Polihexanide: Human health tier II assessment

01 July 2016

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Guanidine, N,N'''-1,6-hexanediylbis[N'-cyano-, polymer with 1,6-hexanediamine, hydrochloride	27083-27-8
Poly(iminocarbonimidoyliminocarbonimidoylimino-1,6-hexanediyl)	28757-47-3

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

The chemicals in this group are polymers of chlorhexidine known and marketed under the trade name polihexanide. The allocation of the Chemical Abstract Service (CAS) numbers depends on how the polymer is described (SCCS, 2014). Polihexanide is normally supplied as a 20 % aqueous solution and is used as a preservative in personal care products at low concentrations. The hydrochloride salt of polihexanide, CAS No. 32289-58-0 (not listed on the Australian Inventory of Chemical Substances (AICS)), is considered toxicologically equivalent for assessment purposes (ECHA, 2010). Hence, data from CAS No. 32289-58-0 are also considered in this assessment.

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified:

Polihexanide has reported cosmetic uses as a preservative and a biocide in personal care products at low concentrations (SCCS, 2014; CosIng).

Polihexanide has reported domestic uses, including:

- as a preservative in fabric softeners and wet wipes;
- an antimicrobial agent in hand washes, rubs and air filter treatments; and
- as a deodoriser for vacuums and toilets (SCCS, 2014).

Polihexanide has reported commercial uses, including:

- to control odour in textiles; and
- as a short term preservative for hides and skins.

Polihexanide has non-industrial uses, including:

- as an active ingredient for recreational water treatment;
- as a polymeric-based sanitiser;
- as a sanitiser for beer glass;
- as a solid surface disinfectant in breweries;
- as a biocidal agent for swimming pools and spas; and
- as a disinfectant in veterinary products (APVMA, 2011).

Polihexanide is also used as an antimicrobial agent in wound irrigation, sterile dressings and medical/dental utensils and trays, farm equipment, animal drinking water and for hard surfaces for food handling institutions and hospitals (SCCS, 2014).

Restrictions

Australian

Polihexanide is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 6 (SUSMP, 2015).

POLIHEXANIDE **except**:

a) in preparations containing 5 per cent or less of polihexanide; or

b) when packed and labelled for therapeutic use.

Schedule 6 chemicals are described as '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'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2015).

International

In the European Union (EU), polihexanide is listed in Cosmetics Regulation 1223/2009 Annex V—List of preservatives allowed in cosmetic products as preservative in cosmetic products at a maximum permitted concentration of 0.3% (SCCS, 2014; CosIng).

Polihexanide is listed in the New Zealand Cosmetic Products Group Standard—Schedule 7: Preservatives cosmetic products may contain with restrictions. The maximum authorised concentration is 0.3 % (NZ EPA).

Existing Worker Health and Safety Controls

Hazard Classification

Polihexanide is not listed on the Hazardous Substances Information System (HSIS)(Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

The toxicokinetics of polihexanide have been investigated in rats.

In an oral study, Wistar-derived Alpk:APfSD rats were given a diet containing 200 ppm or 2000 ppm polihexanide (equivalent to 10 and 100 mg/kg bw) for 14 days. This treatment was followed by a single radiolabelled dose of either 0.08 mg/kg bw or 0.8 mg/kg bw administered through oral gavage (SCCS, 2104). Within 72 hours, the majority of the administered dose (>90 %) was excreted through the faeces. Only a small fraction of the administered dose was excreted via the urine (approximately 1.8 % to 2.3 %) with the majority being excreted within 24 hours of dosing (SCCS, 2014). The plasma and whole blood levels of the chemicals were negligible 72 hours after dosing. At the low dose (200 ppm), polihexanide was bioavailable at 4.7 % and 3.9 % for males and females, respectively. At the high dose (2000 ppm), the bioavailability of polihexanide was 3.0 % in males and 2.6 % in females (SCCS, 2014).

In another publicly available oral gavage study, Wistar-derived Alpk:APfSD rats were exposed to a dose of 20 mg/kg bw radiolabelled or non-radiolabelled polihexanide (fractionated into low, medium and high molecular weight fractions) (APVMA, 2011; SCCS, 2014). This study was subdivided into three experiments: biliary excretion; bioavailability; and excretion and tissue retention. The results from the first experiment showed that majority of the radiolabelled polihexanide (96.8 % for males and 98.9 % for females) was excreted in the faeces over 48 hours. Small amounts of polihexanide were excreted in the urine (3 %) and in the bile (<0.2 %). In the second experiment, over 94 % of the administered dose was eliminated in the faeces. Approximately 5.2, 0.2, and 0.2 % was excreted in the urine in the low, medium and high molecular weight fractions, respectively (APVMA, 2011). This suggests greater absorption of the low molecular fraction. In the residual carcasses, 0.15-0.54 % of the administered dose was identified. In the third experiment, 94.1 and 93.5 % were excreted in the faeces of males and females, respectively. Approximately 7.8 % and 2.6 % of the administered dose were excreted in the urine of males and females, respectively. The highest amounts of radioactivity, observed after three days, were found in the liver (0.18 % of the administered dose in males and 0.19 % in females) and in kidneys (0.03 % in males and 0.04 % in females). The residual carcasses contained 0.22 and 0.28 % of the administered dose. No metabolites were identified (SCCS, 2014).

The dermal absorption of polihexanide has been investigated in humans in vitro. This study was conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 428 using a representative cosmetic formulation of 0.3 % polihexanide (SCCS, 2014). In this study, split skin samples (380-400 µm) from the abdomen of seven donors were mounted on a static diffusion cell and radiolabelled with 0.3 % polihexanide. Effects were monitored at 0.5, 1, 2, 4, 8 and 24 hours after dosing by collecting the receptor fluid. The skin samples were washed and the stratum corneum (outermost layer of the skin) was removed by 20 tape strippings. The analysis revealed a total dermal delivery of 3.49 % radiolabelled polihexanide. This value is the sum of the mean absorbed dose measured in the receptor fluid (0.17 %); the portion in the

epidermis (3.18 %) and the dermis (0.14 %). The high number of tape strippings was likely to remove some absorbable amounts of polihexanide (SCCS, 2014). Whilst there are other publicly available dermal absorption studies in humans and rats in vitro, these were conducted prior to the establishment of good laboratory practices (GLP) and test guidelines. These studies were poorly reported, limiting the regulatory value of the data (SCCS, 2014).

