1,6-Hexanediamine: Human health tier II assessment

12 December 2019

CAS Number: 124-09-4

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.

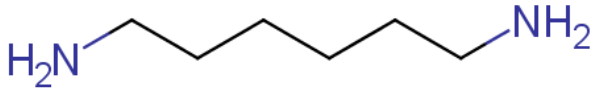
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	1,6-diaminohexane hexamethylenediamine
Structural Formula	
Molecular Formula	C6H16N2
Molecular Weight (g/mol)	116.21
Appearance and Odour (where available)	Colourless crystals
SMILES	C(N)CCCCN

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: the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development Screening Information Data Set (OECD SIDS); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database;

the European Commission Cosmetic Ingredients and Substances (CosIng) database; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use as a buffering agent in cosmetics.

The chemical has reported domestic uses, including in:

- paints, lacquers and varnishes;
- cleaning or washing products; and
- adhesives and binding agents.

The chemical has reported commercial uses, including in:

- electronic equipment;
- reprographic agents;
- corrosion inhibitors;
- thinners;
- epoxies;
- polyurethane coatings;
- paint hardeners;
- building material hardeners;
- printing inks;
- dyes;
- paper;
- fertilisers;
- biocides;
- hydraulic fracturing fluids; and
- construction materials.

The chemical has reported site-limited uses, including:

- in the production of polymers and polyamides;
- in textile treatment products;
- in pH regulators;
- in process regulators;
- in water treatment products;
- in the production of plastic and rubber products;
- in the manufacture of chemicals, basic metals and fabricated metal products;

- in nylon textiles, fibres, leather and fur products;
- as a petroleum additive;
- in phenol purification;
- in the manufacture of oil; and
- in the manufacture of transport equipment.

The chemical has reported non-industrial uses, including in the manufacture of:

- pesticides; and
- agrochemicals.

The chemical is used in food contact materials.

Restrictions

Australian

No known restrictions have been identified.

International

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

- Annex I to Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food, in which the chemical is authorised to be used as monomer or other starting substance or macromolecule obtained from microbial fermentation, and with a specific migration limit (SML) of 2.4 mg/kg of food.
- US Code of Federal Regulations (CFR) Title 21, Part 175–Indirect Food Additives: Additives and Components of Coatings (21 CFR 175.105; 21 CFR 175.300), and CFR Title 21, Part 177–Indirect Food Additives: Polymers (21 CFR 177.1500), in which the chemical is permitted for use in adhesives, in resinous or polymeric coatings, or in the manufacture of nylon resins, that will be used in food contact materials.

Existing Work Health and Safety Controls

Hazard Classification

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

Acute toxicity – Category 4; H302 (Harmful if swallowed)

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

Specific target organ toxicity (single exposure) – Category 3; H335 (May cause respiratory irritation)

Skin corrosion – Category 1B; H314 (Causes severe skin burns and eye damage).

Exposure Standards

Australian

No specific exposure standards are available for the chemical.

International

The following exposure standards are identified (Galleria Chemica):

- an exposure limit of 2.3–2.4 mg/m^3 (0.5 ppm) time weighted average (TWA) in different countries such as Austria, Belgium, Canada (Alberta, British Columbia, Manitoba, Nova Scotia, Quebec), Denmark, Hungary, Italy, Malaysia, Portugal, Singapore, Spain, the United Arab Emirates, the United States of America (California) and Venezuela;
- an occupational exposure limit of 1.0 mg/m^3 in Bulgaria;
- an occupational exposure limit of 0.1 mg/m^3 in Latvia; and
- a maximum allowed concentration in the air of workplace zone of 0.1 mg/m^3 in Russia.

Health Hazard Information

Where data for 1,6-hexanediamine (HDA) are limited or unavailable, health hazard information for 1,6-hexanediamine dihydrochloride (HDDC) (CAS No. 6055-52-3) has been included in this report. HDA is highly basic and, as such, extremely caustic and has a pungent odour, which would be unpalatable in drinking water when administered to animals in studies of systemic toxicity. Therefore, HDA has been replaced by HDDC in a number of toxicological studies. Toxicological data for HDDC can be used as read-across for HDA.

Toxicokinetics

Four male Fischer 344 rats were dosed with ^{14}C-1,6-hexanediamine dihydrochloride at 0.4 mg HDA/kg body weight (bw) by oral gavage. The principal route of excretion was in the urine, which accounted for approximately 47 % of the total dose within 72 hours. Over a 72-hour period, excretion in faeces accounted for 27 % of the administered dose, while another 20 % was recovered as exhaled $^{14}CO_2$. Less than 1.5 % of the total dose was retained by the rats. Gas and thin-layer chromatographic analyses of urine, indicated that 30 % of the radioactivity was in the form of the parent HDA. No further analysis of metabolites was performed. At 72 hours after oral administration to male rats, the prostate contained the highest specific activity of radiolabel, followed by the intestine, kidneys, liver and spleen (David and Heck, 1983).

