5-Pyrimidinamine, 1,3-bis(2-ethylhexyl)hexahydro-5-methyl-: Human health tier II assessment

05 February 2016

CAS Number: 141-94-6

Preface

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

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

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

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

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

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

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

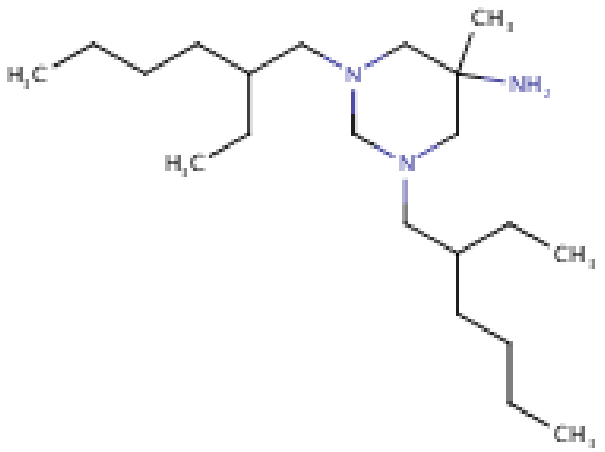
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	hexetidine 5-amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine 1,3-bis(2-ethylhexyl)-5-amino-hexahydro-5-methylpyrimidin 1,3-bis(2-ethylhexyl)-5-methyl-1,3-diazinan-5-amine hexahydropyridimine, 5-amino-1-3-bis(2-ethylhexyl)-5-methyl-
Structural Formula	
Molecular Formula	C21H45N3
Molecular Weight (g/mol)	339.61
Appearance and Odour (where available)	colourless liquid

SMILES	C1(C)(N)CN(CC(CCCC)CC)CN(CC(CCCC)CC)C1

Import, Manufacture and Use

Australian

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

International

The chemical is not registered with the European Chemicals Agency (ECHA) at the time of assessment. It may be solely used in cosmetic products and/or in small quantities, although no current use information is available.

The following international uses have been identified through the European Commission (EC) Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature Cosmetic Ingredient (INCI) dictionary; the US Environmental Protection Agency (US EPA) Developmental and Reproductive Toxicology (DART) database; the US National Library of Medicine Hazardous Substances Data Bank (HSDB); PubChem; and Galleria Chemica.

The chemical has reported cosmetic uses, including:

- as a cosmetic biocide (preservative); and
- as an oral care agent.

The chemical has no reported domestic uses.

The chemical has reported commercial use as an antistatic agent for synthetics.

The chemical has reported non-industrial uses, including as:

- a bactericidal and fungicidal antiseptic (e.g. 0.1 % in mouthwash formulations for treatment of minor local infections, gingivitis and mouth ulcers);
- algaecide;
- an active constituent for agricultural chemical products;
- a disinfectant (0.1 % in horse shampoos), and
- an insect repellent.

Restrictions

Australian

No known restrictions have been identified for industrial uses.

International

The chemical is listed in the following international regulations with the maximum authorised concentration in ready for use preparations of 0.1 % (CosIng; Galleria Chemica):

- EC Cosmetics Regulation Annex V (List of preservatives allowed in cosmetic products);
- New Zealand (NZ) Cosmetic Products Group Standard - Schedule 7 Table 1 (List of preservatives cosmetic products may contain with restrictions);
- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex VI Part 1 (List of preservatives allowed in cosmetic products).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed in 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 oral and dermal absorption of the chemical (also referred to as 'hexetidine' in the **Health Hazard Information** section) is considered low, based on the experience in the therapeutic use of hexetidine at 0.1 % in topical solution (EMEA, 1998). A dermal permeability constant is estimated to be 0.0878 cm/h (Galleria Chemica).

Given its cationic structure, the adsorption of hexetidine to the mucous membranes and dental plaque has been reported, and the adsorption does not easily dissociate or break. Human studies showed that radiolabelled hexetidine was retained in buccal tissues for 8–10 hours, and possibly persisted for up to 65 hours after a single oral rinse (EMEA, 1998; HSDB).

No further information is available on absorption, distribution, metabolism or excretion of hexetidine.

Acute Toxicity

Oral

The available data indicate that the chemical has moderate acute oral toxicity, supporting a recommendation for hazard classification (see **Receommendation** section).

The oral median lethal doses (LD50) are 610–1430 mg/kg bw in rats (FDA, 1998; Galleria Chemica), 1520 mg/kg bw in mice, and 1600 mg/kg bw in dogs (HSDB). The chemical is recommended to be classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in the HSIS.