Acute Toxicity

Oral

Polihexanide has moderate acute toxicity based on results from animal tests following oral exposure. Sufficient data are available to support a hazard classification recommendation (see **Recommendation** section).

A median lethal dose (LD50) of 1049 mg/kg bw was reported following a single oral exposure of Sprague Dawley (SD) rats to polihexanide. In this study, which was conducted in accordance with the OECD TG 425, female rats (n=3) were treated with 550 or 2000 mg/kg bw polihexanide in distilled water via oral gavage. The treated animals were observed for 14 days. Treatment with 2000 mg/kg bw polihexanide caused death in all three animals: two deaths on the day of dosing; and one death after the day of dosing. Observed sub-lethal effects include lethargy, ataxia, salivation, laboured breathing, lacrimation, dropping of the upper eyelid (ptosis), and tiptoe gait (SCCS, 2014). At necropsy, the following effects were identified: haemorrhagic or abnormally red lung; dark coloured kidneys and liver; sloughing of the gastric mucosa and the non-glandular stomach epithelium; and haemorrhage of the small intestine (SCCS, 2014). No treatment-related effects were observed in animals that received 550 mg/kg bw polihexanide (ECHA, 2011; SCCS, 2014).

In an early oral acute study in rats (OECD TG 420 equivalent), LD50 values of 549 mg/kg bw in males and 501 mg/kg bw in females were reported. In this study, various doses of polihexanide (administered in 10 mL/kg solution) were administered by stomach tube in male and female rats (strain not reported) and the animals were observed for 14 days. All treated animals showed signs of toxicity including salivation, lacrimation, piloerection and in some cases, subdued appearance (ECHA, 2011).

Another acute oral toxicity study (OECD TG 401-equivalent) has reported a LD50 of 2747 mg/kg bw in males and 2504 mg/kg bw in female rats (equivalent to 549 and 501 mg/kg bw from the 20 % solution). In this investigation, Alderley Park rats (n=5/sex/dose) were exposed to 0, 700, 1000, 1500, 2000, 2500, 3000, 3500 and 5000 mg/kg bw polihexanide (20 % aqueous solution) by stomach tube and animals were observed for 14 days. A dose-dependent increase in mortalities was reported in both sexes for doses administered between 2000 mg/kg bw and 5000 mg/kg bw. All treated animals showed signs of toxicity including salivation, lacrimation, piloerection, and some animals had subdued appearance. Wheezing and staining around the mouth were also noted in animals treated with 1500 mg/kg bw (ECHA, 2011; SCCS, 2014).

Dermal

Polihexanide has low acute toxicity based on results from animal tests following dermal exposure. The LD50 in SD rats is >5000 mg/kg bw (when tested as solid) (SCCS, 2014). In New Zealand White (NZW) rabbits, the LD50 is >2000 mg/kg bw. In these tests, no mortalities were reported. Observed sub-lethal effects included slight to well-defined erythema and haemorrhage of dermal capillaries. These effects were only observed at the treatment sites (SCCS, 2014).

Inhalation

Polihexanide has moderate acute inhalation toxicity in animal tests (ECHA, 2014; SCCS, 2014). Although the full details of these studies are not publicly available, the reported median lethal concentration (LC50) values reported were 0.29 mg/L in male rats; 0.48 mg/L in females; and 0.37 mg/L in both sexes combined (ECHA, 2014a; ECHA, 2014b; SCCS, 2014). The reports also noted that these studies were guideline-compliant (ECHA; 2014b). Observed sub-lethal effects in these studies included breathing irregularities, abnormal respiratory noise, partial drooping of the upper eyelids (ptosis), decreased activity and pathological changes in the lungs. Sufficient data are available to support a hazard classification recommendation (see **Recommendation** section).

In an acute inhalation study, Alpk:APfSC rats (n=5/sex) were exposed to a single exposure of 1.76 mg/L polihexanide by nose-only inhalation for four hours. Considering the mass median aerodynamic diameters of 1.8-2.0 µm, the corresponding amount of polihexanide reaching the respiratory system was calculated to be 0.36 mg/L (SCCS, 2014). Death of one animal three hours after the exposure was reported. Irregularities in breathing and abnormal respiratory noise were observed in the treated males and females. The lungs of the male that died were mottled red (SCCS, 2014).

Polihexanide is toxic to Wistar CRL:(WI) rats following a single inhalation exposure. In this OECD TG 403-compliant study, the concentrations tested were 0.1, 0.3 and 0.5 mg/L polihexanide with exposure duration of four hours. Mortalities were observed in the following dose groups: 3/5 males in the 0.3 mg/L group; 5/5 males and 3/5 females in the 0.5 mg/L group (SCCS, 2014). At necropsy, the lungs of the animals from the 0.3 mg/L and 0.5 mg/L groups were enlarged and discoloured (dark/red), the fur at the perinasal area also showed discolouration and the trachea contained white foamy material (SCCS, 2014). Clinical signs observed in the treated rats included laboured breathing, coarse rattling sound somewhat like snoring (rhonchus), decreased activity, hunched back, increased respiratory rate, sneezing, and ptosis. The LC50 values reported in this study were 0.29 mg/L for males, 0.48 mg/L for females and 0.37 mg/L for males and females combined (SCCS; 2014).

In the EU, these data were used in a proposal to classify polihexanide for 'acute toxicity (inhalation)' submitted for evaluation by the European Chemicals Agency (ECHA) Risk Assessment Committee (RAC). The proposal also considered results from a 28-day inhalation toxicity study in rats (see **Repeat-dose toxicity: inhalation** section) that was considered relevant in the evaluation (ECHA, 2011). The RAC agreed in its opinion to classify polihexanide as proposed and the 'opinion was adopted by consensus' (ECHA, 2014a; ECHA, 2014b).