Male and female Fischer 344 rats (number of animals unspecified) were injected intravenously with ^{14}C-1,6-diaminohexane dihydrochloride (dose unspecified). At 1 hour post-injection, the intestine contained the greatest amount of radioactivity in males. At 24 hours post-injection, the prostate had the greatest amount of radioactivity in males, followed by the intestine and liver. In females, the uterus had a high amount of radioactivity 1 hour after intravenous injection, but not at 24 hours. The ovaries contained minimal radioactivity at 24 hours post-administration (David and Heck, 1983).

In a human study, HDA (aqueous) at a dose of 0.1 mg/kg bw was given orally after an overnight fast to 6 healthy male volunteers on 2 separate occasions, 3 months apart. Urinary excretion was monitored for 24 hours after intake. Peak amounts of HDA were detected in urine samples 2–5 hours after intake. In 4 out of 6 volunteers, no HDA could be detected 10 hours after intake, while 2 volunteers showed prolonged urinary elimination times of about 20 hours. The estimated elimination half-life was 1.5 hours. In addition to the parent compound, the metabolites 6-aminohexanoic acid and N-acetyl-1,6-HDA were found in the urine. The available human data show considerable inter-individual variation in the elimination of the 6-aminohexanoic acid metabolite and that the elimination of HDA varied according to whether the individuals were fast or slow acetylators (Brorson et al., 1990).

Acute Toxicity

Oral

The chemical is classified as hazardous with the hazard category 'Acute Toxicity Category 4' and hazard statement 'Harmful if swallowed' (H302) in the HCIS (Safe Work Australia). The available data for the chemical (median lethal dose (LD50) in rats—750–1160 mg/kg bw) support this classification.

Sprague Dawley (SD) rats of both sexes (5/sex/dose) were administered liquid HDA by oral gavage at doses of 0, 900, 1170, 1530 or 2000 mg/kg bw in a non-guideline study. The rats were observed for 15 days after administration. Clinical signs observed for all doses included vocalisation after treatment and excessive salivation. At 900 and 1170 mg/kg bw, a decrease in motor activity was observed. Weight loss was observed for the surviving animals at 1170, 1530 and 2000 mg/kg bw. The mortality rates at 900, 1170, 1530 and 2000 mg/kg bw were 1/10, 7/10, 8/10 and 9/10, respectively. Gross pathological findings in the deceased animals included ulceration of the gastric mucosal membrane and blood in the intestine. The reported LD50 for both sexes combined was 1160 mg/kg bw (REACH).

Rats (number of animals, strain and sex unspecified) were administered 3–10 % HDA (in corn oil) by oral gavage as a single dose at 500, 700, 800 or 1000 mg/kg bw for a fasting group, and a single dose at 800, 1000, 1100, 1200, 1250, 1300, 1400, 1600 or 2000 mg/kg bw for a non-fasting group. Rats showed weakness, salivation, staining of the perineal area and weight loss. No deaths occurred in the non-fasted rats at 800 mg/kg bw/day, whereas 7/10 fasted rats at this dose died. The reported LD50 was 750 mg/kg bw/day for the fasted group and 1127 mg/kg bw/day for the non-fasted group (Kennedy, 2005).

The following acute oral LD50 for rats were reported, but no study details are available:

- 750 mg/kg bw (unspecified strain and sex);
- 750 mg/kg bw (female) and 800 mg/kg bw (male), SD; and
- 980 mg/kg bw (male and female), SD (NTP, 1993).

Dermal

The chemical is classified as hazardous with the hazard category 'Acute Toxicity Category 4' and the hazard statement 'Harmful in contact with skin' (H312) in the HCIS (Safe Work Australia). The available data (LD50 in rats—1900 mg/kg bw) support this classification.

In a non-guideline study, male and female SD rats (5/sex/dose) were dermally exposed to a product containing HDA (unknown composition and concentration) at doses of 0, 950, 1400, 2000, 3000 or 4800 mg/kg bw for 24 hours under occlusive conditions and observed for 15 days. Clinical signs observed included decreased motor function, closed eyes and low body temperature at 2000, 3000 and 4800 mg/kg bw. Weight loss was observed in the higher (1400 mg/kg bw) non-lethal dose group (the exact dose was not exactly specified; however, based on the available information the dose of 1400 mg/kg bw may be the higher non-lethal dose) on day 10. Necrosis was observed at the application sites of all animals at 950 mg/kg bw and above, 24 hours after treatment. The mortality rates at 950, 1400, 2000, 3000 and 4800 mg/kg bw were 0/10, 0/10, 6/10, 10/10 and 10/10, respectively. The acute dermal LD50 for both sexes combined was 1900 mg/kg bw (REACH).

