1,3,5,7-Tetraazatricyclo[3.3.1.13,7]decane: Human health tier II assessment

12 September 2013

CAS Number: 100-97-0

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.

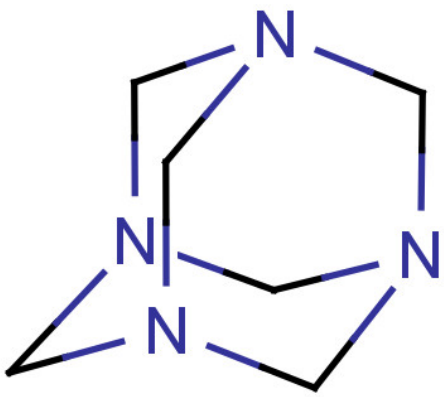
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	hexamethylenetetramine methenamine urotropine hexamine 1,3,5,7-tetraazaadamantane
Structural Formula	
Molecular Formula	C6H12N4
Molecular Weight (g/mol)	140.19
Appearance and Odour (where available)	Odourless, white to colourless lustrous crystals
SMILES	C1N2CN3CN(CN1C3)C2

Import, Manufacture and Use

Australian

The chemical was reported when compiling the High Volume Industrial Chemicals List (HVICL) in 2006, with a total volume of less than 1000 tonnes.

No specific use information has been identified.

The following non industrial uses have been identified (Galleria Chemica):

- as a fungicide/herbicide ingredient; and
- as an ingredient in therapeutic products.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR), Galleria Chemica, Substances in Preparations in Nordic countries (SPIN) database, the European Commission Cosmetic Substances and Ingredients (CosIng) database, United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) directory and other data sources via eChemPortal including the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use:

- as a preservative in cosmetics (up to 0.15 %) (CosIng); and
- as an ingredient in cosmetic preparations (eye makeups, hair conditioners and shampoos).

The chemical has reported domestic use including:

- in adhesives and binding agents;
- in fuels (as fuel tablets for camping stoves containing up to 2 %);
- in paint lacquers and varnishes; and
- in washing and cleaning products.

The chemical has reported commercial use including:

- as a stabiliser and developer in the photo industry (<1 % concentration);
- as a dye fixative;
- as a corrosion inhibitor (<1 % concentration);
- as a lime deposit remover;
- as a preservative in paints and leather (<1 % concentration);
- as a curing or vulcanisation agent; and
- as a fertiliser (<1 % concentration).

The chemical has reported site-limited use including:

- as an intermediate in nitration reactions (explosives);

- in the manufacturing of modified phenolic resins;
- in the manufacturing of textiles and furnitures;
- as a corrosion inhibitor in metal industry;
- in the manufacturing of polymers and rubber; and
- in the extraction of crude petroleum and natural gas.

The chemical has reported food use as a preservative (an antimicrobial food additive). In Hong Kong, the maximum permitted level in food as an additive is 25 ppm (Galleria Chemica).

Restrictions

Australian

The chemical is not specifically listed in the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)). However, specific uses may be included in the following general group entry in Schedule 5 of the SUSMP:

'AMINES for use as curing agents for epoxy resins **except** when separately specified in these Schedules'.

Schedule 5 chemicals are labelled with 'Caution'. These are substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

International

European Commission (EC) Cosmetic Directive 76/768/EEC Annex VI Part 1— List of Preservatives Allowed. The chemical is allowed in cosmetics as a preservative at a maximum authorised concentration of 0.15 %.

The Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex VI, part 1—List of preservatives. The chemical is allowed for use in cosmetic products at a maximum authorised concentration of 0.15 %.

New Zealand Cosmetic Products Group Standard:

Schedule 5—maximum authorised concentration in the finished cosmetic product is 0.5 %; and

Schedule 7—preservatives cosmetic products may contain with restrictions: maximum authorised concentration is 0.15 %.

European Commission Regulation No. 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food, Annex I—The chemical Specific Migration Limit SML(T) is 15 mg/kg (as formaldehyde which is a breakdown product of this chemical).