Corrosion / Irritation

Respiratory Irritation

Based on the data from a mouse study (non-guideline compliant), polihexanide is not expected to cause respiratory irritation. However, polihexanide was reported to cause respiratory irritation in a repeat dose inhalation toxicity study in rats (see **Repeat dose: inhalation** section).

In a mouse study, a group of five female Alpk:APfCD-1 mice were exposed (nose-only inhalation) to spa water containing Bacquacil (20 % polihexanide). The analysed concentrations tested in this non-guideline study were reported to be 11.7, 62.9 and 208 mg/m^3 polihexanide. Compared with the control, there was no significant respiratory depression in treated animals (SCCS, 2014).

Skin Irritation

The skin irritation potential of polihexanide has been investigated in rabbits. Polihexanide is reported to slightly irritate skin in animal studies. The effects were not sufficient to warrant hazard classification.

In an OECD TG 404-compliant study, 0.5 g neat polihexanide (moistened with 0.5 mL water) was applied to three areas of the skin of NZW rabbits. The experiment was conducted under occlusive conditions for three minutes, one hour and four hours. The effects were evaluated for primary irritation at one, 24, 48 and 72 hours following patch removal. The results showed no irritation in skin within three minutes or one hour of polihexanide exposure. Following four hours' exposure, well-defined erythema at one treated skin site was noted. Very slight erythema was seen at two treated skin sites one and 24 hours following patch removal. All treated skin sites showed very slight erythema at the 48 hour observation and this effect was still noted in one treated site at 72 hours. The primary irritation index reported in this study for four hours' exposure was 1.0. Polihexanide caused slight oedema at one treated skin one hour after patch removal and very sight oedema at 24 and 48 hours. After seven days of observation, no skin reactions were reported (SCCS, 2014).

In another study, polihexanide was reported to be moderately irritating to intact skin and severely irritating to the abraded skin of rabbits. In this study, female NZW rabbits were exposed to polihexanide as Vantocil P (20 % aqueous solution) to an intact or abraded skin under occlusive condition for 24 hours. Signs of skin irritation, oedema, and erythema were observed at 24 and 72 hours after the removal of the patch. At the 24 hour observation, the treated skin of female rabbits displayed well defined to moderate erythema (average scores: 2.3 for intact skin; 2 for abraded skin). The animals also showed slight to moderate

oedema. However, these effects were reversible by 72 hours. The sites on abraded skin showed signs of scabbing and healing by day 21 of the study (SCCS, 2014). The average erythema and oedema scores for the observation periods at 24, 48, and 72 hours were 1.9 and 0.5, respectively, for intact skin, and 1.8 and 0.8, respectively, for abraded skin (ECHA, 2010). For histopathological analysis, the same treatment was given to a group of male rabbits. These animals were sacrificed 48 hours and 72 hours after removal of patches and skin samples were analysed. The histopathological findings revealed a moderate to marked acute inflammation indicated by epidermal acanthosis and infiltration of immune cells in the superficial corium (dermis). Areas of focal necrosis were also observed extending into the dermis (SCCS, 2014).

Eye Irritation

Based on the results from eye irritation studies in rabbits, polihexanide was found to be highly irritating (SCCS, 2014). Effects were not reversible within the observation periods. Sufficient data are available to support a hazard classification recommendation (see **Recommendation** section).

In an OECD TG 405-compliant study, 0.1 mL of solid polihexanide was instilled into the conjuctival sac of one eye of a male NZW rabbit. The other eye was used as a control. The treatment-related effects on the cornea, iris, and conjunctivae were evaluated at the following timepoints: 1, 24, 48, 72 hours; and 7, 14, 21 days. This single treatment resulted in corneal opacity (opalescent), iridial inflammation and severe conjunctival irritation. In addition, other treatment-related effects such as vascularisation and pale appearance of the nictating membrane were also observed. These changes were not reversible by 21 days. Considering the severity of the effects, no additional animals were used in the study. Although there were no scores provided, polihexanide was considered corrosive to the rabbit eye following a single application (SCCS, 2014).

Moderate conjunctival redness and corneal opacity were reported in another study (OECD TG 405) one hour following the instillation of 0.1 g polihexanide to one eye of the NZW rabbits. Conjuctival swelling (chemosis) was observed at 24 hours and congestion in the iris was noticeable two days after the instillation. These effects persisted throughout the entire observation period of seven days. Additionally, the nictating membrane and the cornea displayed ulceration after one day, and this remained until 72 hours (SCCS, 2014).

In another study (predating guidelines), 0.1 mL polihexanide (as Vantocil IB, 20 % aqueous solution) was instilled into the conjuctival sac of one eye of NZW rabbits (n=9). The other eye was used as a control. Approximately 20-30 seconds after instillation, three of the treated eyes were washed for one minute. The other six treated eyes remained unwashed. The treatment-related effects were evaluated at one hour to two hours and 1, 2, 3, 4, 7, 8, 15, 25, 26, 28 and 35 days after instillation. Based on the results, all animals with unwashed eyes displayed iritis and conjunctivitis. Corneal opacity was noted in 4/6 animals. These changes were reversible by 25 days after instillation. Only conjuctivitis and slight iritis were observed in animals with washed eyes. In this study, polihexanide is considered a moderate eye irritant when unwashed and a mild irritant when washed (SCCS, 2014).

Observation in humans

Results from a skin irritation study in human volunteers indicate that polihexanide was not a skin irritant at concentrations up to 1.5 %. In this study, Cosmocil CQ (containing 20 % polihexanide) was applied to the skin of 45 volunteers in a Finn chamber plaster for 24 hours. The concentrations tested were equivalent to 0%, 0.3%, 0.6 % and 1.5 % polihexanide. Only one volunteer showed skin reaction at the highest dose tested. Under these conditions, polihexanide was not considered a skin irritant in humans (SCCS, 2014).

A study of six clinical case reports showed that a 0.02% aqueous polihexanide solution was well-tolerated by human corneal and conjunctival epithelium when used for the treatment of *Acanthamoeba* keratitis (Duguid et al., 1996).