In rabbits (n=3, strain unspecified) treated with 85 % HDA for 15 min, the dermal LD50 was 1100 mg/kg bw (limited study details available). Extreme erythema, swelling and necrosis at the treated area were observed (Kennedy, 2005).

Inhalation

Limited acute inhalation toxicity studies are available for the chemical. A study (with limited details) reported a lethal dose low (LDLo) of 750 mg/m^3 in animals (species, strain and sex unknown) following inhalation exposure to HDA for 10 minutes (REACH).

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with hazard category ‘Specific target organ toxicity (single exposure) – Category 3’ and hazard statement ‘May cause respiratory irritation’ (H335) in the HCIS (Safe Work Australia). See the '**Repeat Dose Toxicity: Inhalation**' section for the data which supports this classification.

Animals exhibited signs consistent with respiratory irritation following repeated inhalation of HDDC including nasal discharge, rales and dyspnoea. Inhalation of HDDC resulted in lesions in the respiratory tract including ulceration, necrosis, inflammation and erosion of the respiratory epithelium.

Skin Irritation

The chemical is classified as hazardous with the hazard category ‘Skin Corrosion Category 1B’ and the hazard statement ‘Causes severe skin burns and eye damage’ (H314) in the HCIS (Safe Work Australia). The available data support this classification.

In a skin irritation/corrosion study, 4 New Zealand White (NZW) rabbits were treated with undiluted HDA (0.5 g) by dermal application onto shaved intact or scarified skin with occlusion. Skin reactions were assessed at 24 and 72 hours after exposure. HDA caused severe oedema and erythema in the rabbits following exposure. These effects were not reversible at 72 hours after exposure (REACH). HDA was determined to be corrosive based on these results.

The following in vivo skin irritation/corrosion studies for the chemical are also available for HDA (REACH):

- dermal exposure to HDA (concentration unspecified) resulted in necrosis at the treated site within 1 hour in all 10 male albino guinea pigs;
- HDA diluted at 1 % or 30 % in oil caused necrosis and redness after 15 minutes or 1 minute of dermal exposure, respectively, in rabbits (number of animals, strain unspecified). HDA diluted at 30 % in alcohol caused oedema after 5 minutes of exposure, and necrosis after 15 minutes of exposure;
- dermal exposure to pure HDA for 1, 5 or 15 minutes, with subsequent rinsing with Lutrol (50 %) in water, resulted in necrosis at the treated site in 3 white rabbits (strain unspecified), which turned into a crust after 5–8 days followed by scar formation;
- dermal exposure for 1 minute at 6 % or 10 % HDA (aqueous) with subsequent washing did not cause skin irritation in male albino rabbits (6/dose/exposure duration), while exposure at 6 % or 10 % HDA for 24 hours caused mild to moderate erythema with necrosis;
- dermal exposure for 1, 5 or 15 minutes to HDA (concentration unspecified) resulted in necrosis in rabbits (strain unspecified);
- dermal exposure to a finely ground powder of HDA resulted in swelling and dark red skin within 1 hour, and necrosis at 24 hours, in male and female rabbits. Dermal exposure at 25 % HDA (aqueous) resulted in redness with slight oedema within 1 hour of exposure; and
- dermal exposure to 1 % HDA under occlusive conditions at 24 and 72 hours did not produce erythema or oedema in 4 NZW rabbits.

In an in vitro skin corrosion experiment conducted according to OECD Test Guideline (TG) 435, aqueous dilutions of HDA at 35 %, 70 % and 85 % were evaluated for skin corrosion potential using an in vitro membrane barrier test method known as the Corrositex® assay. At 35 %, 70 % and 85 % HDA, the chemical passed through the membrane in less than 44, 47 and 45 minutes, respectively. In accordance with the OECD TG 435 cut-off times for Corrositex® (>3–60 min), the chemical was concluded to fall into the corrosive sub-category 1B (REACH).

Eye Irritation

The chemical is classified as hazardous with hazard category ‘Skin Corrosion Category 1B' and the hazard statement ‘Causes severe skin burns and eye damage’ (H314) in the HCIS (Safe Work Australia). The available data support this classification.

In a non-guideline eye irritation/corrosion experiment, 0.1 g of HDA (concentration, composition and impurities unspecified) was applied to the eyes of 4 NZW rabbits. The overall irritation score for all the animals at 1, 24, 48 and 72 hours was 3, which indicated severe eye damage, and the reactions were not reversible at 72 hours after application (REACH).