US Cosmetic Ingredient Review (CIR): Cosmetic ingredients found safe, with qualifications at ≤0.16 %; but should not be used in products intended to be aerosolised.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous with the following risk phrase for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Xi; R43 (sensitisation)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following are identified (Galleria Chemica):

An exposure limit (occupational exposure limit (OEL) or time weighted average (TWA)) of 1 - 4 mg/m³ in countries such as Bulgaria, Estonia, Iceland, Latvia, Norway, Poland, Sweden and Switzerland.

Health Hazard Information

Toxicokinetics

Following ingestion, the chemical is rapidly absorbed from the human gastrointestinal tract, freely distributed to body tissues and fluids and excreted unchanged in urine (90 % within 12 hours). At the acidic pH of the stomach, hydrolytic cleavage of the chemical to formaldehyde and ammonia may occur. The mean half-life in blood was reported to be 4.3 hours (OECD, 2007).

The chemical can be present in the placenta and is detectable in breast milk of lactating women, but no accumulation of the chemical in the umbilical vein plasma was observed (OECD, 2007).

Acute Toxicity

Oral

The chemical is of low acute oral toxicity.

The oral LD50 is 9200 - 20000 mg/kg bw in rats; 512 - 1853 mg/kg bw in mice; and 3120 mg/kg bw in rabbits (OECD, 2007).

Dermal

The chemical is of low acute dermal toxicity.

The dermal LD50 is greater than 2000 mg/kg bw in rats. In an acute dermal toxicity study (OECD Test Guideline (TG) 402), the chemical was applied at 2000 mg/kg bw to the skin of rats for 24 hours (semi occlusive). There were no mortalities and no other effects were reported. Yellowish discolouration of the skin was still present at day 14 after exposure (REACH, 2008).

Inhalation

No data are available.

Observation in humans

Accidental exposure to a high dose of hexamine caused inflammation of the bladder and increased concentration of nitrogen in the blood (SCHER, 2007).

Dermal contact with the chemical caused acute dermatitis (OECD, 2007).

Corrosion / Irritation

Respiratory Irritation

No data are available.

Skin Irritation

The chemical is not a skin irritant.

No skin irritation was observed in rabbits in a test conducted according to the OECD TG 404 (OECD, 2007).

Eye Irritation

The chemical is not an eye irritant.

In an eye irritation test (OECD TG 405), the chemical did not irritate the eyes of rabbits. Instillation of 0.1 g into the rabbit eye (n=3) led to excessive secretion in all three animals shortly after application, but symptoms were reversible within 24 hours (OECD, 2007).

Sensitisation

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (Xi; R43) in HSIS (Safe Work Australia). The data available support this classification.

In a maximisation test on guinea pigs (OECD TG 406), 9/10 animals exposed to a 25 % concentration exhibited strong skin sensitisation effects (OECD, 2007).

In a local lymph node assay (LLNA) (OECD TG 429) with the chemical, an EC3 of 30.6 % was calculated. The chemical is reported as a skin sensitiser (REACH, 2008).

In another maximisation test, 20 guinea pigs (female Pirbright White) were exposed intradermally to 0.1 mL of 30 % solution in the induction phase. The chemical (0.5 g) was also applied epicutaneously to the animal skin (occlusive patch) for 48 hours. At the challenge phase, 0.2 mL of 50 % solution was applied to the animal skin resulting in 17/20 guinea pigs exhibiting erythema and swelling of the skin, indicating a positive reaction to the chemical. None of the treated animals exhibited systemic toxic effects (REACH, 2008).

Observation in humans

The human observations indicate that the chemical should also be classified for respiratory sensitisation.

In humans, the application of the chemical did not clearly exhibit skin sensitising properties. However, in a number of human cases, after contact with the chemical (vapours or solution), skin irritation and allergic symptoms such as wheezing and asthma were reported (OECD, 2007).

Sixty workers, exposed to hot rubber containing 0.1 % of the chemical, exhibited acute dermatitis with itching and redness of the exposed skin. The chemical was reported to cause allergic eczema in workers (OECD, 2007).