Sensitisation

Skin Sensitisation

Polihexanide is considered to be a moderate skin sensitiser based on the positive results seen in guinea pig maximisation tests (GPMT). Sufficient data are available to support a hazard classification recommendation (see **Recommendation** section).

The skin sensitisation potential of polihexanide was investigated in an OECD TG 406-compliant maximisation study in Alpk:Dunkin Hartley guinea pigs. A dose-ranging study was conducted to determine the concentrations to be used in the main test. The study was undertaken using 20 female guinea pigs and 10 control animals. Intradermal induction used 0.06 % polihexanide (with or without Freund's complete adjuvant (FCA)) under occlusive conditions for 48 hours. Topical induction was with 20.2 % polihexanide solution. The challenge concentrations used were 20.2 and 6 % polihexanide under occlusive condition for 24 hours. The ensuing skin reactions were observed and scored 24 or 48 hours following patch removal. In the guinea pigs challenged with 20.2 % polihexanide, scattered mild redness or moderate diffuse redness were observed in 18/20 and 16/20 animals 24 and 48 hours after patch removal, respectively. The average scores for redness were 1.4 at 24 hours and 1.2 at 48 hours. Similar effects were observed in some animals challenged with 6 % polihexanide: 5/20 after 24 hours; and 2/20 48 hours after patch removal. The average scores were 0.3 at 24 hours and 0.1 at 48 hours. Under these tests conditions, polihexanide is considered to be a moderate sensitiser. However, the SCCS has noted that, at 20.2 %, polihexanide 'should be considered a strong sensitiser according to Regulation (EC) No 1272/2008 (CLP regulation)' (ECHA, 2011; SCCS, 2014).

The skin sensitisation potential of polihexanide was investigated in a Magnusson Kligman test in female Alderley Park guinea pigs (n=20 test animals; n=8 controls). This test was consistent with OECD TG 406 except no sodium lauryl sulfate (SLS)pretreatment was used. Intradermal induction was performed using 0.2 % polihexanide in deionised water and FCA. Topical induction and challenge exposure were conducted using 20.2 % polihexanide. The results indicated signs of mild to moderate erythema in 14/20 treated animals and mild erythema in 1/8 control animals observed at 24 hours. At 48 hours, mild to moderate erythema was observed in 15/20 treated animals and mild erythema was still noted in 1/8 control animals. Signs of skin irritation were reported in one control animal. Under the conditions of the test, polihexanide was considered to cause moderate to strong skin sensitisation (ECHA, 2011; SCCS, 2014).

Polihexanide was also reported to be a moderate skin sensitiser in a Buehler test (guidelines similar to OECD TG 406) in Alderley Park guinea pigs. In this study, the test animals (n=10) were exposed to Vantocil IB which contained 20 % of aqueous solution of polihexanide. During the induction exposure, 2 % polihexanide (in 0.4 mL solution) was topically administered to the clipped scapular region of the guinea pigs under occlusion for six hours. This treatment was repeated ten times for a total period of six days (within three weeks of the initial induction). Challenge was conducted two weeks after the last induction exposure by applying 2 % polihexanide to the rabbit skin and the patch was removed after six hours. Rechallenge exposures were also performed in these animals using 0.2, 2, and 4 % polihexanide. The treatment-related effects were evaluated and scored 24 and 48 hours after cessation of exposure. Compared with untreated controls, signs of faint erythema were seen in 6/10 animals (challenged with 2 %) at the 48 hour observation period. When rechallenged with 4 % polihexanide, 8/9 animals in the treated group showed faint to moderate erythema and 3/10 of the control animals had faint erythema. On rechallenge at 2 %, only faint erythema was observed in 3/10 animals in the treated group but none in the controls. No treatment-related effects were observed in either treated or control animals rechallenged with 0.2 % polihexanide. Under the conditions of this study, the authors concluded that polihexanide is a moderate skin sensitiser at 2 % (SCCS, 2014).

A similar OECD TG 406-comparable Buehler test has demonstrated that polihexanide is a moderate to strong sensitiser in Alderley Park guinea pigs. The experimental procedures used in this study were similar to the study described in the previous section, with the exception of the concentrations used. Induction exposure was performed by applying 0.3, 0.8, 1.2, 1.3, 1.8, 2.0, or 5 % polihexanide to the skin of animals. A range of concentrations were used for the challenge (0.3 to 15 %) and rechallenge (1.2 to 15 %) exposures. In this study, the authors reported a threshold for eliciting skin sensitisation of approximately 1 %. At concentrations above 1.2 %, polihexanide is considered a moderate to strong sensitiser (SCCS, 2014).

Polihexanide and its related compound, chlorhexidine gluconate (CAS No. 18472-51-0), were examined for their cross-reactivity potential in accordance with the Magnusson and Kligman method. With the exception of SLS pretreatment, the guideline used in this study was comparable to OECD TG 406. The study was undertaken using 20 female Dunkin Hartley guinea pigs and 8 control animals. Intradermal induction used 0.25 % polihexanide in water with and without FCA. Topical induction was with 20 % polihexanide. Challenge concentrations used 20 % polihexanide or 0.05, 0.5 and 4 % chlorhexidine gluconate. No cross-reactivity with chlorhexidine gluconate was observed. Positive skin reactions were noted in 8/20 animals of the treated group and 3/8 animals of the control group following challenge with 20 % polihexanide. When rechallenged with 20 % polihexanide, 3/20 animals from the treated group showed skin reactions. Polihexanide was considered a mild sensitiser by the authors of the study (SCCS, 2014).

Observation in humans

Two cases of severe anaphylaxis were reported following contact with a surgical wound treated with hospital disinfectant containing 0.2 % polihexanide (Olivieri et al., 1998). Additionally, an 81-year old female patient experienced symptoms of a grade III anaphylaxis with palmar pruritus, flush, swelling of lips, swallowing difficulties, hypotension and loss of consciousness while using a new brand of wet toilet paper (brand name not provided) containing polihexanide as a disinfectant (Kautz et al., 2010). The patient had no previously known allergies or atopic diseases. Based on the detailed allergy history, the patient had experienced episodes of grade II anaphylaxis during wound care of an existing leg ulcer: once when using a new wound dressing Suprasorb; and twice after wound cleansing with two different disinfectants, Lavanid 1 and Prontosan. According to the product data sheets (available online), the wound dressing and disinfectants contain the following polihexanide concentrations: 0.3 % for Suprasorb; 0.02 % for Lavanid 1 and 0.1 % for Prontosan (B. Braun Medical Inc.; Ethical Agents Ltd.; Lohmann & Rauscher).

