Hydrazine: Human health tier II assessment

02 March 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Hydrazine	302-01-2
Hydrazine, monohydrate	7803-57-8

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

Grouping Rationale

Hydrazine anhydrous (CAS No. 302-01-2) in aqueous solution exists as hydrazine hydrate. To form hydrazine monohydrate (CAS No. 7803-57-8), one molecule of water is loosely attached to the hydrazine molecule with a weak hydrogen bond. In aqueous solutions, the species/ions present are independent of the initial form of the chemical. Therefore, hydrazine anhydrous and hydrazine monohydrate (both which are volatile liquids) are expected to have similar toxicological properties and are considered together in this assessment report.

Hydrazine is mainly used as a hydrate (with 15 - 64 % hydrazine concentration) with low vapour pressure (EC, 2000).

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 Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; eChemPortal: OECD High Production Volume chemical program (OECD HPV), 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 chemicals have reported commercial use including:

- in propellant fuels for aircraft and spacecraft;

- as corrosion inhibitors in boilers;
- in commercial cleaning agents;
- in metal plating on glass and plastics;
- in photographic developers;
- in textile dyes;
- in explosives;
- as pH adjusters;
- as scavengers for gases (oxygen);
- as water treatment agents; and
- as reducing agents.

The chemicals have reported site-limited use including:

- in manufacturing chemical blowing agents, which are used in plastics production (e.g. vinyl flooring and automotive foam cushioning).

Restrictions

Australian

Hydrazine is listed in Schedule 6 of the Poisons Standard (the Australian Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP).

Schedule 6 chemicals are labelled with 'Poison'. These are substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label.

International

Hydrazine and hydrazine monohydrate are listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products: Hydrazine, its derivatives and their salts.

However, many exceptions to this prohibition are listed, including for hydrazine hydrate (CosIng);

- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain—Table 1: Hydrazine, its derivatives and their salts;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist"): Hydrazine, its derivatives and their salts; and
- The Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1—List of substances which must not form part of the composition of cosmetic products (Hydrazine, its derivatives and their salts).

Existing Worker Health and Safety Controls

Hazard Classification

Hydrazine (CAS No. 302-01-2) is classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

T; R23/24/25 (acute toxicity)

C; R34 (corrosion)

Xi; R43 (sensitisation)

Carc. Cat. 2; R45 (carcinogenicity)

Hydrazine hydrate is not included in the hydrazine HSIS classification entry.

Exposure Standards

Australian

Hydrazine (CAS No. 302-01-2) has an exposure standard of 0.013 mg/m³ (0.01 ppm) time weighted average (TWA) (Safe Work Australia).

Hydrazine hydrate is not included in the above hydrazine TWA entry.

International

The following occupational exposure limits (OEL) or TWA are identified (Galleria Chemica).

Hydrazine (CAS No. 302-01-2):

- 0.01-0.013 mg/m³ (0.01 ppm) in different countries such as USA (California), Canada (Alberta), Denmark, Indonesia, Ireland, Malaysia and Spain;
- 0.03 mg/m³ (0.02 ppm) in United Kingdom;
- 0.1-0.13 mg/m³ (0.1 ppm) in Canada (Quebec, Yukon), France, Germany, Greece, India, Japan, Singapore, South Africa, Switzerland and USA (Minnesota, Hawaii); and
- 1.3 mg/m³ (1 ppm) in Philippines and USA (Vermont).

Hydrazine monohydrate (CAS No. 7803-57-8):

- 0.1 mg/m³ in Russia;
- 0.21 mg/m³ (0.1 ppm) in Japan; and
- 0.13 mg/m³ (0.1 ppm) in Finland.

Health Hazard Information

Toxicokinetics

Animal studies indicated that these chemicals are rapidly absorbed into the blood through inhalation, oral and dermal routes and readily distributed to tissues. After administration to rats, the chemicals are metabolised into monoacetylhydrazine, diacetylhydrazine, pyruvic acid hydrazone and urea. The metabolites are excreted in the urine (CERI, 2007).