In a patch test with 1 % of the chemical in petroleum jelly (occlusive exposure for 48 hours), a 54-year old foundry worker exhibited a positive reaction indicating allergic contact dermatitis (REACH, 2008; Wiley VCH).

Seven patients exposed to 1 % of the chemical by inhalation showed severe positive reactions characterised by immediate allergic reactions. The reactions included wheezing, heaviness on the chest, severe asthma, allergic coryza (acute inflammation of the mucous membrane of the nose) and allergic skin reactions (REACH, 2008).

Repeated Dose Toxicity

Oral

Based on the data available, the chemical is not considered to cause serious damage to health from repeated oral exposure.

Several repeated dose studies indicated no systemic effects in rats:

- oral gavage doses of 200 mg/rat for 90 days and 400 mg/rat (strain BDII) for 333 days;
- in drinking water at 5000 mg/kg bw/day for two weeks in Wistar rats; and
- in the diet at 1500-2500 mg/kg bw/day for 2 years in Wistar rats.

Yellowish discolouration of the fur was observed due to reaction of formaldehyde formed in the urine and kynurenine in rat hair. The no observed adverse effect level (NOAEL) ranged between 1130-2500 mg/kg bw/day (OECD, 2007; REACH, 2008).

The chemical was also administered orally in three strains of mice—up to 12500 mg/kg bw/day for 30 or 60 weeks in CTM mice; and up to 2500 mg/kg bw/day in C3hf/Dp and SWR/Dp mice for 60 weeks. In CTM mice treated for 30 weeks, a significant reduction in survival rates and slight reduction of growth in the surviving animals were observed at 12500 mg/kg bw/day. A NOAEL of 2500 mg/kg bw/day is reported for mice (REACH, 2008).

Dermal

Based on the limited data available, the chemical is not considered to cause serious damage to health from repeated dermal exposure.

In a repeat dose dermal toxicity study, a group of six male rabbits (strain not available) were exposed (non-occlusive patch) to the chemical at 1.3 mg/kg bw/day, five days/week for six weeks. No erythema, oedema or variation of the cutaneous fold were observed. Body weight gain, hair growth and general behaviour were comparable to the control group. No systemic effects were reported (REACH, 2008).

Inhalation

No data are available.

Observation in humans

In patients receiving the chemical or its salts as a urinary antibacterial antiseptic at 8000 mg/day (corresponding to 114 mg/kg bw/day) for three to four weeks showed effects such as bladder irritation, painful and frequent urination, albuminuria and haematuria. However, at 2000 to 4000 mg/day, no such effects were reported. The NOAEL was reported as 57 mg/kg bw/day (OECD, 2007).

Genotoxicity

Based on the data available, the chemical is not considered genotoxic.

In vitro mutagenicity studies showed that very high concentrations of the chemical have weak mutagenic effects (resulting from the hydrolytic cleavage of the chemical to formaldehyde at lower pH). Weak positive mutagenic effects were reported in a chromosomal aberration assay (in human HeLa cells at 1 to 70 mM) and a bacterial gene mutation assay, with or without metabolic activation, but only at high concentrations of 10000 µg/plate and above in *Salmonella typhimurium* strains TA 97, TA 98 and TA 100. However, negative results were reported for *S. typhimurium* strains TA 1535, TA 1537, TA 1538 and *E. coli* strain WP2uvrA, with or without metabolic activation at up to 10000 µg/plate (REACH, 2008; OECD, 2007).

In vivo studies showed negative results in a chromosomal aberration test and a dominant lethal assay. However, weak mutagenic effects were seen at very high sublethal doses in C3H mice (at 25000 mg/kg bw) (OECD, 2007).

Carcinogenicity

Based on the data available, the chemical is not considered carcinogenic.

No carcinogenic effects were reported in various strains of rats and mice following oral exposure to the chemical at doses up to 12500 mg/kg bw/day for up to 104 weeks (OECD, 2007). However, local tumours were reported after subcutaneous injection of the chemical at 20000-30000 mg/rat, probably caused due to chronic local irritation at the injection site (Wiley VCH).