By contrast, following patch tests at a concentration of 2.5 % polihexanide on individuals with known contact allergen responses to cosmetics and medications, only six out of 1554 patients showed a positive skin reaction (SCCS, 2014). In another report, no adverse effects were noted following the exposure of 29 patients to Lavasept, a pre-operative antiseptic for cataract surgery containing 0.2 % polihexanide (Hansmann et al., 2004).

The skin sensitisation potential of polihexanide, administered as Vantocil IB (20 % aqueous polihexanide solution), was investigated in 191 human volunteers in a human repeat insult patch test (HRIPT) (SCCS, 2014). Induction patches containing 2 % and 4 % polihexanide were applied to the dorsal surface of the upper arms of volunteers for 24 hours three times a week up to 10 applications. The challenge was performed using 0.05, 0.1, 0.2, 0.5, 1, and 2 % polihexanide. The results indicated that 2 % polihexanide is capable of causing skin sensitisation in humans which can be elicited from 0.2 % (SCCS, 2014).

Due to concerns over the current cut-off level for polihexanide in the SUSMP in light of conclusions made by the SCCS (2014), a detailed evaluation of the available studies on skin sensitisation for polihexanide was carried out by the Australian Government Department of Health (Australian Government Department of Health, 2016). The conclusion of this evaluation is that polihexanide is a possible skin sensitiser in humans in product formulations at 0.5 %, with a potential for causing sensitisation at 0.2 % in sensitive individuals.

Repeated Dose Toxicity

Oral

Based on the treatment-related effects reported in various repeated dose toxicity studies, repeated oral exposure to polihexanide is not considered to cause serious damage to health.

In a 90-day oral rat study (Wistar-derived Alpk:APfSD), a no observed adverse effect level (NOAEL) of 1000 ppm (equivalent to approximately 83.9 mg/kg bw/day in males and 92.3 mg/kg bw/day in females) was reported (ECHA, 2011; SCCS, 2014). Effects observed at higher concentrations of 2000 to 6000 ppm (approximately 171 to 617.4 mg/kg bw/day) include:

- reduced bodyweight;
- increase in haemoglobin and haematocrit levels in males; and
- changes in the kidney function (decreased urine volume and increased specific gravity).

In a mouse (C57Bl/10JfAP/Alpk) study, animals with long-term exposure to polihexanide displayed treatment-related effects. Mice were given a diet containing 0, 400, 1200 or 4000 ppm polihexanide (equivalent to approximately 0, 54.7, 167 and 715 mg/kg bw/day in males and 0, 69, 216.5 and 855.5 mg/kg bw/day for females) for two years (APVMA, 2011). In addition to cancer-related effects (see **Carcinogenicity** section), the animals displayed a number of non-neoplastic changes including reduced body weight, swollen (thickened, discoloured/prolapsed) anus or inflammation in the recto-anal junction and changes in the liver (hepatitis and extramedullary haematopoiesis) and gallbladder (luminal dilatation). These changes were mainly observed in animals exposed to 1200 or 4000 ppm (ECHA, 2011; SCCS, 2014). However, no adverse effects were reported following exposure of mice to diet containing polihexanide at doses 0, 1000, 2000, 4000 ppm (equivalent to 0, 162, 328, 736 mg/kg bw/day in males and 0, 224, 445, 963 mg/kg bw/day in females) for 90 days (ECHA, 2011; SCCS, 2014).

A no observed adverse effect level (NOAEL) of 1500 ppm or 54 mg/kg bw/day was reported in a comprehensive one-year dietary study in beagle dogs (ECHA, 2011; SCCS, 2014). In this OECD TG 452 compliant study, male and female dogs were

given a diet containing polihexanide at doses 0, 300, 1500, 4500 ppm (equivalent to approximately 0, 11, 54, 169 mg/kg bw/day). The highest dose was reduced to 3000 ppm (108 mg/kg bw/day) during week 11 or 12 due to severe effects noted in three males from this group. Results from the clinical and histopathological examination showed the following treatment-related changes in the liver, kidney, skin and testes of animals exposed to the highest dose (4500/3000 ppm):

- decreased liver and testes weights in males;
- increased plasma alanine aminotransferase (ALT) and reduced plasma cholesterol;
- presence of eosinophilic intracytoplasmic inclusion bodies and minimal to slight cellular swelling in the liver;
- formation of tubular hyaline droplet in the kidneys;
- dermatitis (reddening/peeling of the scrotal skin in males and in the chin and limbs in one female); and
- degenerative testicular changes.

Results from a long term (two years) oral study in rats (Wistar-derived Alpk:APfSD) reported NOAEL values of 36 and 45 mg/kg bw/day, for males and females, respectively (SCCS, 2014). In this study, rats were given a diet containing 0, 200, 600, 2000 ppm polihexanide (equivalent to approximately 0, 12.1, 36.3, 126.1 mg/kg bw/day in males; 0, 14.9, 45.3 and 162.3 mg/kg bw/day in females). The results indicated reductions in bodyweight gain and slightly raised plasma alkaline phosphatase activity, predominantly in females at 2000 ppm or 162.3 mg/kg bw/day. In males, mild liver effects were observed including slightly increased incidence of hepatocyte fat and spongiosis hepatis at 2000 ppm or 126.1 mg/kg bw/day (SCCS, 2014). Cancer-related effects were also observed at these doses (see **Carcinogenicity** section).