The chemicals can be metabolised by enzymatic and non enzymatic pathways, producing free radicals including acetyl, hydroxyl and hydrogen radicals. This metabolism is increased with an introduction of cytochrome P450 inducers and is decreased by P450 inhibitors. The formation of free radicals during metabolism may contribute to the toxicity of hydrazine (US Health, 1997).

In some humans who are deficient in acetylase enzyme, hydrazine metabolism (acetylation) is extremely slow and the absorbed chemical could be accumulated in the plasma (CERI, 2007; US Health, 1997).

Acute Toxicity

Oral

Hydrazine is classified as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in HSIS (Safe Work Australia). Based on the data available, this classification is supported for both hydrazine and hydrazine monohydrate.

Hydrazine

The oral median lethal dose (LD50) is 60–90 mg/kg bw in rats; 59–83 mg/kg bw in mice; 55 mg/kg bw in rabbits; and 40 mg/kg bw in guinea pigs (ChemIDplus; IUCLID, 2000).

Hydrazine monohydrate

The oral LD50 is 129 mg/kg bw in rats, 83 mg/kg bw in mice, 40 mg/kg bw in guinea pigs and 55 mg/kg bw in rabbits with excitation and muscle contraction effects in all species (ChemIDplus).

Dermal

Hydrazine is classified as hazardous with the risk phrase ‘Toxic in contact with skin’ (T; R24) in HSIS (Safe Work Australia). The available data support this classification for hydrazine. In the absence of data for hydrazine monohydrate and considering its similarity to hydrazine, this classification should also be applicable to hydrazine monohydrate.

The dermal LD50 for hydrazine is 91 mg/kg bw in rabbits and 190 mg/kg bw in guinea pigs (ChemIDplus).

No data are available for hydrazine monohydrate.

Inhalation

Hydrazine is classified as hazardous with the risk phrase ‘Toxic by inhalation’ (T; R23) in HSIS (Safe Work Australia). The available data support this classification for hydrazine. In the absence of data for hydrazine monohydrate and considering its similarity to hydrazine, this classification should also be applicable to hydrazine monohydrate.

The median lethal concentration (LC50) for hydrazine is 750 mg/m³/four hours (570 ppm) in rats and 330 mg/m³/four hours (252 ppm) in mice with sublethal effects such as dyspnoea (shortness of breath) in both rats and mice (ChemIDplus).

No acute inhalation toxicity data for hydrazine monohydrate are available.

Observation in humans

Accidental oral exposure (details not available) to hydrazine or hydrazine hydrate caused vomiting, hepatotoxicity, neurological and cardiovascular effects (CERI, 2007).

Corrosion / Irritation

Corrosivity

Hydrazine is classified as hazardous with the risk phrase 'Causes burns' (C; R34) in HSIS (Safe Work Australia). The available data for aqueous solutions support this classification for both hydrazine and hydrazine monohydrate.

Hydrazine monohydrate (0.5 mL of 55 % solution) was applied to the shaved skin of Japanese albino rabbits (n=11) for four hours (occlusive). The chemical was reported to be corrosive, based on the results of ulcers and tissue destruction in 7/11 rabbits (IUCLID, 2000).

In a skin irritation/corrosion study, 0.5 mL of a 35 % hydrazine aqueous solution was applied to the shaved back skin (occlusive) of New Zealand White rabbits (n=6) for four hours. Two rabbits died after four or six hours due to the treatment. The Draize scores are not available, but the number of animals with adverse skin reactions is reported (at four, 28, 48 and 72 hours) as: 5/6 defined erythema, 1/6 severe erythema and 4/6 slight oedema after four hours; 4/4 defined erythema and no oedema after 28 hours; 3/4 defined erythema and 1/4 slight erythema after 48 hours and 2/4 defined erythema and 2/4 slight erythema after 72 hours. No ulceration or necrosis were observed. The chemical was considered irritating to the skin (IUCLID, 2000).

