determined from the study (REACH).

Based on the available information, hazard classification for repeated dose inhalation toxicity is not recommended. However, classification for respiratory irritation is warranted.

Genotoxicity

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

Experimental results from direct bacterial, microsomal mutagenesis and host-mediated assays using *Salmonella typhimurium* with or without metabolic activation gave negative results for the chemical (US EPA, 2003).

Negative results were also obtained from a bacterial assay using *Escherichia coli* and a reverse mutation assay using *S. typhimurium,* with or without metabolic activation (US EPA, 2003).

In an in vitro mammalian cell forward mutation assay, the chemical produced increases in mutation frequency, indicating a positive result, without metabolic activation (US EPA, 2003).

In an in vitro DNA alkaline unwinding assay using mouse lymphoma cells, the chemical gave a negative response without metabolic activation and an equivocal response with metabolic activation (US EPA, 2003).

Carcinogenicity

The available data indicate that the chemical is not likely to be carcinogenic.

In a rat liver foci bioassay in vivo, the ability of the liver cells to proliferate as focal lesions in the presence of environment that inhibits the original or surrounding hepatocytes from proliferation was determined using rats subjected to partial hepatectomy. The foci, which are assumed to be preneoplastic lesions, were investigated for gamma glutamyl transpeptidase (GGT) activity. A single intraperitoneal (i.p.) dose of the chemical of 50 mg/kg bw was administered to Fischer 344 (F344) rats for18 hours after partial hepatectomy. There was no difference in the number, area and size of the GGT-positive foci in animals treated with piperidine compared with that of the control animals (REACH).

Strain A mice (20/sex) were administered the chemical (total dose of 950 mg/kg bw) by i.p. injection, 3 injections /week for 8 weeks. No difference in the number of lung tumours was found in treated animals and control animals in this study (REACH).

Reproductive and Developmental Toxicity

Based on the limited information available, the chemical does not cause specific reproductive or developmental toxicity.

In a developmental toxicity study (non-guideline), rats were exposed by three inhalation exposure regimens: (1) exposure throughout pregnancy (until gestation day 21) at 3, 15 or 100 mg/m^3; (2) implantation period - on day 4 of pregnancy, rats were exposed to 3 mg/m^3; and (3) placental period - on day 9 of pregnancy, rats were exposed to 3, 15 or 100 mg/m^3. Animals exposed to 15 and 100 mg/m^3 showed significant reduced weight gain. Foetal body weight was statistically reduced at all doses in animals exposed throughout the pregnancy. The number of implantation sites and the number of foetuses per female was statistically significantly reduced at 100 mg/m^3 during implantation period. A no observed effect concentration (NOEC) for both maternal and developmental toxicity of 3 mg/m^3 was determined in the study (US EPA, 2003; REACH).

In another developmental toxicity study (non-guideline), SD rats (25/dose) were exposed to the chemical vapour by whole body inhalation at 5, 20 or 80 ppm (17, 71 and 280 mg/m^3) for 6 hours/day during GD 6-15. At the highest dose group, piloerection, hunched posture, salivation and increased respiration in dams were reported. Decrease in maternal body weight gain was observed. The maternal no observed adverse effect concentration (NOAEC) was determined to be 71 mg/m^3 in the study. No significant foetal effects were reported (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from oral, dermal and inhalation exposure) and local effects (corrosivity).

Public Risk Characterisation

Although use in cosmetic and/or domestic products in Australia is not known, the chemical is reported to be used overseas as fragrance compound in perfumes and deodorisers. Considering the perfume products and deodorisers that could contain the chemical, the main route of public exposure is expected to be by dermal application and by inhalation. There is no information on the concentration of the chemical in these products. Concentrations that are sufficiently high to cause corrosive effects would be expected to create undesirable amine odours which are inappropriate for perfume products and deodorisers. Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

Given the critical health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, ocular and inhalation exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

Based on the available data, the hazard classification in HSIS are considered appropriate for the chemical.

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.

If any information becomes available to indicate significant consumer exposure to the chemical in Australia (i.e. higher concentrations or quantities in cosmetic or domestic products), risks to public health and safety may have to be managed by changes to the Poisons Standard.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2015).

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22) Toxic in contact with skin (T; R24)* Toxic by inhalation (T; R23)*	Harmful if swallowed - Cat. 4 (H302) Toxic in contact with skin - Cat. 3 (H311) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Causes severe burns (C; R35)	Causes severe skin burns and eye damage - Cat. 1A (H314)

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

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

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

Advice for consumers

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

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

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

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

Obligations under workplace health and safety legislation

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

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

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

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

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

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