No adverse effects were reported in three publicly available non-guideline 90-day oral studies in rats, beagle dogs and mice (SCCS, 2014). In Alderley Park Wistar rats, no mortality was observed following dietary exposure to 0, 625 and 1250 ppm of polihexanide (equivalent approximately to 0, 30, and 60 mg/kg bw/day). At 60 mg/kg bw/day, retardation of body weight gain (likely due to reduced food consumption) and iron pigment deposits in the liver were observed. In beagle dogs, no signs of toxicity or mortality were reported following exposure to diet containing 0, 1375, and 2750 ppm polihexanide (equivalent approximately to 0, 34, and 69 mg/kg bw/day) (SCCS, 2014). In a 90-day drinking water study in C57BL/10JfAP/Alpk mice, a reduction in bodyweight and a dose-related reduction in water consumption were reported following exposure to polihexanide at 0.1 mg/mL in the first week and 0.3 mg/mL in the second week until the end of the study. This study was poorly reported. No further details were supplied (SCCS, 2014).

Dermal

Based on the treatment-related effects reported in repeated dose toxicity studies, repeated dermal exposure to polihexanide is not considered to cause serious damage to health.

Polihexanide was applied to the clipped dorsal skin at doses of 0, 20, 60 or 200 mg/kg bw/day (as Vantocil P containing 20.2 % polihexanide) for 30 days under occlusive conditions for a total of 21 six-hour applications in rats (n=5; Wistar-derived Alpk:APfSD). The study was conducted in accordance with test guidelines similar to OECD TG 410. Local irritation (scabbing and erythema) at the site of application was observed. No overt signs of treatment-related systemic toxicity were reported in this study (ECHA, 2011; SCCS, 2014).

In a repeat dose dermal study (21 days), no signs of systemic toxicity or skin irritation were reported in female albino rabbits (strain not specified). In this study, 1 mL of solution containing 1200 ppm (equivalent to approximately 36 mg/kg bw/day) was applied daily to the clipped dorsal skin of rabbits for 23 hours. The exposed skin was washed with soap and water after 23 hours, then the solution was re-applied an hour after washing (SCCS, 2014).

Inhalation

Based on the treatment-related effects reported in repeated dose toxicity studies, repeated inhalation exposure polihexanide is considered to cause serious damage to health. Sufficient data are available to support a hazard classification recommendation (see **Recommendation** section).

In a 28-day repeated dose inhalation toxicity study in male and female Wistar-derived [Alpk:APfSD] rats, the no observed adverse effect concentration (NOAEC) for polihexanide was nominally reported to be 0.0239 mg/m^3. In this OECD TG 412-compliant study, rats were exposed nose-only to 0.025, 0.25, and 2.5 mg/m^3 polihexanide for six hours a day, five days a week for 28 days. Measured concentrations were 0.0239 mg/m^3 (particle size range - 0.32-1.30 µm); 0.257 mg/m^3 (particle size range - 0.48-5.06 µm); and 2.47 mg/m^3 (particle size range - 0.67-1.67 µm). The treated animals were allowed to recover for 13 weeks. Changes in bodyweight and food consumption were observed in males exposed to 0.25 or 2.5 mg/m^3 polihexanide. No deaths occurred in any of the treatment groups. Histopathological analysis showed transient changes in the larynx and trachea in animals from 0.25 and 2.5 mg/m^3 groups. In these groups, increased liver, lung and thymus weights (males only) were reported. Irreversible pneumonitis (severity reduced at the end of the recovery period) and bronchitis were seen in the lungs of animals treated with 2.5 mg/m^3 polihexanide (ECHA, 2011; SCCS, 2014).

In another repeat dose toxicity study, predating establishment of test standards (non-guideline compliant), a NOAEC of 0.025 mg/m^3 was reported. Rats (Alderley Park SPF albino) were exposed (nose-only) to polihexanide at doses 0.025, 0.25, 2.75, 12.5, and 26 mg/m^3, six hours a day, five days a week for 21 days. Treated animals at the top four doses exhibited signs nasal irritation and difficulties in breathing ranging from mild to severe. In animals in the 0.25 and 2.75 mg/m^3 groups, significant levels of methaemoglobin were formed. In addition, slight to severe pneumonitis was identified in the lungs of animals in these groups (SCCS, 2014). Severe nasal irritation and shortness of breath (dyspnoea) were noted in animals from 12.5 mg/m^3. All animals died in this group after the fourth day of exposure at 12.5 mg/m^3. At the highest concentration tested (26 mg/m^3), severe nasal irritation was noted just after six hours of exposure in which all animals died (SCCS, 2014).

Genotoxicity

Based on the limited publicly available data, polihexanide is not considered genotoxic in vivo or in vitro.

In vitro, polihexanide gave negative results in a bacterial reverse mutation assay (ECHA, 2011). Considering the use of polihexanide as an antimicrobial agent, the bacterial reverse mutation test is not deemed appropriate (SCCS, 2014). Negative results were also reported in chromosomal aberration test in human lymphocytes with or without metabolic activation (APVMA, 2011; ECHA, 2011).

In vivo, polihexanide was negative for micronucleus formation in the bone marrow cells of C57BL/6JfCD-1 mice (250 and 400 mg/kg bw) and in unscheduled DNA synthesis in hepatocytes of Alpk:APfSD rats (375, 750 & 1500 mg/kg bw) (APVMA, 2011).

Carcinogenicity

The potential carcinogenic effects of polihexanide have been studied in laboratory animals. Induction of vascular tumours was reported following long term oral exposure of rats and mice to high doses of polihexanide. Sufficient data are available to support a hazard classification recommendation (see **Recommendation** section).

In the rat (Wistar derived Alpk:APfSD) study, animals were given a diet containing polihexanide at doses of 0, 200, 600 or 2000 ppm (approximately equivalent to 0, 12.1, 36.3 and 126.1 mg/kg bw/day in males and 0, 14.9, 45.3 and 162.3 mg/kg bw/day in females) for two years. The experimental protocols used in this study were in accordance with the United States Environmental Protection Agency (EPA) guideline 83-5 (ECHA, 2011). The results showed haemangioma (2/64 males and 2/64 females) and haemangiosarcoma (1/64 females) in the liver of animals exposed to the highest dose (APVMA, 2011).