Sensitisation

Skin Sensitisation

Hydrazine is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in HSIS (Safe Work Australia). No animal data are available. The human case reports below support this classification for both chemicals.

Observation in humans

Hydrazine and hydrazine hydrate have caused skin sensitisation reactions in humans.

Hydrazine

In a maximisation test, 23 volunteers were pretreated with a 5 % lauryl sulfate solution for 24 hours and then with a 5 % hydrazine solution for 48 hours under occlusive patches (induction phase). This was repeated four times and then the chemical (0.5 %) was applied epicutaneously for 48 hours (challenge phase). All volunteers were sensitised. The chemical was considered to be an extremely strong sensitiser (IUCLID, 2000).

Occupational exposure to hydrazine at concentrations of 0.15 % and 0.015 % for 24–72 hours resulted in skin sensitisation (IUCLID, 2000).

Hydrazine hydrate

A 36-year-old man (a chemical factory worker) suffering from contact dermatitis was patch tested (occlusive) with the chemical at 0.005 % concentration. A positive reaction was observed after one week of the test (IUCLID, 2000).

Occupational exposure to the chemical at a 15 % concentration resulted in eczema on the hands of a worker (IUCLID, 2000).

Hydrazine hydrate applied to a man at 1 % concentration in a patch test (for 48 and 96 hours) resulted in skin sensitisation (Health Canada, 2011).

Repeated Dose Toxicity

Oral

There are treatment-related adverse effects reported in rats and mice receiving these chemicals at low oral doses (i.e. doses within the hazard classification range for repeated dose oral toxicity). The information available (e.g. mortality seen in some studies) is sufficient to justify a hazard classification.

In a repeated dose toxicity study (non-guideline), groups of 10 albino rats were administered hydrazine in drinking water at 0, 6.4 or 12.8 mg/kg bw/d for 14 weeks and at 0, 32, 64 or 128 mg/kg bw/d for 3–4 weeks. A dose-dependent reduction in body weight gain and water consumption were observed in all treated groups. Some animals died (5–7/10) or were sacrificed after 3–4 weeks at 32 mg/kg bw/d, 4/10 died at 6.4 mg/kg bw/d after 5–9 weeks and 6/10 died at 12.8 mg/kg bw/d after 4–6 weeks. No explanation for these deaths was reported and no histopathological changes were observed (IUCLID, 2000).

In a repeated dose toxicity study, CBA mice and Syrian golden hamsters were administered the chemical (hydrazine sulfate) orally at 0, 1.1, 2.3 or 4.9 mg/kg bw/d in drinking water for 15 to 25 weeks. The following effects were reported:

- increased mortality at 2.3 mg/kg bw/d and above in both mice and hamsters;
- adrenal degeneration in female mice at 1.1 mg/kg bw/d and above;
- cirrhosis, bile duct hyperplasia, reticuloendothelial cell (cells of the immune system, primarily comprising macrophages and monocytes); and
- proliferation and degeneration of fibrous cells in the livers of hamsters at 4.9 mg/kg bw/d (Biancifiori et al., 1970 cited in CERI, 2007).

In a 28-day study (OECD Test Guideline (TG) 407), a group of Crj:CD(SD)IGS rats were administered hydrazine monohydrate by gavage at 0, 1, 3, 10 or 30 mg/kg bw/d. No mortality was observed in any treatment group. The effects observed at 10 and 30 mg/kg bw/d were increased absolute kidney weights in both male and female rats and elevated liver weights in female rats. At 30 mg/kg bw/d, elevated extramedullary haematopoiesis (formation of blood cellular components outside the bone medulla) in both sexes and elevated spleen weights in female rats were observed. Fatty changes in hepatocytes were observed in female rats at all doses including in the control group, and in the two high dose group male rats. The no observed adverse effect level (NOAEL) is 3 mg/kg bw/d for both male and female rats (REACH).

No liver effects were reported in NMRI mice receiving hydrazine hydrate at 9.5 mg/kg bw/d in drinking water for two years (Steinhoff et al., 1990 cited in SCOEL, 2010).

