Cyclohexanamine: Human health tier II assessment

05 February 2016

CAS Number: 108-91-8

Preface

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

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

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

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

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

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

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

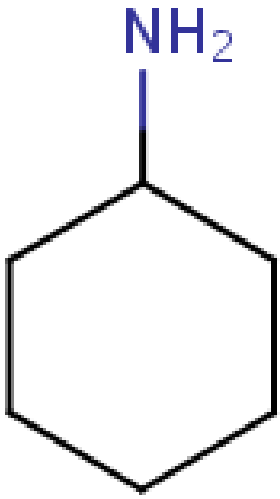
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	cyclohexylamine aminocyclohexane aminohexahydrobenzene hexahydroaniline hexahydrobenzenamine
Structural Formula	
Molecular Formula	C6H13N
Molecular Weight (g/mol)	99.17
Appearance and Odour (where available)	Colourless to yellow liquid with a strong, fishy amine-like odour
SMILES	C1(N)CCCCC1

Import, Manufacture and Use

Australian

The following Australian industrial uses have been identified through the Australian Chemical Supplier database (ACS).

The chemical has reported commercial uses in:

- boiler water treatment; and
- water and pool treatment.

The chemical has reported site-limited uses:

- as a rubber accelerator; and
- as an intermediate in organic chemical synthesis.

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Household Product database; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the US Open Chemistry database (PubChem); and international assessments including from the Internation Agency for Research on Cancer (IARC, 1980).

The chemical has reported cosmetic use in aerosol hairsprays. The concentration in hairspray was reported to be <0.5 % (US Household Product database). However, no cosmetic use was reported outside the US.

The chemical has reported domestic/commercial uses:

- in adhesive and binding agents;
- in paints and coatings;
- in bleaching agents;
- in cleaning agents;
- as a corrosion inhibitor in boiler water treatment (reported to be the major use representing 55-70 % of the use in the USA);
- in cutting fluid;
- as a pH regulating agent;
- as a process regulator; and
- in lubricants and additives.

Domestic uses are reported in the SPIN database. However, it should be noted that SPIN does not distinguish between direct use of the chemical, or use of the materials that are produced from chemical reactions involving the chemical.

The chemical has reported site-limited uses:

- as an intermediate;
- as a reducing agent; and
- as a vulcanising agent in rubber. This was reported to represent 12-30 % of the use in the USA (HSDB).

The following non-industrial uses have been identified internationally:

- in the manufacture of pharmaceutical products;
- in the manufacture of pesticides; and
- in the synthesis of the food sweetener cyclamate.

Restrictions

Australian

No known restrictions have been identified for the chemical, specifically. However, there is a general group entry in Schedule 5 of the *Poisons Standard —the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) for: 'AMINES for use as curing agents for epoxy resins except when separately specified in these Schedules'. This general entry may cover the use of this chemical in some adhesive applications.

International

The chemical is listed on the 'List of substances banned for use in cosmetic products as from 1 December 2010' (European Commission).

The chemical is also restricted by Annex XVII to the REACH Regulations: the chemical cannot be used 'in aerosol dispensers where these aerosol dispensers are intended for supply to the general public for entertainment and decorative purposes' (Galleria Chemica).

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):

- Xn; R21/22 (acute toxicity)
- C; R34 (corrosivity)
- Repr. Cat. 3; R62 (reproductive toxicity)

Exposure Standards

Australian

The chemical has a time weighted average (TWA) of 41 mg/m^3 (10 ppm).

International

The following exposure standards are identified (Galleria Chemica).

The chemical has a TWA of:

- 40–41 mg/m^3 (10 ppm) in most countries including the United States of America, Canada, France, the United Kingdom, most member States of the European Union, Indonesia, Malaysia and Singapore;
- 20 mg/m^3 (5 ppm) in Bulgaria, Estonia and Sweden;
- 8.2 mg/m^3 (2 ppm) in Germany and Switzerland.

Based on an inhalation study (see **Acute Toxicity: Inhalation** section), acute exposure guideline levels (AEGL), defined as 'threshold exposure limits for the general public', were determined for exposure periods ranging from ten minutes to eight hours (AEGL, 2007):

- AEGL-1 (notable discomfort, irritation or any other reversible and not disabling effects) of 1.8 ppm for all exposure periods;
- AEGL-2 (irreversible or other serious, long-lasting adverse health effects) of 11 ppm (10 min) to 2.7 ppm (8 h); and
- AEGL-3 values (life-threatening health effects or death) of 38 ppm (10 min) to 9.5 ppm (8 h).