The following in vivo eye irritation/corrosion studies for the chemical are also available for HDA (REACH):

- 25 % HDA applied to the eyes of albino rabbits (2 males and 1 female) for a duration of 2, 4 or 30 seconds resulted in severe ocular effects occurring within 1 hour; and
- 1 % HDA applied to the eyes of NZW rabbits (4/application duration) at 1, 24, 48 or 72 hours resulted in slight irritation of the eyes based on low scores for ocular effects.

Observation in humans

Incidents involving human occupational exposure to HDA have been reported. Twenty workers at an Italian nylon manufacturing plant were exposed to HDA and adiponitrile in air. HDA concentrations ranged from 2–5.5 mg/m^3 during normal plant operations and from 32.7–131.5 mg/m^3 during autoclaving (information on the manufacturing plant conditions that resulted in the reported concentrations of HDA in the air is not available). Symptoms reported included irritation of the conjunctiva and respiratory tract. In another incident, 488 workers in an epoxy resin plant were exposed to HDA. Symptoms reported included itching, allergic rhinitis, bronchial asthma and impairment of bronchial permeability (NTP, 1993).

Exposure of workers by inhalation to 7–28 ppm of HDA caused irritation of the conjunctivae and upper respiratory tracts. Blood tests were normal. One out of 20 workers developed eczema due to hypersensitivity to HDA; however, limited details are available on their working conditions (Kennedy, 2005).

Sensitisation

Respiratory Sensitisation

No data are available for the chemical.

Skin Sensitisation

The results observed for the chemical in a skin sensitisation animal study are inconclusive.

In a skin sensitisation study, 2 % HDA was applied epicutaneously on the clipped back of 10 guinea pigs in 3 successive applications on the same area on the first day. Six successive intradermal injections of 1 % HDA were administered on the left side over a 13-day period for induction. For challenge, 1 % and 2 % HDA were applied by epicutaneous and intradermal routes. After initial patch application within 10 minutes, erythema was observed. At 1–3 hours post-treatment, the application site became necrotic and dark brown, and was swollen at 6 days after treatment. The results of this test are inconclusive due to the corrosive effects of the chemical (REACH).

Observation in humans

Some reports of allergic reactions to HDA in occupational settings are available; however, there is limited information, such as medical history, exposure conditions and other possible causes, which make it difficult to determine whether HDA can produce skin sensitisation. One worker out of 20 in a manufacturing plant developed hepatitis followed by eczema due to hypersensitivity

to HDA. Dermatitis caused by HDA occurred in 4 workers in a factory producing nylon. The condition reappeared rapidly if the same work involving HDA was resumed. In another incident, 310 workers involved in the production of condensers in which they had contact with TiO_2, cellulose nitrate, styrene, HDA, lacquer and epoxide tar. The workers developed allergic diseases, such as atopic forms of bronchial asthma, allergic rhinitis and dermatitis (Kennedy, 2005). Due to the multiple substances contacted by the workers, the allergic reactions cannot be attributed to HDA with certainty.

Repeated Dose Toxicity

Oral

No data are available for the chemical. HDDC (CAS No. 6055-52-3) has been assessed in oral repeated dose toxicity studies. Hazard classification is not warranted.

In a 15-day toxicity study conducted in accordance with the US FDA Good Laboratory Practice (GLP) Regulations (21 CFR 58), HDDC was orally administered by drinking water to Fischer 344/N rats (5/sex/dose) at concentrations of 0, 0.83, 1.7, 3.3, 5.0 or 6.7 mg/mL for females (equivalent to 0, 126, 263, 422, 517 and 634 mg HDDC/kg bw/day, respectively), and at 0, 0.75, 1.5, 3.0, 4.5 or 6.0 mg/mL for male rats (equivalent to 0, 96, 187, 357, 449 and 545 mg HDDC/kg bw/day, respectively). All rats survived to the end of the study. No clinical abnormalities, gross lesions, or microscopic histopathological lesions, related to chemical exposure were observed. Water consumption was reduced for males in 2 highest dose groups, and for females in 3 highest dose groups. Decreases in absolute and relative liver weights were observed in the females exposed to 263, 517 and 634 mg HDDC/kg bw/day (equivalent to 162, 318 and 390 mg HDA/kg bw/day). At the 357 mg HDDC/kg bw/day dose (equivalent to 219 mg HDA/kg bw/day), relative liver weight in males was significantly reduced. The weights of the other organs were not affected. No adverse effects were observed up to the highest HDDC dose (545 mg/kg bw/day for males and 634 mg/kg bw/day for females). Therefore, the no observed adverse effect levels (NOAEL) corresponded to 335 mg HDA/kg bw/day for males, and 390 mg HDA/kg bw/day for females (NTP, 1993; REACH).