In life-time toxicity studies, groups of NMRI mice and Wistar rats were administered hydrazine monohydrate at 0, 0.3, 1.1 and 3.7 mg/kg bw/d and 0.13, 0.64 and 3.2 mg/kg bw/d, respectively. The lowest observed adverse effect levels (LOAELs) were 0.3 and 0.13 mg/kg bw/d for mice and rats respectively, based on body weight gain suppression seen in both species. Only slight body weight suppression was observed in female mice at 0.3 mg/kg bw/d with no changes in organ weights or histopathology. Bile duct hyperplasia was observed in female rats at 0.64 mg/kg bw/d and above and at all doses in male rats. No other changes were observed (IUCLID, 2000).

Dermal

No data are available.

Inhalation

There are treatment-related adverse effects reported in animals exposed to hydrazine at very low doses (i.e. doses within the hazard classification range for repeated dose inhalation toxicity). Although detailed information is lacking in some studies, considering the very low doses that have caused liver and haematological effects in exposed animals, hydrazine is considered to have severe repeated dose inhalation toxicity, warranting a hazard classification. Considering the similarity of the two chemicals, the same hazard classification is also applicable to hydrazine monohydrate. Both chemicals are classified as corrosive (see ***Irritation/Corrosivity***), indicating they are respiratory tract irritants.

In 12-month inhalation studies, rats (Fischer 344) exposed to hydrazine vapour showed higher sensitivity to the chemical in the respiratory mucosa, compared with mice, Syrian golden hamsters and Beagle dogs. The no observed adverse effect concentration (NOAEC) was not established in these studies due to the inflammatory effects observed at all treatment doses. The lowest observed adverse effect concentration (LOAEC) in rats was reported as 0.066 mg/m^3. The NOAECs for hepatotoxicity were reported to be between 0.33 and 1.33 mg/m^3 in mice, rats and dogs (CERI, 2007).

The effects reported in 12-month studies include (IUCLID, 2000; CERI, 2007):

- dose-dependent reductions in body weight gains; amyloidosis (deposition of amyloid proteins) in the liver, spleen, kidneys, thyroid and adrenal gland; haemosiderosis (abnormal deposition of haemosiderin); bile duct hyperplasia; inflammation of lymph nodes; and senile atrophy of the testis in hamsters.
- significantly reduced body weight gain and inflammation in the larynx and tracheal mucosa epithelium and squamous metaplasia in all treated rats; atrophy of the ovaries and inflammatory effects on upper genital tract in females and significant interstitial hyperplasia of the testis in males at the highest dose. These effects occurred at 0.066–6.65 mg/m^3.

In 26-week studies (non-guideline), four animal species (Sprague Dawley rats, ICR mice, Beagle dogs and Rhesus monkeys) were exposed to hydrazine at 0.2 or 1 ppm (0.26 or 1.33 mg/m^3) continuously, or at 1 or 5 ppm (1.33 or 6.55 mg/m^3) six hours a day for five days/week. Fatty degeneration in the liver was observed in mice, dogs and monkeys exposed to the chemical at 0.26 and 1.33 mg/m^3**.** Haemoglobin, haematocrit and red blood cell counts were all significantly reduced (25–30%) in dogs at 1.33 mg/m^3. The hepatotoxic effects were more severe in mice than in the other species and were responsible for their increased mortality. Lethargy, rough and yellowed fur and fatty liver changes were reported in mice at all doses. Chronic bronchopneumonia was observed in rats at 1.33 mg/m^3 (IUCLID, 2000; CERI, 2007; SCOEL, 2010).

No data are available for hydrazine monohydrate.

Genotoxicity

Based on the data available, hydrazine is considered to be genotoxic, including in germ cells, and warrants a hazard classification. The same classification is also supported for hydrazine monohydrate. Two in vivo tests in mice (dominant lethal tests and unscheduled DNA synthesis) showed negative results and therefore the possibility of hydrazine to induce heritable mutations in the germ cells of humans is uncertain.