Health Hazard Information

The chemical is a strong base (pKa=10.7) (AEGL, 2007) with a fishy, amine-like odour. The level of distinct odour awareness (LOA), representing the concentration above which half of the exposed population will detect a distinct odour, and 10 % a strong odour, was calculated to be 2 ppm (AEGL, 2007).

Toxicokinetics

After oral administration, the chemical is rapidly and almost completely absorbed in animals (rat, dog, rabbit, guinea pig) and humans. In rats, it is distributed into the lungs, spleen, liver, adrenals, heart, gastrointestinal tract (GI) and kidneys. In pregnant monkeys, the chemical was reported to diffuse freely across the placenta to enter the foetal tissues (Health Council of the Netherlands, 2001).

Pharmacokinetic studies in rats and mice showed that mice absorbed and eliminated the chemical more rapidly than rats. Clearance in mice was about two fold higher than in rats, leading to plasma concentrations decreasing more rapidly in mice. The concentration of the chemical in testes was four times higher than in plasma for both species. While there was little temporal fluctuation in the levels of the chemical in mice, there was a marked diurnal variation in rats reflecting the nocturnal feeding habits of the animals. The authors concluded that the difference in pharmacokinetics between rats and mice could be an explanation of the difference in sensitivity to testicular atrophy and of the dose-response relationship of testicular toxicity in rats (Roberts & Renwick, 1989).

The chemical was reported to be excreted mostly unchanged (90 % of the administered dose) in the urine of rats, guinea pigs and humans. In rabbits, about one third of the dose was metabolised and the rest eliminated unchanged through urinary excretion (Renwick and Williams, 1972).

The chemical was shown to be metabolised by deamination and/or ring hydroxylation at various rates in rats, guinea pigs, rabbits and humans. In human urine, only two metabolites were found, following deamination: trans-cyclohexanol-1,2-diol (1.4 % of the dose) and cyclohexanol (0.2 % of the dose). The

main metabolites found in the rat were aminocyclohexanols resulting from ring hydroxylation, the trans-3-isomer being predominant (2.2 % of the dose) (Renwick and Williams, 1972).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in the HSIS (Safe Work Australia). The available data support this classification.

In a study in Wistar rats (n=15 per dose) orally administered the chemical at 25, 50, 100, 250, 300, 350, 500, 600, 750 or 1000 mg/kg bw, the median lethal dose (LD50) was reported to be 432 mg/kg bw. No clinical signs were reported at the lowest dose. All animals dosed at 750 and 1000 mg/kg bw died a few minutes after dosing (REACH).

Other LD50 values, 156 mg/kg bw and 224 mg/kg bw, were reported for rats and mice, respectively (HSDB). The reliability of these values cannot be assessed as there were no study details available.

Dermal

The chemical is classified as hazardous with the risk phrase 'Harmful in contact with skin' (Xn; R21) in the HSIS (Safe Work Australia). While the available data do not fully support this classification, in the absence of more comprehensive information, there is insufficient evidence to support a recommendation to amend this classification.

A dermal study was conducted using solitary male and female New Zealand White rabbits and applying the chemical as single doses of 398, 631, 1000 or 1580 mg/kg bw for 24 hours. No LD50 was determined. Two rabbits, treated at 1000 and 1580 mg/kg bw doses respectively, died within 16 hours of treatment. All treated rabbits had reduced appetite and activity, increasing weakness and collapse (HSDB; REACH).

In another study using male New Zealand White rabbits (n=4 per dose), a dermal LD50 of 275 mg/kg bw was reported for the chemical (REACH). Animals were exposed to doses (not stated) of the chemical applied under occlusive patches for 24 hours.

Inhalation

The chemical has moderate acute toxicity in animal studies following inhalation exposure. No median lethal concentration (LC50) was determined, but there is sufficient evidence from rat studies to warrant hazard classification.