Epidemiological studies were conducted in workers at a steel foundry and in a tyre and rubber factory. Some skin, lung and bladder cancers reported in the workers cannot be conclusively attributed to exposure to this chemical, as the workers were also simultaneously exposed to other suspected carcinogenic chemicals. In addition, there is no evidence for the formation of tumours in the urinary tract of humans from the use of this chemical as a drug (REACH, 2008; OECD, 2007).

Reproductive and Developmental Toxicity

Based on the data available, the chemical is not considered to have reproductive or developmental toxicity.

In fertility studies (non guideline), groups of rats (Wistar) were exposed to the chemical in drinking water at up to 2500 mg/kg bw/day for four weeks (before mating until after weaning). No adverse effects on fertility, litter size, lactation, body weight or growth were observed. The NOAEL for fertility was reported as 1000 mg/kg bw/day (OECD, 2007).

In a reproductive and developmental toxicity study, rats (Alpk:AP) were administered the chemical at 1000 mg/kg bw/day by oral gavage, on days 7-17 after mating. Reduced body weight gain in dams was observed but no effects on the litter size, survival or postnatal body weight gain of pups were noted. The NOAEL for developmental toxicity was 1000 mg/kg bw/day (OECD, 2007; Wiley VCH).

In another study, groups of female beagle dogs were exposed orally to the chemical at 15 mg/kg bw/day (n=9) or 31 mg/kg bw/day (n=10) on days 4-56 after mating. The effects observed in the high dose group included slight increase in the number of stillborn pups and slight reduction in body weight gain and survival of the pups. There were no treatment related effects on pregnancy rate, weight gain, length of gestation or litter size at both doses. The NOAEL for developmental toxicity was reported as 15 mg/kg bw/day (OECD, 2007; Wiley VCH).

Women (n=206) who were treated during pregnancy with the salts of this chemical (therapeutic doses of 2 g methenamine hippurate or 4 g methenamine mandelate per day, corresponding to approximately 13 and 27 mg chemical/kg bw/day, respectively) had no indications of any adverse effects on pregnancy or the development of the children. A NOAEL of 27 mg/kg bw/day was established for developmental toxicity (OECD, 2007).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are skin and respiratory sensitisation.

Public Risk Characterisation

Although use in cosmetic/domestic products in Australia is not known, the chemical is reported to be used in cosmetics (at concentrations up to 0.15 %) and domestic products (such as adhesives and binding agents, paint lacquers and varnishes, and washing and cleaning products; concentrations not reported) overseas.

The general public may be exposed to the chemical via the dermal route if it is used in cosmetic/domestic products. In the absence of any regulatory controls for cosmetic/domestic use of this chemical, the characterised critical health effects (skin and respiratory sensitisation) may pose an unreasonable risk under the uses identified. The risks could be mitigated by implementing concentration limits and restricting uses to limit dermal exposure. Inhalation exposure is less probable given the range of public uses identified.

Occupational Risk Characterisation

Given the critical health effects, the risk to workers from this chemical is considered high if adequate control measures to minimise occupational exposure to the chemical are not implemented.

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 the chemical 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 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

Given the risk characterisation, it is recommended that the concentration of the chemical in cosmetics/personal care products and domestic products be restricted through poisons scheduling. Exemptions to scheduling may be applicable at low concentrations.

Matters to be taken into consideration include skin and respiratory sensitisation effects of the chemical and the maximum concentrations authorised in cosmetics overseas (see **Restrictions**).

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 hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Sensitisation	May cause sensitisation by inhalation (Xn, R42) May cause sensitisation by skin contact (Xi; R43)*	May cause allergy or asthma symptoms or breathing difficulties if inhaled - Cat. 1 (H334) May cause an allergic skin reaction - Cat. 1 (H317)

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

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

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

Advice for consumers

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

Advice for industry

Control measures

Control measures to minimise the risk from dermal exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures 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;
- 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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