The International Agency for Research on Cancer (IARC), Chemicals Evaluation and Research Institute (CERI) and Health Canada reported hydrazine as genotoxic (IARC, 1999; CERI, 2007; Health Canada, 2011). Hydrazine and hydrazine hydrate showed positive results in many in vitro and in vivo genotoxicity tests. These include in vitro studies such as bacterial reverse mutation assay (Ames tests) and clastogenicity tests (mammalian chromosome aberration, mammalian gene mutation, unscheduled DNA synthesis, DNA damage and repair test and *Saccharomyces cerevisiae* gene mutation test). Positive in vivo data were reported in somatic cell mutagenicity assays (mouse spot tests) and germ cell mutagenicity assays (gene mutation test in *Drosophila melanogaster*). However, in vivo dominant lethal tests in mice and unscheduled DNA synthesis in mice showed negative results (CERI, 2007).

Two nitrosamine-related DNA adducts (*N7*-methylguanine and *O6*-methylguanine) in the liver DNA are formed during in vivo treatment of mice, rats and Syrian hamsters with hydrazine (IARC, 1999).

Carcinogenicity

Hydrazine is classified as a Category 2 carcinogen with the risk phrase ‘May cause cancer’ (T; R45) in HSIS (Safe Work Australia). The available data support this classification for hydrazine and hydrazine monohydrate.

The International Agency for Research on Cancer (IARC) classified hydrazine as a Group 2B carcinogen (possibly carcinogenic to humans) based on "inadequate evidence in humans but sufficient evidence in experimental animals" for the carcinogenicity of hydrazine (IARC, 1999) (see Note below).

In oral and inhalation toxicity studies, hydrazine produced lung, liver and nasal tumours and a few colon tumours in Wistar rats; liver tumours and thyroid adenomas in Syrian hamsters; and mammary and lung tumours in NMRI mice (IARC, 1999).

Oral exposure to hydrazine monohydrate at 50 mg/L produced increased lung tumours in mice, and malignant uterine cancer and liver tumours in rats (Steinhoff and Mohr, 1988 and 1990 cited in CERI, 2007).

Several epidemiological studies concluded that hydrazine did not enhance cancer risk (CERI, 2007).

Note

In 2016, IARC changed the classification of hydrazine from Group 2B carcinogen (possibly carcinogenic to humans) based on "inadequate evidencne in humans but sufficient evidence in experimental animals" to Group 2A carcinogen (probably carcinogenic to humans) based on "limited evidence in humans that it causes lung cancer, and sufficient evidence of carcinogenicity in experimental animals". As reported in the Lancet Oncology, the IARC assessment on hydrazine will be published as volume 115 of the IARC Monographs (Grosse Y, Loomis D, Guyton KZ et al., 2016).

Reproductive and Developmental Toxicity

Although there were treatment-related effects in animal studies at low doses, the limited data available (i.e. non-guideline studies with no details on experimental conditions or single dose studies) are not sufficient to warrant a hazard classification. As these chemicals are recommended for classification for repeated dose toxicity, some of the adverse effects reported in the studies below may be secondary effects from other systemic effects.

Oral administration of hydrazine to albino rats at 0, 0.00016, 0.0014 or 0.016 mg/kg bw/d in drinking water for six months (timing of exposure not available) caused decreased number of surviving embryos and increased resorptions (non-guideline study). No developmental anomalies were found in 293 foetuses of the treated groups. Lesions in the gonadal epithelial cells of male rats were observed at 0.0014 mg/kg bw/d and above. The no observed adverse effect level (NOAEL) is 0.00016 mg/kg bw/d (CERI, 2007).

Reproductive effects such as ovarian and testicular atrophy, endometrial inflammation and low sperm levels were observed in hamsters exposed to hydrazine at 1–5 ppm, through inhalation (exposure length/timing not available). No developmental toxicity was observed in hamsters dosed at 166 mg/kg bw on gestation day (GD) 12. However, rats receiving the chemical (injection) at 8 mg/kg bw/d during gestation days 11–21 showed increased prenatal and perinatal mortality (US Health, 1997).