In an acute inhalation toxicity study, Sprague Dawley (SD) rats (n=5 per sex/dose) were exposed to nominal concentrations of the chemical (vapour) at 0.57, 6.4 or 8.8 mg/L for four hours and observed for two to three weeks. Analytical measurements revealed that rats were actually exposed to concentrations of 0.22, 2.3 and 2.2 mg/L respectively. In the high dose group, rats were also exposed to 612 mg/m^3 of the chemical as an aerosol, formed by reaction of vapours of the chemical with moisture from the animals. Two deaths were recorded at the high dose. The animals that died showed alopecia and lesions in the nose, lungs and urinary bladder. At the low dose, rats showed reversible respiratory effects and sensory irritation. At the mid and high doses, animals exhibited dyspnoea, gasping, tremors, partly or completely shut eyes, lacrimation, corneal opacity and ulceration of the eyes, red nasal discharge, rales, ano-genital stains, alopecia and marked body weight loss. Necropsy revealed eye lesions including ulceration, corneal scars, tissue damage and discolouration (AEGL, 2007). This study was used to determine AEGLs (see **Exposure Standards: International** section).

In another study, six male SD rats were exposed to an atmospheric concentration of the chemical of 13.7 mg/L for six hours and observed for 14 days. No mortalities were observed. Signs of toxicity observed during the exposure included nasal and ocular discharge, laboured breathing, roughened fur and lethargy. Reduced appetite and activity lasted for one day after treatment. After the treatment, rats exhibited mostly ocular signs of toxicity, including near blindness due to corneal cloudiness for two to six days. Two of the rats had complete loss of sight with corneal blistering upon the final day of observation, while all other (4/6) rats were cleared of any clinical signs of toxicity. All viscera appeared normal during necropsy (HSDB).

In a subacute study (see **Repeat Dose Toxicity: Inhalation** section), the chemical at 4900 mg/m^3 for seven hours was lethal for rats, rabbits and guinea pigs (numbers exposed were not available) following the first dose. The chemical caused irritation of the respiratory tract and eye irritation with the development of corneal opacity (Health Council of the Netherlands, 2001).

Observation in humans

Several cases of acute poisoning by inhalation were reported in places where the chemical was used as a corrosion inhibitor in boiler water systems or when used in manufacturing processes.

In a hospital, nurses experienced upper respiratory distress and eye irritation after the chemical was added to the humidification system (Orlando & Lao, 1993).

In a manufacturing plant, 64 % of the staff became ill after inhaling boiler steam that contained abnormally high levels of the chemical (levels not reported). Effects included vomiting, dizziness, nausea, headaches, upper respiratory tract irritation and eye irritation. A 'strong ammonia-like odour' was reported (Orlando & Lao, 1993).

A chemical worker exposed to the chemical in the air (detectable by a 'strong, fishy smell') for about an hour complained of anxiety, loss of appetite, burning in the throat and rapid heartbeat. Anxiety persisted until the following day. Other workers exposed to 4–10 ppm of the chemical for a duration <8 hours reported 'no symptoms of any kind' (AEGL, 2007).

Corrosion / Irritation

Corrosivity

The chemical is classified as hazardous with the risk phrase 'Causes burns' (C; R34) in the HSIS (Safe Work Australia). The available data support this classification.

In a rabbit study, a solution (concentration not stated) of the chemical (0.5 mL) was applied to the intact and abraded skin of six male rabbits (duration not stated). All tested sites turned 'charred black' and the chemical was described as 'extremely irritating and destructive' to the skin (HSDB).

Applied on the skin of guinea pigs for 24 hours, the undiluted chemical produced oedema, necrosis and persistent eschar (HSDB).

Corrosive chemicals are also considered to cause irreversible effects on the eyes. The available eye irritation data for the chemical support this finding. In rabbit studies, a solution of the chemical (0.1 mL) was instilled into one eye of six male rabbits for five minutes, before rinsing. Maximal irritation was observed, consisting of conjunctival redness and corneal opacity. Moderate iridial effects were also reported (HSDB). In another test, unrinsed eyes of treated rabbits (n=3) showed identical effects similar to the above study, following 24 hours of exposure to the chemical. The authors of the studies concluded that the chemical was 'extremely irritating and destructive' to the eyes (HSDB).

A 50 % solution of the chemical applied into the conjunctival sac of a rabbit's eye was reported to destroy the eye completely (HSDB).

A 27-year old worker who was accidentally splattered on the face with a solution of the chemical was reported to show reddening of the skin, small white spots characteristic of coagulated necrosis, drowsiness, nausea and vomiting. The worker recovered on the day after exposure (AEGL, 2007).