In a study conducted similarly to the 15-day rat study, B6C3F1 mice (5 mice/sex/dose) were administered HDDC by drinking water at concentrations of 0, 0.2, 0.4, 0.8, 1.5 or 3.0 mg/mL (equivalent to 0, 36, 66, 139, 267 and 564 mg HDDC/kg bw/day, respectively, for males; 0, 48, 116, 208, 391 and 632 mg HDDC/kg bw/day, respectively, for females) for 14 days. In the 208 mg HDDC/kg bw/day dose group (equivalent to 128 mg HDA/kg bw/day), significant decreases in relative liver weights in females were observed. No adverse effects were observed up to the highest HDDC doses (564 mg/kg bw/day for males and 632 mg/kg bw/day for females). Therefore, the NOAEL corresponded to 347 mg HDA/kg bw/day for males, and 388 mg HDA/kg bw/day for females (NTP, 1993; REACH).

Dermal

The chemical is not expected to cause serious systemic health effects from repeated dermal exposure.

In a repeated dose dermal toxicity study (limited study details available), 6 white rats (strain unspecified) were treated daily, on shaved backs with a 1 % paste containing crude HDA in petrolatum. Animals were treated for 5 days per week, with a total of 16 applications over 21 days. Another 6 rats were treated with 2 % paste of crude HDA, with a total of 7 applications over 9 days. Application of HDA on the skin produced erythema, scaling and cracking. The liver and kidneys were mildly hyperaemic upon necropsy. Mild degenerative changes in the liver (3 out of 6 rats), and mild to moderate regressive lesions in the renal tubules (2 out of 6 rats) were found. Microscopically, the skin showed small ulcerative defects of the epidermis, with evidence of atrophy and had purulent reaction, as well as inflammation in the lower layers of the skin. The authors concluded that HDA is strongly alkaline, extremely irritating, and produces kidney damage secondary to the dermal inflammatory damage (REACH).

Inhalation

Based on the available data, HDA causes serious health damage from repeated inhalational exposure (see **Respiratory Irritation** section). Observed effects were generally in the respiratory tract, consistent with respiratory irritation.

In a 13-week study, SD rats (15/sex/dose) were exposed to HDA aerosols at concentrations of 0, 12.8, 51 or 215 mg/m^3 for 6 hours per day, 5 days per week. Exposure at 51 and 215 mg/m^3 resulted in increased incidence of respiratory symptoms including rales, rapid, laboured or gasping breathing pattern, as well as signs of irritation of ocular and nasal mucosa. The highest concentration resulted in a higher rate of mortality and treatment-related microscopic lesions in tracheas, nasal passages and lungs. A no observed adverse effect concentration (NOAEC) of 12.8 mg HDA/m^3 was reported (REACH).

Fischer 344/N rats and B6C3F1 mice (5/species/sex/dose) were exposed via whole body inhalation to HDDC at concentrations of 0, 10, 30, 89, 267 or 800 mg/m^3 (equivalent to 0, 6.2, 18, 55, 164 and 491 mg HDA/m^3, respectively) for 6.5 hours per day, 5 days per week, for 12 days. At the highest exposure group, the body weights of female rats, male and female mice were significantly reduced. All of the rats, all female mice and 2 male mice died at the highest exposure concentration. At the highest exposure level, mice showed ruffled fur, abnormal posturing, tremors, prostration, decrease in body mass compared with controls, as well as reduced spleen size. In mice and rats, clinical signs related to the highest HDDC concentration included nasal discharge, rales, dyspnoea, diarrhoea, ocular discharge and hypoactivity. Exposure-related histopathologic lesions in mice and rats included inflammation, necrosis and ulceration in the larynx, trachea and olfactory epithelium. At the highest exposure level, slight testicular degeneration was observed in 2 male mice. In the larynx, focal areas of inflammation and necrosis with ulceration were observed at 6.2 mg HDA/m^3 in male rats and 55 mg HDA/m^3 in female rats. Nasal lesions were present in both male and female rats at ≥55 mg HDA/m^3. At the 2 highest exposure levels, inflammation and necrosis were observed in the larynx and trachea in mice. The NOAEC for male rats could not be determined from this study, while the NOAEC for female rats was 30 mg HDDC/m^3, equivalent to 18 mg HDA/m^3. The NOAEC for both male and female mice was 89 mg HDDC/m^3, equivalent to 55 mg HDA/m^3 (NTP, 1993; REACH).