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Respiratory Irritation

No data are available. However, the chemical is classified with the risk phrase H335 'May cause respiratory irritation' under GHS by Sigma-Aldrich (2013).

Skin Irritation

The chemical is reported to cause moderate to strong skin irritation, supporting a recommendation for hazard classification (see **Receommendation** section).

An evaluation by the Non-Prescription Drugs Advisory Committee of the United States Food and Drug Administration (FDA, 1998) indicated that hexetidine is a moderate irritant using the Draize primary irritation index, although the study and scoring details are not available. It is classified as 'Irritating to the skin' in the Chemical Classification and Information Database (CCID NZ EPA), and classified by Sigma-Aldrich (2013), a major manufacturer of hexetidine, with the risk phrase H315 'Causes skin irritation' under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Eye Irritation

The chemical is reported to cause severe or corrosive eye irritation, supporting a recommendation for hazard classification (see **Receommendation** section).

The chemical is found to be corrosive in primary eye irritation tests, although the study and scoring details are not available (FDA, 1998). It is classified as 'Corrosive to ocular tissue' (CCID NZ EPA), and classified with the risk phrase H319 'Cause serious eye irritation' under GHS (Sigma-Aldrich, 2013).

Observation in humans

In the Handbook of Pharmaceutical Excipients (Rowe et al., cited in PubChem and HSDB), hexetidine in oil (5–10 % w/v) is described as 'causing strong primary irritations' in humans.

Exposure to a test dentifrice containing 0.1 % hexetidine for three minutes caused no irritation to the gingival tissues or oral mucous membranes (EMEA, 1998).

Sensitisation

Skin Sensitisation

No animal data are available.

Observation in humans

There is no evidence of sensitisation with 1 % hexetidine solution.

None of 212 subjects showed any irritant or sensitising reactions following induction and challenge applications on the forearm with an ointment containing 1 % hexetidine (EMEA, 1998; HSDB).

Repeated Dose Toxicity

Oral

Limited data are available on the repeated oral dose toxicity of hexetidine.

In rats, a no observed effect level (NOEL) of 20 mg/kg bw/d was identified from a one-year dietary study (observed effects at 50 mg/kg bw/d were not reported), and a NOEL of 0.5 mg/kg bw/d from a 13-week study. In the latter study, slight decreases in platelet count and prothrombin time (at 8 mg/kg bw/d), and in serum urea levels (at all treated doses, i.e. 0.5, 2 and 8 mg/kg bw/d) were reported for male rats (EMEA, 1998; FDA, 1998).

In dogs, a NOEL of 40 mg/kg bw/d was determined from a 6-month dietary study; however, there was no information available for effects at higher doses (i.e. 80 and 160 mg/kg bw/d) (EMEA, 1998).

It was reported that long-term animal studies with 0.1 % hexetidine in food for one year did not result in any toxic effects. No further information was available (HSDB).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the limited data available, hexetidine is not expected to cause genotoxic effects at the current industrial use conditions.

Negative results were reported from a bacterial Ames test (at an unusually low concentration of 10 µg/plate, compared with 5 mg/plate from a test guideline; assumed to be due to the bactericidal effects of the chemical) in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 with or without metabolic activation, and from a chromosome aberration test (test conditions not specified) (FDA, 1998; HSDB).

Carcinogenicity

The available data are considered inadequate for hazard classification of hexetidine.

The chemical is a nitrogen-containing compound, which has been reported to undergo acidic nitrosation and form nitrosamines, the large group of known potent carcinogens, under nitrosating conditions. The major nitrosamine product of hexetidine, called "HEXNO", forms rapidly in yields as high as 60 % over the pH range of 1.0–4.8 under one-hour incubation time at 37°C (Bae et al., 1994; FDA, 1998). In addition, strong acids can cause opening of the hexahydropyrimidine ring and release formaldehyde, also a known human carcinogen (HSDB). These outcomes are not considered likely under normal formulation and use conditions.

Reproductive and Developmental Toxicity

The available data are considered inadequate for hazard classification of hexetidine.

The chemical is listed in the US EPA DART database, based on a publication in the journal *'Chemically Induced Birth Defects'* (Schardein, 1993); however, no further information is available.

Two studies on embryo-foetal toxicity and teratogenicity of hexetidine are identified. Exposure of rats during gestational days (GD) 6–15 showed no foetal abnormalities at doses up to 50 mg/kg bw/d, although maternal toxicity (reduced weight gain, food and water intake) was observed at this dose level (FDA, 1998; HSDB). During GD 6–18 exposure in rabbits (20/dose), hexetidine was considered to cause embryotoxic effects at doses of 10 and 20 mg/kg bw/d, without showing teratogenicity. Reduced maternal weight gain was also reported at these doses. Two dams dosed with 5 mg/kg bw/d, three with 10 mg/kg bw/d, and eleven with 20 mg/kg bw/d died due to gastric ulcers and intestinal haemorrhages attributable to hexetidine. Metabolism of hexetidine has potential to release 2-ethylhexanol (CAS No. 104-76-7), which is a known reproductive toxin (NICNAS IMAP).