Respiratory Irritation

Based on the available data and observations in humans (see **Acute Toxicity: Observations in humans** section), the chemical is a respiratory irritant. The classification of the chemical as 'Causes burns' (C; R34) includes the respiratory irritation (Xi; R37) under the Approved Criteria (Approved Criteria, NOHSC: 1008 (2004)).

Male Swiss OF1 mice were exposed to increasing concentrations of the chemical for 15 minutes in order to evaluate sensory irritation of the upper respiratory tract. No other study details were reported. The 'airborne concentration resulting in a 50% decrease in the respiratory rate (RD50)' was 210 mg/m^3 (51 ppm) (Health Council of the Netherlands, 2001).

The chemical was found to be 'essentially an upper respiratory tract-irritating compound' in a study investigating pulmonary toxicity in mice (Health Council of the Netherlands, 2001). In this study, non-anaesthetised, tracheally cannulated (TC) mice were exposed to the chemical for 120 minutes. The RD50 (TC) was found to be 750 mg/m^3 (184 ppm) (Health Council of the Netherlands, 2001).

In another study, the RD50 and RD50 (TC) in male mice were determined to be 110 and 320 mg/m^3 (27 and 78 ppm), respectively (Health Council of the Netherlands, 2001).

In acute inhalation studies (see **Acute Toxicity: Inhalation** section), the chemical was reported to cause reversible respiratory effects and sensory irritation in rats exposed to the chemical vapour at 0.22 mg/L for four hours, and irritation of the respiratory tract in animals exposed for seven hours at 4900 mg/m^3.

Sensitisation

Skin Sensitisation

Only limited data are available due to the corrosive nature of the chemical.

The undiluted chemical was applied to the skin of animals (species not stated) for 48 hours, then applied again 14 days later. Skin reactions were rated as 'moderate', including the following potential symptoms: dull red discolouration with oedema, slight maceration, and possibly petechiae (spots on the skin caused by bleeding). The chemical was reported to be moderately sensitising in this study (Health Council of the Netherlands, 2001; REACH).

Observation in humans

A solution of the chemical at 25 % was used in patch tests on volunteers for 48 hours. A total of 52 % of the volunteers had slight irritation and only 3 % presented severe irritation. In 45 % of the volunteers, the chemical induced no reaction. A challenge after 14 days (concentration not stated) induced a positive reaction in 13 % of the volunteers. The chemical was considered slightly sensitising (Health Council of the Netherlands, 2001).

The chemical 'was found negative in a patch test performed on an agricultural worker having occupational allergic contact dermatitis caused by rubber gloves and other rubber parts' (Health Council of the Netherlands, 2001).

Repeated Dose Toxicity

Oral

Based on the available data on the hydrochloride salt of the chemical (CAS No. 4998-76-9), the chemical is not expected to cause serious damage to health following repeated oral exposure.

Studies in rats have shown that the chemical was quite unpalatable, leading animals to reduce their food intake when provided with a diet containing high doses of the chemical (Gaunt et al., 1974).

In a 13-week feeding study, the hydrochloride salt of the chemical (CAS No. 4998-76-9) was administered to groups of CFE rats (n=15 per sex/dose) at concentrations of 0, 600, 2000 or 6000 ppm in the diet (0, 41, 143 and 468 mg/kg bw/day, respectively). Body weight gain and food intake were significantly reduced at the mid and high doses, especially during the first 24 hours. Female rats receiving 600 ppm also had reduced food intake, due to the unpalatability of the chemical. Treatment-related changes in haematological examinations, serum analyses or urinary cell excretion values were not observed. Apart from reduced body weight gain and food intake, reduced weight for most organs and reduced spermatogenesis at mid and high doses were observed (see also **Reproductive & Developmental Toxicity** section). No other histopathological effects were reported (Gaunt et al., 1974).

In a two-year feeding study, groups of Wistar rats (n=48 per sex/dose) were administered cyclohexylamine hydrochloride in the diet at concentrations of 0, 600, 2000 or 6000 ppm. Actual intakes of the chemical were calculated to be 0, 24, 82 and 300 mg/kg bw/day for males and 0, 35, 120 and 440 mg/kg bw/day for females, respectively. Histopathological changes included significantly increased number of rats with foamy macrophages in the lungs and bilateral atrophy of the testes at the high dose. Other histopathological lesions, including myocardial fibrosis, mild hepatic changes, hyperplasia of the parathyroids and glomerulonephrosis (non-inflammatory disease of the kidney, occuring in the glomerulus) were observed but their frequency was markedly decreased at mid and high dose groups compared with controls. Animals produced less urine at the high dose and males had fewer spermatids in the tubules at 2000 ppm (Gaunt et al., 1976). No adverse effects were reported at 600 ppm.

