1,3,5-Triazine-1,3,5(2H,4H,6H)-triethanol: Human health tier II assessment

25 November 2016

CAS Number: 4719-04-4

Preface

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

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

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

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

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

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

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

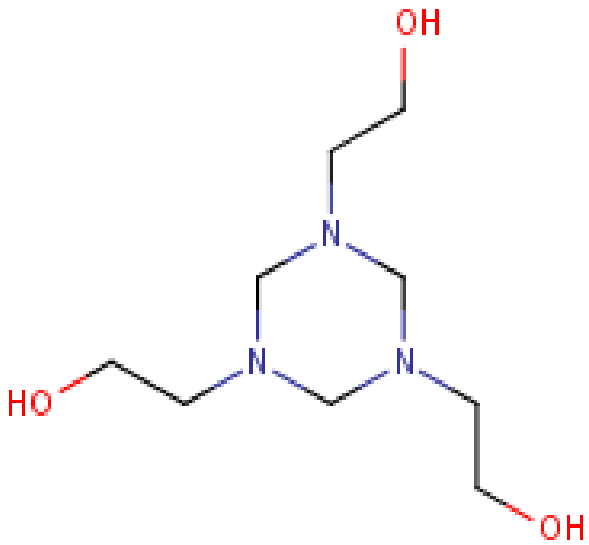
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	hexahydro-1,3,5-tris(hydroxyethyl)triazine triazinetriethanol Grotan BK 1,3,5-tris(2-hydroxyethyl)hexahydro-1,3,5-triazine 2,2',2''-(hexahydro-1,3,5-triazine-1,3,5-triyl)triethanol
Structural Formula	
Molecular Formula	C9H21N3O3
Molecular Weight (g/mol)	219.2829
SMILES	C(O)CN1CN(CCO)CN(CCO)C1

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

The chemical has reported possible domestic use as:

- a surface-active agent.

The chemical has reported commercial use as:

- a lubricant and an antimicrobial biocide.

International

The following international uses have been identified through Galleria Chemica; and the Substances and Preparations in Nordic countries (SPIN) database.

The chemical has reported domestic uses, including:

- in pigments, dyes and printing inks;
- in adhesives and binding agents;
- in anti-setoff and anti-adhesive agents;
- in paints, lacquers and varnishes;
- as a cleaning/washing agent; and
- as a corrosion inhibitor.

The chemical has reported commercial uses, including:

- in cutting fluids;
- in hydraulic fluids;
- in reprographic agents;
- as a fuel additive; and
- as a process regulator.

The chemical has reported site-limited uses, including as a:

- preservative; and
- heat treatment agent.

The chemical has reported non-industrial use as a non-agricultural pesticide and preservative.

Restrictions

Australian

No known restrictions have been identified.

International

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

- Council of Europe Resolution AP (92) 2 on control of aids to polymerisation for plastic materials and articles - Limits for finished articles: 0.25 mg/kg.
- EU Cosmetic Directive 76/768/EEC Annex VI Part 1 List of Preservatives Allowed (German) - Maximum authorized concentration - 0.3 %.

Existing Work Health and Safety Controls

Hazard Classification

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

- Xn; R22 (acute toxicity)
- Xi; R43 (skin sensitisation)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica).

US DOE Temporary Emergency Exposure Limits (TEELs)

TEEL 1: 2.3 mg/m^3; TEEL 2: 25 mg/m^3 and TEEL 3: 150 mg/m^3.

Health Hazard Information

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). The available data support this classification (HSIS).

In the only available oral acute toxicity study (OECD Guideline 401) groups of 10 fasted Wistar rats (5 per sex) were given a single oral dose of the test substance at dose levels of 500, 1000 or 2000 mg/kg bw (REACH).

Four males and all females in the 2000 mg/kg bw dose group and two males and four females in the 1000 mg/kg bw dose group died within two days after administration. Necroscopy findings of the animals that died included agonal congestion, erythema, erosion in the glandular stomach and discolouration of the mucosa of the forestomach and the glandular stomach. Observed sub-lethal effects included general depressed activity, staggering, paresis and diarrhoea.

The median lethal dose (LD50) was calculated as 763 mg/kg bw in rats.

Dermal

The chemical has low acute toxicity based on results from an animal test following dermal exposure. The LD50 in rats in this study was >4000 mg/kg bw.