In a developmental toxicity study, a group of pregnant F344 rats received a single dermal application of hydrazine at 0, 5 or 50 mg/kg bw/d on GD 9 then a caesarean section was performed on GD 20. There were no effects on implantation and resorption rates, foetal body weight and external visceral or skeletal anomalies. However, significant complete resorptions were noted in 10/12 maternal rats at 50 mg/kg bw/d. Suppression of maternal body weight gain in treated rats and epidermal necrosis in the application site 24 hours after treatment were observed (CERI, 2007; IUCLID, 2000). A NOAEL of <5 mg/kg bw/d was reported based on the reduced maternal body weight gain (IUCLID, 2000).

A 10 mg/kg bw/d intraperitoneal injection of hydrazine administered to pregnant rats from GD 7–9, and at 4, 12, 20, 30 or 40 mg/kg bw/d to ICR pregnant mice from GD 6–9 showed some developmental effects:

- anomalies such as extra or fused ribs;
- delayed osteogenesis and moderate dilation of the renal pelvis and lateral ventricles in rats; and
- extra ribs in mice.

Decreased maternal body weights at 12 mg/kg bw/d and above, decreased foetal body weights at 12 and 20 mg/kg bw/d and an increased number of resorptions at 30 mg/kg bw/d in mice were reported (CERI, 2007).

In a developmental toxicity study, groups of Crj:CD(SD)IGS rats (n=12/sex) were orally exposed to hydrazine monohydrate at 0, 2, 6, or 18 mg/kg bw/d in drinking water for 39 days (two weeks prior to mating, throughout gestation and up to day three of lactation) (non-guideline study). At 6 mg/kg bw/d, reduction in weights and the viability index of pups on day four of lactation were reported. Histological effects were reported in the liver and spleen in male rats at 6 mg/kg bw/d and in both sexes at higher doses (MHLW, 2005 cited in Health Canada, 2011). Based on the available information, a NOAEL of 2 mg/kg bw/d could be established.

In a reproductive toxicity study, a group of albino rats was exposed (inhalation) to the chemical at 0, 0.01, 0.13, 0.85 mg/m^3 (for five hours a day and five days a week) for four months. A no observed adverse effect concentration (NOAEC) for reproductive toxicity was 0.01 mg/m^3 bw/d, based on increased resorption and foetal deaths at 0.13 mg/m^3 and above. No anomalies were found in 315 foetuses and no effects on gonads of male rats were observed (CERI, 2007).

The Chemical Evaluation and Research Institute (CERI), reported that hydrazine has reproductive and developmental toxicity based on the intraperitoneal administration. The adverse effects reported are reduced foetal body weight, increased resorptions and incidences of exencephalia (brain located outside the skull), hydronephrosis (swelling of kidneys) and extra ribs in mice and rats. However, the information available on reproductive and developmental toxicity studies that used oral and inhalation administration of the chemical are limited (i.e. experimental conditions unknown) (CERI, 2007).

Other Health Effects

Neurotoxicity

Based on the data available, hydrazine and hydrazine monohydrate are considered to have some neurotoxic effects in humans. However, the reported human data are from accidental exposure to larger quantities (exact doses are not available). As the chemical is already classified as hazardous based on acute exposure and repeated inhalation exposure, a separate classification for neurotoxicity is not recommended.

Neurological effects have been reported in humans after inhalation, oral and dermal exposure to hydrazine and hydrazine hydrate (US Health, 1997).

Neurological effects with episodes of violent behaviour such as ataxia, coma, convulsions, hypaesthesia of the hands and paraesthesia (abnormal skin sensations such as tingling, tickling, itching or burning) of the arms and legs were the results of accidental ingestion of a large dose (up to a cupful of the chemical). Ingestion of a mouthful of the chemical by a 24-year-old man led to confusion, lethargy, restlessness, paraesthesia and neurogenic atrophy (US Health 1997).