In another two-year feeding study, FDRL rats (n=30 per sex/dose) were administered cyclohexylamine hydrochloride at doses equivalent to 0, 15, 50, 100 or 150 mg/kg bw cyclohexylamine/day. Apart from decreased food consumption at the highest dose, clinical observations did not show any differences between control and treated groups. At the highest dose, mucosal thickening of the bladder walls and evidence of renal calcification were observed. A higher incidence of testicular atrophy was also reported at 150 mg/kg bw/day (Oser et al., 1976).

Dermal

No data are available.

Inhalation

The available data are not sufficient to derive a conclusion on systemic effects following repeated inhalation exposure.

In a subacute study, rats, rabbits and guinea pigs (numbers not specified) were exposed for ten days to vapours of the chemical at concentrations of 620 mg/m^3 (150 ppm), 3300 mg/m^3 (800 ppm) or 4900 mg/m^3 (1200 ppm), seven hours per day, for five days per week. At the highest concentration, all animals but one died after the first exposure, with symptoms of extreme irritation of mucosal membranes and haemorrhage of the lungs. At 3300 mg/m^3, one rabbit and two guinea pigs died after the second exposure. At the lowest dose, one rabbit died immediately after the first exposure. Signs of toxicity included irritation of the respiratory tract and corneal opacity (Health Council of the Netherlands, 2001).

The chemical was reported to induce some systemic effects in rats after repeated inhalation exposure for two to five months, but only limited information was available on the effects observed. In this study, groups of Wistar rats were exposed to 0 or 700 mg/m^3 (170 ppm) of the chemical, two hours a day, for two months or, 0 or 100 mg/m^3 (25 ppm) of the chemical, four hours a day, for five months. At 700 mg/m^3, 3/6 animals died. Clinical signs of toxicity included weight loss, gradually decreased body temperature and respiratory rate, soft stools (after day 70) and increased relative heart and kidney weights. Exposure to 700 mg/m^3 also resulted in reduced haemoglobin, reduced number of erythrocytes and increased number of reticulocytes, deposition of haemosiderin in liver, spleen, and lungs and elongated follicles with squamous epithelium in the thyroid. At 100 mg/m^3, clinical signs included body weight increase after three months of treatment, increase in the relative kidney weight, decreased body temperature and respiratory rate

and soft stools and significantly reduced oxygen consumption. Exposure at 100 mg/m^3 also caused changes in the thyroid (details not available), increase in the number of neutrophils and leucocytosis but no sign of haemosiderosis. Animals (dose not specified) also exhibited vascular changes, fatty and granular degeneration of the myocardium and kidneys, inflammatory changes in the trachea and lungs and elimination of fat from the adrenal cortex (Health Council of the Netherlands, 2001). The information available is not sufficient to assess the severity of these effects.

Genotoxicity

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

The following in vitro genotoxicity data are available for the chemical:

- in vitro gene mutation studies with strains of *Salmonella typhimurium* or *Escherichia coli*, or mammalian cells gave negative results with the chemical (Health Council of the Netherlands, 2001);
- out of five cytogenetic studies, four showed positive results with human leukocytes and Chinese hamster fibroblasts (Health Council of the Netherlands, 2001); the chemical was reported to induce slight increase in the frequency of chromosomal breaks and gaps in cytogenetic assays (MAK, 2012); and
- in vitro sister chromatid exchange assays using Chinese hamster ovary cells (CHO) and human lymphocytes gave positive results with the chemical at 10–100 µg/mL (Health Council of the Netherlands, 2001).

Most in vivo studies with the chemical gave negative results (Health Council of the Netherlands, 2001):

- out of eight in vivo cytogenetic studies, five studies showed that the chemical was negative for micronucleus induction in the bone marrow cells and leukocytes of rats and Chinese hamsters, against two positive in similar test systems. One reported positive results in leukocytes of lamb foetus, after intravenous injection of doses up to 250 mg/kg bw of the chemical;
- five germ cell studies did not demonstrate any genetic damage in spermatogonia and/or spermatocytes in rats, mice and Chinese hamsters, although one germ cell study in rats showed positive results in spermatogonia at intraperitoneal (i.p.) doses of 1–50 mg/kg bw;
- the chemical gave negative results in *Drosophila melanogaster* studies;
- in dominant lethal assays in mice, the chemical at doses up to 100 mg/kg bw gave negative results seven times and positive twice for the induction of dominant lethal mutations; and
- in two dominant lethal assays in rats, the chemical induced pre-implantation loss and decreased fertility at doses up to 300 mg/kg bw.