In an acute dermal toxicity study (OECD Guideline 402) one group of Wistar rats (5 per sex) was administered a dose of the test substance at 4000 mg/kg bw. The chemical was applied to the clipped epidermis of each animal and was covered by a semi-occlusive dressing for 24 hours. The animals were then observed for 14 days (REACH).

No mortality was observed in the study. No systemic pathologic findings were noted at necroscopy of animals euthanised at the end of the study. Local effects such as varying severity of erythema, slight oedema, scaling and superficial scabbing were observed.

Inhalation

The chemical has high acute toxicity following inhalation exposure based on results from animal tests. The median lethal concentration (LC50) in rats is 0.371 mg/L.

In the acute inhalation toxicity study (OECD Guideline 403) groups of 10 Wistar rats (5 per sex) were exposed for four hours to either 0.257, 0.485 or 1.068 mg/L of the target chemical as an aerosol (REACH).

Two females and one male died at 0.257 mg/L. Three females and three males died at 0.485 mg/L. At 1.068 mg/L all animals died or were euthanised in a moribund state. Lethality was observed either during exposure or shortly after exposure on days 0 to 2. Reported signs of toxicity included breathing difficulties. Recovery immediately post exposure was poor as there was little return of the respiration frequency towards the control levels (REACH).

It is recommended that the chemical be classified as very toxic by inhalation.

Corrosion / Irritation

Skin Irritation

In a dermal irritation study (OECD Guideline 404) six New Zealand White (NZW) rabbits were exposed dermally to 0.5 mL of the unchanged substance for four hours via a test patch moistened with the substance (REACH).

No local effects were observed in any of the animals. The study was subsequently terminated 72 hours after the removal of the patches. Under the test conditions, the chemical did not cause irritation to the skin (REACH).

Eye Irritation

In a bovine corneal opacity and permeability test (OECD Guideline 437), three bovine corneas were treated with 750 µL of the chemical for 10 minutes, followed by a post exposure period of two hours (REACH).

The corneal opacity was measured quantitatively, by the amount of light transmission through the cornea. The measurements were used to calculate the in vitro irritancy score of the chemical relative to the untreated corneas. The scores indicated that the chemical did not cause serious damage to bovine corneas (REACH).

In an acute eye irritation study (OECD Guideline 405), 6 (sex unspecified) NZW rabbits were administered 0.1 mL of the chemical in the conjunctival sac of the right eye. The chemical was washed out of the eye 24 hours later and the eyes were examined for signs of irritation at 1, 24, 48 and 72 hours, and further after 8, 15 and 21 days (REACH).

There was slight iritis observed in all animals which was reversible within 8 days. No eye lesions remained in any of the test animals at the end of the three week observation period (REACH).

Sensitisation

Skin Sensitisation

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

A guinea pig maximisation test was conducted in 19 female Dunkin-Hartley guinea pigs (Anderson et al, 1984). Intradermal induction used 1 % of the chemical in propylene glycol which was injected intracutaneously. Topical induction used 25% of the chemical in petrolatum occlusively. The animals were challenged with 0.1 %, 0.5 % or 1 % of the chemical in petrolatum epicutaneously. Control animals were also exposed to the test chemical at the same concentrations at challenge (REACH).

The number of sensitised animals at 48 hours after challenge on day 21 was as follows:

- 0.1 % - 1/19 (all 20 controls were negative);
- 0.1 % - 1/19 (all 20 controls were negative); and
- 0.5 % - 13/19 (1 out of 20 controls was scored positive).

The substance was considered to be a skin sensitiser.

In an open epicutaneous study (G. Klecak, 1977) groups of 8 guinea pigs were administered 100 µL of the test solution to an 8-cm^2 area of the right flank skin, once daily on working days (5/wk) for four weeks at 15 %, 4 %, 0.4 % or 0.15 %. The control group animals were not treated. Skin readings were performed 24 h after application (REACH).

Three days after the last induction treatment, test group animals and control group animals were challenged with 25 µL of each of 4 different concentrations (15 %, 4 %, 1.5 % or 0.4 %) to a 2-cm^2 area on the previously untreated flank. Skin reactions were read at 24, 48 and 72 h after application of the solutions. The second challenge treatment was performed 17 days after the last induction treatments.