Nausea, vomiting, tremors and impaired cognitive functions were reported in humans after inhalation exposure to hydrazine (doses not reported) (Richter et al. 1992; Sotaniemi et al. 1971 cited in US Health 1997).

Narcosis, coma, and polyneuritis in two workers were reported with dermal exposure to the chemical as a result of an accidental industrial explosion (Dhennin et al. 1988; Kirklin et al. 1976 cited in US Health 1997).

Neurological effects such as depression, seizures, convulsions, tremors, lethargy, behavioural changes have also been reported in a number of animal species following inhalation exposure to 1 ppm of the chemical. Dermal exposure to the chemical at up to 480 mg/kg in dogs showed effects on the central nervous system (US Health 1997).

Endocrine-mediated effects

Limited data are available indicating degenerative effects of the adrenals of female mice exposed to hydrazine orally at 1.1 mg/kg bw/day for 25 weeks.

Mice exposed to hydrazine orally at 9.3 mg/kg bw/day for 25 weeks showed no adverse effects in the thyroid. No effects in the thyroid or adrenals of hamsters were observed when exposed to the chemical at 5.3 mg/kg bw/day for 15–20 weeks (US Health, 1997).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic long-term effects (carcinogenicity, mutagenicity and repeated dose toxicity);

- local effects (corrosivity and skin sensitisation); and
- systemic acute effects (acute toxicity from oral, dermal and inhalation exposure).

While these chemicals may cause reproductive toxicity effects, reproductive toxicity is not likely to be the main risk.

Public Risk Characterisation

These chemicals have no identified domestic or cosmetic uses in Australia or overseas. However, Canada, New Zealand and the European Union (EU) have prohibited the use of hydrazine, its derivatives and their salts in cosmetic products, but with some exceptions such as hydrazine monohydrate in the EU.

In Australia, hydrazine is on Schedule 6 of the SUSMP, including the salts and derivatives, which includes hydrazine monohydrate. Schedule 6 chemicals require distinctive packaging with strong warnings and safety directions on the label if they are used in consumer products. The characterised critical health effects for these chemicals (corrosivity, skin sensitisation, carcinogenicity and mutagenicity) have the potential to pose an unreasonable risk if the chemicals are used in domestic or cosmetic products.

Occupational Risk Characterisation

During manufacturing and product formulation, (dermal, ocular and inhalation) exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may 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 long-term/systemic acute/local) health effects, the chemicals may pose an unreasonable risk to workers unless adequate control measures to minimise (dermal, ocular and inhalation) exposure to the chemicals are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

NICNAS Recommendation

Further risk management is required. Risks for workplace health and safety should be managed through changes to classification and labelling.

Assessment of these chemicals is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

The current regulatory controls are sufficient.

Hydrazine is on Schedule 6 of the SUSMP. Considering the serious health effects possible from exposure to these chemicals, any consumer/domestic products containing these chemicals should be labelled in accordance with the state and territory poisons scheduling.

Work Health and Safety

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Toxic if swallowed (T; R25)* Toxic in contact with skin (T; R24)* Toxic by inhalation (T; R23)*	Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Causes burns (C; R34)*	Causes severe skin burns and eye damage - Cat. 1 (H314)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23) Toxic: Danger of serious damage to health by prolonged exposure if swallowed (T; R48/25)	Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)

[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(s) should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent 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 assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

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

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

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

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

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Last Update 02 March 2018

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Hydrazine** hydrazine anhydrous diamide or diamine nitrogen hydride levoxine H 70
CAS Number	302-01-2
Structural Formula	

	
Molecular Formula	H4N2
Molecular Weight	32.05

Chemical Name in the Inventory and Synonyms	**Hydrazine, monohydrate** hydrazine hydrate hydrazine hydroxide hydrazinium hydroxide diamine hydrate
CAS Number	7803-57-8
Structural Formula	

	
Molecular Formula	H4N2.H2O
Molecular Weight	50.06

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