Carcinogenicity

Based on the available data on the hydrochloride salt of the chemical, the chemical is not expected to be carcinogenic.

In a two-year feeding study, Wistar rats were administered cyclohexylamine hydrochloride in the diet at concentrations of 0, 600, 2000 or 6000 ppm (see **Repeat Dose Toxicity: Oral** section). Most of the tumours observed occurred in the control groups alone or with a similar frequency in control and treated groups. Scattered findings included three tumours occuring at the highest dose, consisting in a basal cell carcinoma of the skin and an osteosarcoma of the skull in males, and a glioma in the brain of a female. Other tumours were identified in the lower dose groups, including reticulum-cell neoplasms of the intestine (in two males at 2000 ppm) and uterus (one rat at 2000 ppm), a pancreatic lipoma (in a female at 600 ppm), adrenal cortical-cell tumours (two at 600 and one at 2000 ppm in females), lymphosarcomas (in males at 600 and 2000 ppm), subcutaneous lipomas (in two males at 600 ppm), a papillary cystadenoma of the salivary gland (in a female at 600 ppm), a sarcoma of the rib (in a male at 2000 ppm), an ovarian adenoma (at 600 ppm), uterine adenocarcinomas (two at 600 ppm), a uterine fibrosarcoma (at 2000 ppm), a uterine squamous-cell carcinoma (at 600 ppm), a prostatic adenocarcinoma (at 600 ppm) and benign testicular interstitial-cell tumours (two at 600 ppm and one at 2000 ppm). These tumours had no parallel findings in the control groups but were considered to be commonly observed tumours in rats. Overall, there were no statistically significant findings on carcinogenicity related to the treatment (Gaunt et al., 1976).

In another two-year feeding study, FDRL rats were administered cyclohexylamine hydrochloride in the diet at doses of 0, 15, 50, 100 or 150 mg/kg bw cyclohexylamine/day. Scattered tumours occurred in all groups including controls. They included reticulum cell sarcomas in the lungs and mammary adenomas or fibromas. Three testicular interstitial cell tumours were found in two rats at 15 mg/kg bw/day and one rat at 50 mg/kg bw/day. Overall, there was no significant difference between treated and control groups regarding the tumour incidence (Oser et al., 1976).

Reproductive and Developmental Toxicity

The chemical is classified as hazardous—Category 3 substance toxic to reproduction)—with the risk phrase ‘Possible risk of impaired fertility’ (Xn; R62) in the HSIS (Safe Work Australia). The available data support this classification.

A number of studies were conducted to investigate the toxicity of the chemical for reproduction. Overall, they show that while the chemical can impair fertility in male rats, it does not affect significantly fertility in mice or female rats (Health Council of the Netherlands, 2001). The major studies are described below.

Testicular toxicity of the chemical was investigated in a 90-day feeding study using male rats of Wistar and SD strains (Mason & Thompson, 1977). Groups of 25 rats were fed with cyclohexylamine hydrochloride at concentrations of 0, 600, 2000 or 6000 ppm. Actual intakes were calculated as 0, 46, 149, and 416 mg/kg bw/day for Wistar rats and 0, 44, 140 and 406 mg/kg bw/day for SD rats (Health Council of the Netherlands, 2001). As observed in several feeding studies (see **Repeat Dose Toxicity: Oral** section), there were significant decreases in food consumption, body weight and body weight gain at the two highest concentrations, likely due to the unpalatibility of the chemical. In the high-dose group, absolute testes weight decreased and motility and count of spermatozoa were significantly reduced compared with the other groups. Testicular lesions included almost complete absence of motile sperm and increased number of decapitated spermatozoa. Histological examinations reported a reduction or absence of spermatogenesis in over 80 % of the tubules. No testicular toxicity was observed at 2000 ppm, and no treatment-related effect was reported at the lowest dose of 600 ppm. A no observed adverse effect level (NOAEL) of 600 ppm (45 mg/kg bw/day) was established for reproductive toxicity (Health Council of the Netherlands, 2001; Mason & Thompson, 1977).