The test was considered to be positive if at least one guinea pig of the particular concentration group exhibited positive skin reactions with a non-irritant concentration 24, 48 or 72 h after application of the test substance with the control animals showing a negative reaction. Under the experimental conditions of this study, the test substance was sensitising at challenge with concentrations of 0.4 % and above. The test substance was considered a skin sensitiser.

Observation in humans

Case studies on humans have indicated that the chemical is a skin sensitising agent.

A study (Dahl, 1981) of nine factory workers who have been exposed to the chemical in soluble cooling oil and suffer from eczema undertook a closed patch test. The patch was placed on their backs and 25 µL of the chemical was added in concentrations ranging from 0.2 to 10% and left for 48 hours (REACH).

Positive reactions were observed on day three in 8 of the 9 subjects. All 8 had positive reactions with 10 % and 5 % test solutions; however, only 5 patients at 2 % and 3 patients at 1 % concentrations also had a positive reaction. A patch test with a 10 % solution resulted in negative results in 18 control patients with eczema but without occupational exposure to the chemical (REACH).

Repeated Dose Toxicity

Oral

In a repeated dose oral toxicity 90-day study conducted according to the OECD TG 442, the chemical was administered to Wistar CrlGlxBrlHan rats (10/sex/dose) at dietary concentrations of 200 ppm (14 mg/kg bw/day in males; 21 mg/kg bw/day in females), 1000 ppm (64 mg/kg bw/day in males; 91 mg/kg bw/day in females), and 5000 ppm (285 mg/kg bw/day in males; 339 mg/kg bw/day in females).

The animals were observed for signs of toxicity or mortality up to twice a day for 3 months (REACH). At the end of the study, neither mortality nor clinical symptoms of toxicity were observed and the appearance and behaviour of the animals showed no treatment related changes (REACH).

Dermal

Repeat dose exposure to the chemical via dermal route is not considered to be hazardous.

In a subchronic dermal toxicity 90 day study, male and female Charles River rats (10 animals per sex per dose) were treated with the chemical under semi-occlusive conditions for 6 hours/day, 5 days/week for 90 days. Doses were 0, 5, 50 or 250 mg/kg bw/day. The application site was not washed between doses (REACH). No mortality occurred during the test. There were no treatment related clinical signs. Yellow staining at the site of application in the 50 and 250 mg/kg bw/day groups was seen (REACH).

Inhalation

In a repeated dose inhalation toxicity study (OECD Guideline 412) Wistar rats (10 animals per sex per dose) were exposed (nose only) to the aerosol chemical at 3, 10, 30 and 100 mg/m³. The highest concentration was decreased to 50 mg/m³ after the first exposure day for females and the second exposure day for males due to clinical signs indicative of a severe irritant response (REACH). The animals were exposed for 6 hrs/day for 5 consecutive days per week for 4 weeks. The target concentrations were maintained throughout the exposure period.

Severe clinical signs of toxicity (gasping, intermittent respiration, respiration sound, red encrusted nose, hypothermia, poor general state and yellow discoloured fur), significantly reduced body weight change in males and premature death of 5 of the 10 males were observed in the highest dose group (initially 100 mg/m³, then lowered to 50 mg/m³). In the 30 mg/m³ and 10 mg/m³ groups, intermittent respiration, rales, red encrusted nose, squamous metaplasia occured in all treated groups. The presence of erosion/ulceration of the larynx, squamous metaplasia of the nasal cavity, squamous metaplasia of the carina epithelium, necrosis of the u-shaped cartilage of the larynx, epithelial hyperplasia of the larynx and degeneration of the bronchial epithelium for both sexes were noted. In the lowest dose group (3 mg/m³): multifocal squamous metaplasia of the larynx in all animals; necrosis of the u-shaped cartilage of the larynx in 1/10 males; degeneration of the bronchial epithelium in 3/10 males and 7/10 females and squamous metaplasia of the carina epithelium in 4/10 males and 3/10 females were noted (REACH).

In conclusion, exposure of male and female Wistar rats to the aerosol of the chemical caused concentration-related local irritation of the respiratory tract. Systemic toxicity was not observed in clinical chemistry, haematology or in histological examinations up to 30 mg/m³. The reduced body weight gain and premature death were considered to be associated with the severe local irritation. Based on histopathology findings in larynx, trachea and lung, a no observed adverse effect concentration (NOAEC) could not be established for the local irritation effect under the current study conditions. For systemic effects the NOAEC is 30 mg/m³ (REACH).