In a 13-week study in Fischer 344/N rats and B6C3F1 mice (10/species/sex/dose) were exposed via whole body inhalation to HDDC at concentrations of 0, 1.6, 5, 16, 50 or 160 mg HDDC/m^3 (equivalent to 0, 1.0, 3.1, 10, 31 and 100 mg HDA/m^3) for 6.5 hours per day, 5 days per week. No mortality occurred during the study. A dose-related increase in the incidence and severity of microscopic lesions was observed in the larynx and nasal passages in the 2 highest exposure groups (31 and 100 mg HDA/m^3) for mice and rats. These lesions included erosion, ulceration, inflammation and hyperplasia of the respiratory epithelium. The NOAEC for both male and female mice and rats was 16 mg HDDC/m^3, equivalent to 10 mg HDA/m^3, for local respiratory damage (NTP, 1993; REACH).

Genotoxicity

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

In vitro

The chemical HDA was not mutagenic in:

- any of the strains of *Salmonella typhimurium* tested (TA100, TA1535, TA1537 and TA98) at 33–10000 µg/plate (in distilled water or dimethylsulfoxide), with and without SD rat or Syrian hamster liver S9 metabolic activation (NTP; 1993);
- *S. typhimurium* strains TA1535, TA1537 and TA1538 at 1, 10, 25, 50, 75 or 100 µg/plate (purity unspecified, in ethanol), with and without metabolic activation by rat liver S9 (NSF, 2006);
- *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 at 0.1, 1, 10, 100, 500 or 1000 µg/plate (99 % purity, vehicle unspecified), with and without metabolic activation (NSF, 2006); and
- a cytogenetic test in Chinese hamster ovary (CHO) cells with and without S9 metabolic activation. The total number of aberrations with metabolic activation was increased at 500 µg/mL, but the aberrations were in less than 5 % of the total cells scored, and thus, not considered a positive response. It was concluded that there were no significant increases in sister chromatid exchanges or chromosomal aberrations after exposure to HDA (NTP; 1993; REACH).

The chemical HDA at concentrations of:

- 25, 50, 100, 175, 250, 300, 450 and 600 µg/mL did not induce mutations in the hypoxanthine-guanine phosphoribosyltransferase (HGPRT) locus in CHO cells in the absence and presence of metabolic activation (REACH); and

- 5, 10, 25, 50, 100, 250 or 500 nL/mL did not induce DNA damage in a primary rat hepatocyte unscheduled DNA synthesis (UDS) assay (REACH).

In an in vitro mammalian cell transformation assay in BALB/3T3 Clone A31 mouse embryonic fibroblast cell line, no cytotoxicity was observed at HDA concentrations up to 100 µg/mL in the presence of metabolic activation. No transforming activity was observed in the absence or presence of metabolic activation (REACH).

In vivo

In a 13-week inhalation study (see **Repeat Dose Toxicity** section) in mice exposed to HDDC, no significant increase was seen in the frequency of micronucleated polychromatic erythrocytes. The percentage of polychromatic erythrocytes among the total erythrocyte population was increased at the highest exposure level for both sexes indicating that the chemical reached the bone marrow (NTP, 1993).

In an in vivo chromosomal aberration assay, single oral gavage doses of HDA (99 % purity in water) were administered to rats (unspecified strain, 24 rats/sex/dose) at 0, 75, 250 or 750 mg/kg bw. No increase in frequency of chromosomal aberrations was observed compared with controls, and thus, HDA was not considered to be clastogenic (NSF, 2006).

No significant increase in the frequency of chromosomal aberrations was observed after administration by oral gavage of HDA at 0, 75, 250, or 750 mg/kg bw to SD rats (24/sex). No difference was found between the vehicle control and the test groups when comparing modal numbers or mitotic index in a mammalian bone marrow chromosomal aberration test. HDA was not considered to be clastogenic in the rat under the test conditions (REACH).

Carcinogenicity

No data are available for the chemical.

Reproductive and Developmental Toxicity

The chemical does not cause specific reproductive or developmental toxicity. Many of the treatment-related adverse effects observed in these studies were considered to be related to the corrosivity of HDA.

In a 2-generation reproductive toxicity study, SD male and female rats (26/sex/dose) received HDA at doses of 0, 50, 150 or 500 mg/kg bw/day in the diet daily for 56 days pre-mating for the P0 generation, 98 days pre-mating for the F1 generation, and throughout the rest of the study period (including 21 days of lactation for both P0 and F1). The study was conducted in accordance with GLP and US EPA Guidelines. In the parental group, 2 males (P0 generation) from the low- and mid-dose groups died, and 2 females (F1 generation) in the control and low-dose groups died. No mortality was observed in the other groups. In the high dose parental groups, reduced body weight gain in males (P0 and F1 generation), and in females (F1), as well as decreased food consumption were observed. In the high dose group, viable litter size was significantly reduced, as well as pup weight. The decrease in body weight could be attributed to the unpalatability of HDA inducing a decrease in food consumption by the P0 and F1 parents. No adverse effect on survival during lactation was observed in any of the treated groups. A NOAEL of 500 mg/kg bw/day for the parental was reported (REACH). For the developmental and fertility effects, the NOAEL was 150 mg/kg bw/day due to reduced litter size and pup weight secondary to decreased food consumption and reduced weight gain by the parents in the high dose group.