In a 13-week feeding study using CFE rats (see **Repeat Dose Toxicity: Oral** section), the chemical caused decreased spermatogenesis and tubular atrophy in the testes of 4/11 and 18/20 rats in the 2000 and 6000 ppm dosed groups, respectively. In the high dose group, the effect was more severe, with 8/20 rats showing complete arrest of spermatogenesis and loss of germinal epithelium. A reproduction study conducted in parallel showed no evidence of impaired fertility or abnormalities in the offspring. In the reproduction study, groups of five male CFE rats were fed with 0 or 6000 ppm of cyclohexylamine hydrochloride for ten months. Each male was then caged for mating with three untreated females for ten days, during which time treatment was continued. In terms of fertility, litter size and growth, there were no statistically significant differences between treated and control groups (Gaunt et al., 1974). However, effects regarding testicular toxicity were not reported.

In a two-year multigeneration study in rats, cyclohexylamine hydrochloride was administered in the diet to provide 0, 15, 50, 100 or 150 mg/kg bw cyclohexylamine/day. At 50 and 150 mg/kg bw/day, there were higher incidences of testicular atrophy (9/13 and 12/20 of examined testes, respectively) compared with controls (5/19), leading to decreased fertility. There were no significant differences in the implantation sites and live foetuses between control and treated groups. However, increased post-implantation resorptions (10/77) in the F4 generation were reported at the highest dose. The study highlighted a possible link between testicular toxicity and impaired fertility (Oser et al.,1976).

A few studies have assessed the developmental toxicity of the chemical. The chemical is reported to have no significant effects on prenatal and postnatal development in rats and mice (Health Council of the Netherlands, 2001). The critical study is described below.

The hydrochloride salt of the chemical was administered at oral doses of 0, 10, 30 or 100 mg/kg bw/day to female rats and female mice on GD 6-15 (Lorke & Machemer, 1983). At the highest dose, female rats had a decreased weight gain during the treatment period. In parallel, foetal and placental weights were significantly reduced. In female mice treated at up to 100 mg/kg bw/day and female rats treated at up to 30 mg/kg bw/day, the following parameters were not affected: the number of implantations, the resorption rate, sex ratio, incidence of malformations and skeletal development. The chemical had no teratogenic effect in either species (Health Council of the Netherlands, 2001; Lorke & Machemer, 1983).

Other Health Effects

Neurotoxicity

The chemical is reported to have sympathomimetic effects (physiological effect similar to that produced by stimulation of the sympathetic nervous system). In anaesthetised dogs, the chemical (dose not specified) was reported to increase contractile force, heart rate and systemic arterial pressure in the cardiovascular system, by inducing the release of neuronally stored catecholamines (Wechsler et al., 1969). Other sympathomimetic symptoms in anaesthetised dogs intravenously administered the chemical included restlessness, piloerection, mydriasis (dilation of the pupil of the eye), tachycardia and muscular rigidity (Health Council of the Netherlands, 2001).

In humans accidentally exposed to the chemical by inhalation, neurotoxic effects have been reported, including drowsiness, anxiety, apprehension and nausea (see **Acute Toxicity: Observation in humans** section). Oral administration of the chemical to adults was reported to cause headaches, blurring of vision, shivering and also a dose-dependent rise in arterial blood pressure (HSDB).

Endocrine Disruption

The chemical is listed on the 'Universe of Chemicals list for potential endocrine disruptor screening and testing' (US EPA, 2012).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- local effects (corrosivity);
- systemic acute effects from oral, dermal and inhalation exposure; and
- systemic long-term effects (reproductive toxicity).

Public Risk Characterisation

Given the uses identified for the chemical in Australia (commercial and site-limited use), it is unlikely that the public will be exposed to the chemical. The public could be exposed if the chemical is used in domestic pool treatments. However, this is considered as a non-industrial use.

Although use in cosmetic products in Australia is not known, the chemical was reported to be used in personal care products in the USA at concentrations around 0.5 % (US Household Product database). However, use in cosmetic products was not reported outside the USA. The European Union has banned the use of this chemical in cosmetics (European Commission).

Currently, there are no restrictions in Australia on using this chemical in cosmetics or domestic products (such as paints and coatings).