Risk Characterisation

Critical Health Effects

The chemical has moderate acute oral toxicity. It is a skin irritant, and may cause severe or corrosive eye irritation.

Public Risk Characterisation

The chemical has reported cosmetic uses; however, usually at low concentrations as a preservative in oral care products. Exposure of the public is expected to be limited by the possible irritant or oral toxic effects from short-term exposure. In addition, there is no evidence of any significantly toxic effects (e.g. if swallowed when being used as a mouthwash), from the therapeutic use of hexetidine as an antiseptic agent for over 40 years (HSDB). Therefore, the risk to public health of hexetidine is not considered to be unreasonable under the current conditions of use.

Occupational Risk Characterisation

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

The data available support an amendment to the HSIS (Safe Work Australia) (refer to **Recommendation** section).

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

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to work health and safety be managed through changes to classification and labelling.

There is no evidence to suggest that the current conditions of consumer hexetidine use are likely to change. Should additional information become available on potentially high public exposure to hexetidine, a recommendation that the chemical be risk managed for public safety through scheduling may be warranted.

Assessment of the chemical 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

Products containing the chemical should be labelled in accordance with state and territory legislation.

Work Health and Safety

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41) Irritating to skin (Xi; R38)	Causes serious eye damage - Cat. 1 (H318) Causes skin irritation - Cat. 2 (H315)

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

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

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

Advice for consumers

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

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal and ocular exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls.

Measures required to eliminate or minimise risks arising from storing, handling and using of the hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

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

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

References

Bae JY, Mende P, Shevlin G, Spiegelhalder B, Preussmann R, Loeppky RN. 1994. The nitrosation of hexetidine and hexedine: characterization of the major nitrosamine from common antimicrobial agents. Chemical Research in Toxicology 7:868–876

Chemical Classification and Information Database (CCID). Wellington: New Zealand Environmental Protection Authority. Accessed January 2016 at http://www.epa.govt.nz/search-databases/Pages/ccid-details.aspx?SubstanceID=7220

ChemIDPlus Advanced. Accessed January 2016 at http://chem.sis.nlm.nih.gov/chemidplus/

Developmental and Reproductive Toxicology Database (DART). Accessed January 2016 at http://toxnet.nlm.nih.gov/newtoxnet/dart.htm

European Commission Cosmetic Ingredients and Substances (CosIng) Database. Accessed January 2016 at http://ec.europa.eu/consumers/cosmetics/cosing/

European Medicines Evaluation Agency (EMEA). 1998. Hexetidine summary report - Committee for Veterinary Medicinal Products, EMEA/MRL/382/98-final. London: European Medicines Agency. Accessed January 2016, http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500014401.pdf

Food and Drug Administration (FDA) 1998. Center for Drug Evaluation and Research (CDER) Meeting Documents. Nonprescription Drugs Advisory Committee. Dental Plaque Subcommittee. Accessed January 2016 at http://www.fda.gov/ohrms/DOCKETS/ac/98/transcpt/3425t1.pdf

Galleria Chemica. Accessed January 2016 at http://jr.chemwatch.net/galleria/

Globally Harmonized System of Classification and Labelling of Chemicals, 3rd rev (GHS). 2009. Geneva: United Nations Economic Commission for Europe (UNECE). Available: http://www.safeworkaustralia.gov.au/sites/swa/whs-information/hazardous-chemicals/ghs/pages/ghs

Hazardous Substances Data Bank (HSDB). National Library of Medicine. Accessed January 2016 at http://toxnet.nlm.nih.gov

National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II assessment for 2-ethylhexanol (CAS No. 104-76-7). Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Available: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments

Personal Care Products Council International Nomenclature Cosmetic Ingredient (INCI). Accessed May 2013 at http://www.ctfa-gov.org/jsp/gov/GovHomePage.jsp

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

Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed January 2016 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

Schardein JL. 1993. Antimicrobial agents. Chemically Induced Birth Defects 2:316–401

Sigma-Aldrich Safety Data Sheet. Accessed January 2016, http://www.sigmaaldrich.com/safety-center.html

United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary. Accessed January 2016 at http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp

Last update 05 February 2016

Share this page