In a 1-generation reproduction study, HDDC was administered to Fischer 344/N rats and B6C3F1 mice (20 males and 40 females/species/dose) at concentrations of 0, 16, 50 or 160 mg HDDC/m^3 (equivalent to 0, 10, 31 and 100 mg HDA/m^3) via whole-body inhalation for 13 weeks. Mating trial animals were bred for 10 nights (approximately study days 68–80, weekdays only) prior to the end of the 13-week exposure period. No reproductive toxicity was observed in rats. Three female mice exposed to 10 mg HDA/m^3, 1 female and 1 male exposed to 31 mg HDA/m^3 died before scheduled termination; however, these deaths were not considered to be related to HDDC. A statistically significant increase in the mean gestation length of mice in the 31 and

100 mg HDA/m^3 exposure groups was noted, but without biological significance in the absence of other reproductive effects.

Pups in the 100 mg HDA/m^3 exposure group had mean body weights lower than that of controls on lactation days 14 and 21.

NOAECs of 100 mg HDA/m^3 (for the parental and the F1 generation) were reported (NTP, 1993; REACH).

In a study similar to OECD TG 414 (prenatal developmental toxicity study), pregnant female SD rats (22/dose) were treated by oral gavage on days 7–16 of gestation with diluted 85.8 % w/w aqueous solution of HDA (in water) at doses of 0, 112, 184 or 300 mg/kg bw/day. At a dose of 300 mg/kg bw/day, maternal toxicity was observed as evidenced by reduced body weight gain, transiently decreased food consumption, decreased number of dams without clinical signs, death of 10 % of animals at this dose group, and clinical signs such as hunching, red stained fur, wheezing and rales. One maternal death occurred in each dose group and 1 female in the highest dose group was sacrificed moribund. Dams treated with 300 mg/kg bw/day had foetuses that were slightly retarded in development as evidenced by reduced foetal body weight, retardation of skeletal development, and increased number of foetuses with liver spottiness. In the 184 and 300 mg/kg bw/day dose groups, there were significantly greater frequencies of occurrence in foetuses with poorly ossified or unfused vertebra. Although the delayed ossification observed in the foetuses from the dams treated at the highest dose were likely to be secondary to maternal toxicity, the retardation in skeletal development observed at the middle dose level occurred in the absence of overt maternal toxicity. Slight ossification retardation is considered to be nonlethal and not detrimental to postnatal survival. A NOAEL of 184 mg/kg bw/day for maternal toxicity was reported (REACH). Due to the delayed ossification in foetuses observed in the high dose group secondary to subclinical maternal toxicity, the NOAEL was 184 mg/kg bw/day for developmental effects.

In an OECD TG 414 study, 3 groups of 24 mated female NZW rabbits were administered HDA by oral gavage, once daily from days 6–28 postmating, at doses of 12.5, 25 or 50 mg/kg bw/day. Three additional animals for satellite investigations were also treated per group. There were no unscheduled deaths or abortions in the control, 12.5 and 25 mg/kg bw/day groups. In the 50 mg/kg bw/day group, 3 premature sacrifices for poor health condition (emaciated appearance, absence of faeces/urine, nearly no food consumption and/or abortion) were considered to be treatment-related. At 50 mg/kg bw/day, a higher percentage of foetuses with malrotated paws, and a higher incidence of foetuses with unossified first metacarpals were found. From 25 mg/kg bw/day, the incidence of foetuses with coloured foci on the gall bladder was increased. All external, soft tissue and cartilage/skeletal variations were treatment-related. It was hypothesised that the observed toxicity in the dams was caused by local effects in the gastrointestinal tract and did not reflect systemic toxicity, and foetal effects were secondary to maternal ill-health. HDA did not demonstrate a teratogenic potential. A NOAEL of 25 mg/kg bw/day for maternal parameters (due to the mortalities in the high dose group) was reported (REACH). Due to the increased incidence of foetuses with gall bladder foci, the NOAEL was 12.5 mg/kg bw/day for embryo-foetal development.