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

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

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (refer to **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. No further assessment is required unless new information regarding the uses of the chemical in cosmetic or domestic products/scenarios in Australia becomes available.

Regulatory Control

Public Health

The need for regulatory control for public health will be determined if any cosmetic or domestic uses are identified in Australia.

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)* Harmful in contact with skin (Xn; R21)* Harmful by inhalation (Xn; R20)	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Causes burns (C; R34)*	Causes severe skin burns and eye damage - Cat. 1B (H314)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)*	Suspected of damaging fertility - Cat. 2 (H361f)

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

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

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

Advice for industry

Control measures

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

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

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

Personal protective equipment should not 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.

References

Acute Exposure Guideline Levels (AEGL) Committee 2007. Acute Exposure Guideline Levels for Selected Airborne Chemicals Volume 5. Committee on Acute Exposure Guideline Levels; Committee on Toxicology; Board on Environmental Studies and Toxicology; National Research Council. Available at: http://www.nap.edu/catalog/11774/acute-exposure-guideline-levels-for- selected-airborne-chemicals-volume-5

Approved Criteria for Classifying Hazardous Substances [NOHSC: 1008(2004)] Third edition. Accessed at http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

Australian Chemical Suppliers (ACS) database. Accessed at: http://www.australianchemicalsuppliers.com/list/a

European Commission (EC). List of substances banned for use in cosmetic products as from 1 December 2010 (updated July 2015). Accessed at: http://ec.europa.eu/growth/sectors/cosmetics/products/cmr-substances/index_en.htm

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

Gaunt IF, Hardy J, Grasso P, Gangolli SD and Butterworth KR 1976. Long-term toxicity of cyclohexylamine hydrochloride in the rat. Fd Comet. Toxicol.14, Issue 4, 1976, Pages 255-267.

Gaunt IF, Sharratt M, Grasso P, Lansdown ABG and Gangolli SD (1974). Short-term toxicity of cyclohexylamine hydrochloride in the rat. Fd Comet. Toxicol.12, Issues 5–6, October 1974, Pages 609-624.

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

Health Council of the Netherlands: Committee on Updating of Occupational Exposure Limits 2001. Cyclohexylamine (CAS reg no: 108-91-8); Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands, 2001; 2000/15OSH/021. Available at: http://www.gezondheidsraad.nl/sites/default/files/0015021osh.pdf

International Agency for Research on Cancer (IARC) 1980. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Some Non-Nutritive Sweetening Agents. Volume 22. Available at: http://monographs.iarc.fr/ENG/Monographs/vol1-42/mono22.pdf

Lorke D and Machemer L 1983. The effect of cyclohexylamine on the embryo following oral administration to mice and rats. Toxicol Lett. 1983 Jun;17(1-2):137-43 (Abstract).

Mason PL and Thompson GR 1977. Testicular effects of cyclohexylamine hydrochloride in the rat. Toxicology. 1977 Oct;8(2):143-56.

Orlando RA and Lao YJ 1993. An assessment of exposure to cyclohexylamine arising from steam humidification of indoor air. Journal of Environmental Health 01/1993; 56(5):6-9. Accessed at http://www.thefreelibrary.com/An+assessment+of+exposure+to+cyclohexylamine+arising+from+steam...-a014853657

Oser BL, Carson S, Cox GE, Vogin EE and Sternberg SS 1976. Long-term and multigeneration toxicity studies with cyclohexylamine hydrochloride. Toxicology. 1976 Jun;6(1):47-65.

PubChem Open Chemistry Database. Available at https://pubchem.ncbi.nlm.nih.gov/

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossiers. Available: http://echa.europa.eu/information-on-chemicals/registered-substances

Roberts A and Renwick AG 1989. The pharmacokinetics and tissue concentrations of cyclohexylamine in rats and mice. Toxicol Appl Pharmacol. 1989 Apr;98(2):230-42.

Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

Substances in Preparations in Nordic Countries (SPIN). Available at: http://195.215.202.233/DotNetNuke/default.aspx

United States Household Products Database. US National Library of Medicine. Available: http://householdproducts.nlm.nih.gov/

Wechsler AS, Epstein SE and Glick G 1969. Mechanism of the sympathomimetic action of cyclohexylamine and hexylamine: release of catecholamines from nerve endings. J Pharmacol Exp Ther. 1969 Nov;170(1):62-71 (Abstract).

Last update 05 February 2016

Share this page