Genotoxicity

Based on the weight of evidence from the available data, the chemical is not considered to be genotoxic.

Genotoxicity potential of the chemical was tested in several in vitro and in vivo genotoxicity tests.

- Positive results were obtained in a chromosome aberration test with Chinese hamster lung fibroblasts with and without metabolic activation.
- Negative results were obtained in three bacterial mutation tests with and without metabolic activation.
- Negative results were obtained in a mammalian cell gene mutation test using Chinese hamster lung fibroblasts with and without metabolic activation.
- Negative results were obtained in a chromosomal aberration test in rats.
- Negative results were obtained in two erythrocyte micronucleus tests in mice.
- Negative results were obtained in an unsheduled DNA synthesis test with rat liver cells without metabolic activation.

Carcinogenicity

Carcinogenicity studies for the chemical are not available.

In a poorly documented dermal study with only limited number of animals (NMRI mice), limited scope of parameters examined and with short study duration, the chemical did not result in any carcinogenic effects. Many methodological details of the study are lacking. The test substance was applied to a shaved area of the upper part of the back. Applications, 0.15%, 1.5 % and 15% of the chemical (purity not specified) were made three times a week, over 31 consecutive weeks.

All mice survived to the end of the study. Slight dysplasia was reported in two high-dose animals. Hyperplasia occurred in one mid-dose and seven high-dose mice. Three of the high-dose animals had degenerative changes (amyloid deposition) in the kidney, but not the spleen or liver. The test substance did not induce papillomas. No information is provided on clinical observations in the treated animals.

Reproductive and Developmental Toxicity

Studies for reproductive toxicity are not available.

In a prenatal developmental toxicity study in rats, artificially inseminated female Sprague-Dawley rats (24/group) were administered the aqueous chemical (78.5% 1,3,5-tris(2-hydroxyethyl)hexahydro-1,3,5-triazine) by gavage at doses of 0, 250, 500, and 750 mg/kg/day in deionised water on gestation days 6 through 15.

All animals survived the duration of the study. High dose females exhibited post-dosing salivation. Rales, laboured breathing, wheezing, and tachypnea were observed occasionally in the mid and high dose groups toward the end of the dosing period. No other clinical signs were reported. Maternal body weight gain and food consumption were significantly lower in the high dose females during the dosing period than the controls. Stomach lesions, characterised by ulceration and/or scarring of the mucosa were observed in 14 of 20 high dose females. No gross abnormalities were reported in the other dosage groups (REACH).

No differences were seen between the control and treated dams with respect to pregnancy rates, number of corpora lutea, implantation sites, number of live foetuses, or early and late resorptions. There were no abortions and no premature deliveries. At these doses, developmental toxicity as measured by foetal pup weight, external, or visceral, abnormalities was not seen. There were increased incidences of vestigial 14th ribs and retarded ossification of the vertebral thoracic centra which appeared to be dose-related. The effects were not statistically significant, and the incidence of these abnormalities is highly variable in rats, they are not considered treatment-related (REACH).

The maternal no observed adverse effect level (NOAEL) is 500 mg/kg bw/day, based on decreased body weight gain, ulcerations and/or scarring of the stomach mucosa at the higher dose. The NOAEL for developmental toxicity is 750 mg/kg bw/day (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include acute toxicity effects from oral and inhalation exposure and skin sensitisation.

Public Risk Characterisation

Although domestic use is indicated, the chemical is not generally present in household products, or it is present at very low concentrations. Risk to public from exposure to the chemical is considered negligible.

Occupational Risk Characterisation

Where this chemical is handled in a pure or highly concentrated form during formulation, it could pose unreasonable risks to workers unless adequate control measures to minimise potential dermal and/or inhalation exposures to this chemical are implemented.

The chemical should be appropriately classified and labelled.

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

NICNAS Recommendation

Assessment of this chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety legislation as adopted by the relevant state or territory.

Regulatory Control

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)* Toxic by inhalation (T; R23)	Harmful if swallowed - Cat. 4 (H302) Toxic if inhaled - Cat. 3 (H331)
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)

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

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

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

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

Obligations under workplace health and safety legislation

Information in this report should be taken into account to 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.

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