In the mouse (C57Bl/10J/CD-1 Alpk) study, animals were given diet containing 0, 400, 1200 or 4000 ppm polihexanide (approximately equivalent to 0, 54.7, 167 and 715 mg/kg bw/day in males and 0, 69, 216.5 and 855.5 mg/kg bw/day in females) for two years (APVMA, 2011). This study was conducted according to guidelines comparable to OECD TG 453. In animals exposed to the highest dose of 4000 ppm (715 mg/kg bw/day), the following cancer-related effects were observed:

- increased incidence of haemangiosarcoma in the liver (males and females);

- gall bladder papillomas in two males;
- increased incidence of squamous cell carcinoma at the recto-anal junction (males and females); and
- adenocarcinoma at the recto-anal junction in one male.

Compared with controls, mice in the 400 ppm and 1200 ppm groups had reduced incidence of lymphosarcoma in the lymphoreticular system (SCCS, 2014). Other treatment related effects (non-neoplastic) were also observed in the liver, gall bladder and recto-anal junction of mice from the 1200 ppm and 4000 ppm groups (see **Repeat dose toxicity: oral** section). Administration of 4000 ppm was above the maximum tolerated dose based on the reported changes in bodyweight and food consumption (ECHA, 2011). The no observed effect level (NOEL) reported in this study was 400 ppm (55 mg/kg bw/day) based on the changes in the liver and recto-anal junction (APVMA, 2011).

The presence of haemangiosarcoma in the liver was also reported in the another long term dermal exposure study in Alpk:APfCD-1 mice. Clipped dorsal skin of mice were treated at 0, 0.6, 6.0 or 30 mg/mouse/day polihexanide for five days/week for 80 weeks. At the highest dose, 2/50 females had haemangiosarcoma in the liver. However, this effect was within the range of historical controls and therefore was not considered to be treatment related. The study was conducted prior to the establishment of good laboratory practice (GLP) and standard experimental guidelines (ECHA, 2011; SCCS, 2014).

The mechanism of action for carcinogenicity of polihexanide is still not fully understood. Polihexanide is not genotoxic. Results from the in vivo and in vitro mechanistic study (liver haemangioma induction) showed that polihexanide did not have a direct effect on the endothelial cells (SCCS, 2014).

Although the evidence is weak (due to non-GLP and non-guideline-compliant experimental procedures and the tumours only seen at high doses), the potential carcinogenicity of polihexanide following exposure cannot be ruled out. The ECHA RAC has concluded that 'classification as Carc 2 H351 (suspected of causing cancer) according to CLP would be appropriate' (SCCS, 2014).

According to the report published by the Australian Pesticides and Veterinary Medicines Authority (APVMA) in 2011, whilst the cancer-related effects of polihexanide may be relevant to human health, the tumours in rodents were only observed in high doses, above the maximum tolerated dose. Hence, this is not likely to be relevant under the conditions of human exposure (APVMA, 2011). The Cancer Review Committee of the United States Environmental Protection Agency (US EPA) classified polihexanide as 'Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential by oral and dermal routes' (APVMA, 2011).

Reproductive and Developmental Toxicity

Based on the data available from several animal studies, there is no evidence of reproductive toxicity.

Results from a two-generation reproductive toxicity study in Wistar-derived Alpk:APfSD rats showed no treatment-related changes in reproduction parameters or in growth and development of the offspring, up to the highest tested dose of 2000 ppm (239-249 mg/kg bw/day in males and 258-270 mg/kg bw/day in females) (SCCS, 2014). In another study, feeding SD rats with diet containing polihexanide for up to 130 mg/kg bw/day did not cause teratogenicity or reproductive toxicity (SCCS, 2014).

Developmental toxicity

Polihexanide does not show specific developmental toxicity. The developmental effects observed in studies are secondary to maternal toxicity.

In an early developmental toxicity study (OECD TG 414 comparable), polihexanide was given to Alderley Park rats in the diet at doses 0, 200, 1000, or 2000 ppm (approximately equivalent to 0, 13, 54, or 112 mg/kg bw/day) during gestation days 1-20. Significant reductions in maternal weight gain and food consumption were seen in groups treated with 1000 or 2000 ppm (54 or 112 mg/kg bw/day) polihexanide (SCCS, 2014). At 2000 ppm (112 mg/kg bw/day), offspring showed an increase in extra ribs. This effect was considered to be secondary to maternal toxicity. No other treatment-related changes were reported (SCCS, 2014).

In another study (comparable to OECD TG 414), pregnant Alderley Park mice were exposed to 0, 10, 20, 40 mg/kg bw/day polihexanide (administered as Bacquacil SB in 0.5 % aqueous Tween 80) via oral gavage during gestation days 6-15 (SCCS,

2014). No deaths or signs of toxicity were observed in animals exposed to the 40 mg/kg bw/day polihexanide. The only maternal effect reported in this study was slight reduction of mean maternal body weight at 40 mg/kg bw/day (SCCS, 2014). In foetuses, the only treatment-related effects detected were slight retardation of digit ossification and numbers of caudal vertebrae in groups exposed to 20 and 40 mg/kg bw/day polihexanide. In these dose groups, wide fontanels and poorly ossified frontal bones in the skull were also identified (SCCS, 2014).

The developmental toxicity of polihexanide was investigated in NZW rabbits (SCCS, 2014). In this study, polihexanide was administered to 20 mated females (n=20) by oral gavage at doses 0, 10, 20, 40 mg/kg bw/day (in deionised water) during gestation days 8-20. The treated animals were observed for mortalities or clinical signs of toxicity twice daily during the treatment period and were sacrificed at gestation day 30. Treatment-related changes in the reproductive parameters such as gravid uterine weights, number of corpora lutea, the number and location of live and dead foetuses, sex ratio, external abnormalities, intra-uterine deaths and foetal weights were evaluated. No information on historical control ranges was reported in this study (SCCS, 2014). Exposure of the animals to the highest dose (40 mg/kg bw/day) polihexanide caused premature deaths in six dams. At necropsy, these animals had irritated and inflamed stomach or caecum. The animals that survived until the termination of the study showed loss of appetite. In this group, food intake and body weight gain were significantly reduced. No treatment-related effects were noted on the number or survival of the foetuses. Although slight pre-implantation loss was observed at 40 mg/kg bw/day, this was not considered significant. At 20 mg/kg bw/day polihexanide, a significant increase in post-implantation loss was reported, attributed to intrauterine deaths. Increased percentages of foetuses with unossified 5th sternebrae or with fused 4th and 5th sternebrae were observed at 40 mg/kg bw/day group. However, this observation was not considered treatment-related due to the lack of polihexanide-induced changes in foetal development. This study reported a maternal NOAEL of 20 mg/kg bw/day and a developmental NOAEL of 40 mg/kg bw/day (SCCS, 2014).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include the following:

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

Polihexanide can cause irritation to the skin and eyes following a single exposure and can also cause harmful effects following repeated exposure through inhalation. Polihexanide is potentially carcinogenic by a non-genotoxic mechanism but this is not likely to be relevant under the conditions of human exposure.