Other Health Effects

Neurotoxicity

Acute neurotoxicity of HDA was studied in albino Wistar rats. Rats were fitted with electroencephalogram electrodes. HDA (unspecified purity in saline) was administered at doses of 1.7, 3.4, 6.8, 17 or 34 µmol into a cannula inserted in the lateral ventricle in the brain. There were 2–4 rats of unspecified sex per dose. The authors concluded HDA did not seem to be directly excitatory to neurons (NSF, 2006).

Immunotoxicity

The effects of HDDC on mitogen-induced lymphocyte proliferative response and stimulation of ornithine decarboxylase activity were studied in vitro. Splenocytes from female C57BL/6J mice were incubated with mitogens (concanavalin A, phytochaemagglutinin, or lipopolysaccharide) and HDDC at concentrations up to 16 mM for up to 68 hours. The authors concluded that HDDC suppressed lymphocyte proliferation in vitro by alteration of ornithine decarboxylase and polyamine activity (NSF, 2006). Limited conclusions on the immunotoxic effects of HDA can be drawn from this in vitro study in the absence of supporting in vivo studies.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are local effects corrosivity (skin and eyes) and respiratory irritation. The chemical can also cause, harmful systemic effects following a single exposure through oral and dermal exposure.

Public Risk Characterisation

Although use in cosmetic and domestic products in Australia is not known, the chemical is reported to be used in cosmetic and domestic products overseas.

When the chemical is used in cosmetic products as a buffering agent at neutral pH (ie. 7–8), the chemical is present as salts that does not have corrosive effects through dermal, ocular, or inhalational exposure. Therefore, the risk of skin, eye and respiratory irritation from the use of the chemical in these products is absent.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure might 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 systemic acute and local 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.

Based on the available data, the hazard classification in the HCIS (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Work Health and Safety

The chemical is classified as hazardous for human health in the Hazardous Chemicals Information System (HCIS). This does not consider classification of physical hazards and environmental hazards.

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)* Harmful in contact with skin - Cat. 4 (H312)*

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Not Applicable	Causes severe skin burns and eye damage - Cat. 1B (H314)*
Repeat Dose Toxicity	Not Applicable	May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)*

[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 dermal, ocular or 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;
- 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

Brorson T, Skarping G, Sandstrom JF & Stenberg M 1990. Biological monitoring of isocyanates and related amines. I. Determination of 1,6-hexamethylene diamine (HDA) in hydrolysed human urine after oral administration of HDA. Int. Arch. Occup. Environ. Health 62 pp. 79-84.

David RM & Heck HD 1983. Localization of 1,6-[14C]diaminohexane (HMDA) in the prostate and the effects of HMDA on early gestation in Fischer-344 rats. Toxicology Letters 17 pp. 49-55.

European Commission Cosmetic Ingredients and Substances (CosIng) Database. Accessed July 2019 at http://ec.europa.eu/consumers/cosmetics/cosing/

Galleria Chemica. Accessed July 2019 at http://jr.chemwatch.net/galleria/

Kennedy, G.L., Jr. 2005. Toxicity of hexamethylenediamine (HMDA). Drug and Chemical Toxicology. 28 pp. 15-33.

National Sanitation Foundation (NSF) International 2006. Oral risk assessment document. Hexamethylenediamine (CAS No. 124-09-4).

National Toxicology Program (NTP) Technical Report No. 24 (1993). 1,6-Hexanediamine dihydrochloride (CAS No. 6055-52-3) Administered by drinking water and inhalation to F344/N rats and B6C3F1 mice. Accessed July 2019 at https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox024.pdf

Organisation for Economic Co-operation and Development Screening Information Dataset (OECD SIDS) 1994. Hexamethylenediamine (CAS No. 124-09-4) SIDS Initial Assessment Report For SIAM 2. Accessed July 2019 at https://hpvchemicals.oecd.org/UI/handler.axd?id=89e149fc-3080-4cac-a767-04cd8678a926

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. Hexamethylenediamine (CAS no. 124-09-4). Accessed August 2019 at https://echa.europa.eu/registration-dossier/-/registered-dossier/16081

Safe Work Australia (SWA). Hazardous Chemical Information System (HCIS). Accessed July 2019 at http://hcis.safeworkaustralia.gov.au/

Substances in Preparations in Nordic countries (SPIN) database. Accessed August 2019 at http://www.spin2000.net/spinmyphp/

The Poisons Standard October 2019. The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) No. 25. Accessed October 2019 at https://www.tga.gov.au/publication/poisons-standard-susmp

The United States (US) Environmental Protection Agency's (EPA) Aggregated Computational Toxicology Resource (ACToR). Accessed October 2019 at https://actor.epa.gov/actor/home.xhtml

US National Library of Medicine’s Hazardous Substances Database (HSDB). National Library of Medicine. Accessed July 2019 at http://toxnet.nlm.nih.gov

Last update 12 December 2019

Share this page