Public Risk Characterisation

Although use in cosmetic and/or domestic products in Australia is not known, the chemicals are reported to be used in these products overseas.

Polihexanide is currently listed on Schedule 6 of the SUSMP, in preparations containing more than 5 %, with a number of warning statements, first aid instructions and safety directions applying to the use of polihexanide.

In the EU, the Scientific Committee for Consumer Safety (SCCS) concluded that polihexanide 'is not safe for consumers when used as a preservative in all cosmetic products up to the maximum concentration of 0.3 %.' The SCCS also concluded that polihexanide is 'not safe when used as a preservative in cosmetic spray formulations up to a concentration of 0.3 %' (SCCS, 2014). This conclusion is based on polihexanide being concurrently present in multiple cosmetic products. The chemical is not reported in Compilation of Ingredients Used in Cosmetics in the United States, and is listed as only being present in three products in the Environmental Working Group (EWG) Skin Deep database. Based on this, the total exposure is expected to be much lower than estimated by SCCS. Based on its sensitising properties, where SCCS reported it as being sensitising at 1 %, with potential elicitation at 0.2 %, the risk of sensitisation in users of these products should be controlled by changes to poisons scheduling to further restrict use of this chemical in cosmetic products.

Occupational Risk Characterisation

During product formulation, 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 chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation exposure are implemented. Hence, 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 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

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of polihexanide in cosmetics and/or domestic products be managed through changes to poisons scheduling, and risks for workplace health and safety be managed through changes to classification and labelling.

Assessment of the 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

It is recommended that an amendment to the current listing of polihexanide in the SUSMP be considered. Given the risk characterisation, it is recommended that the concentration of polihexanide in cosmetics and personal care products be restricted. Matters to be taken into consideration include:

- restrictions on using polihexanide in cosmetics overseas, including in the EU and NZ, with maximum permitted concentration of 0.3% (see **Restrictions: international section**);
- acute and repeat dose inhalation toxicity;
- dermal bioavailability of polihexanide (see **Toxicokinetics** section); and
- evidence of skin sensitisation potential.

A detailed evaluation of the skin sensitisation studies available to SCCS has been carried out by the Australaian Government Department of Health due to concerns over the current cut-off level for polihexanide in the SUSMP (Australian Government Department of Health, 2016). The conclusion of this evaluation is that polihexanide is a possible skin sensitiser in humans in product formulations at 0.5 %, with a potential for causing sensitisation at 0.2 % in sensitive individuals.

Work Health and Safety

The 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 and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22) Toxic by inhalation (T; R23)	Harmful if swallowed - Cat. 4 (H302) Fatal if inhaled - Cat. 2 (H330)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)	Causes serious eye damage - Cat. 1 (H318)
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)	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)	Suspected of causing cancer - Cat. 2 (H351)

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

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

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

Advice for consumers

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

Advice for industry

Control measures

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

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

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

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

Obligations under workplace health and safety legislation

Information in this report should be taken into account to 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 chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

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

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

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

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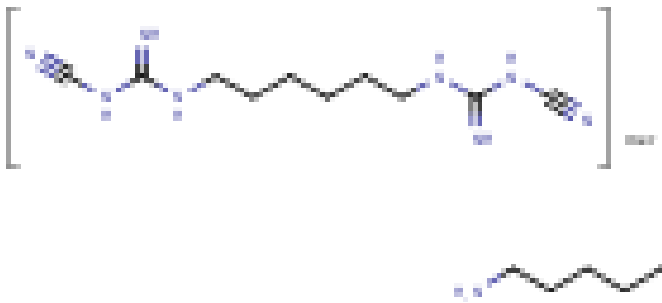
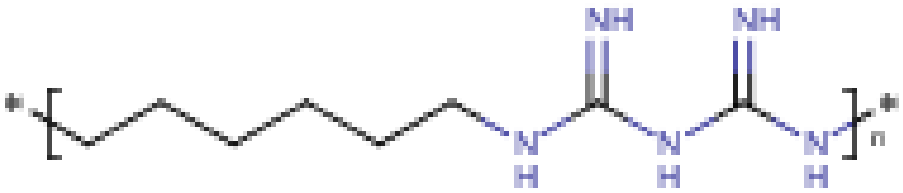
Last Update 01 July 2016

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Guanidine, N,N'''-1,6-hexanediylbis[N'-cyano-, polymer with 1,6-hexanediamine, hydrochloride** N,N-1,6-hexanediylbis(N-cyanoguanidine), hexamethylenediamine polymer, hydrochloride 1,6-hexanediamine, polymer with N,N'''-1,6-hexanediylbis(N'-cyanoguanidine), hydrochloride N,N'''-1,6-hexanediylbis(N'-cyanoguanidine), hexamethylenediamine polymer, hydrochloride
CAS Number	27083-27-8

Structural Formula	
Molecular Formula	(C10H18N8.C6H16N2)x.xClH
Molecular Weight	402.98

Chemical Name in the Inventory and Synonyms	**Poly(iminocarbonimidoyliminocarbonimidoylimino-1,6-hexanediyl)** poly(iminoimidocarbonyliminoimidocarbonyliminohexamethylene) polyhexamethylene biguanide PHMB polihexanide
CAS Number	28757-47-3
Structural Formula	

	
Molecular Formula	(C8H17N5)n
Molecular Weight	183.26

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