1-Butanaminium, N,N,N-tributyl-, hydroxide: Human health tier II assessment

12 December 2019

CAS Number: 2052-49-5

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.

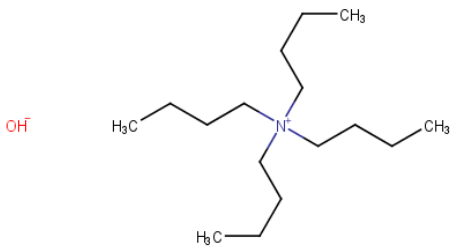
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	tetrabutylammonium hydroxide (TBAH) tetra-n-butylammonium hydroxide ammonium, tetrabutyl-, hydroxide 1-butanaminium, N,N,N-tributyl-, hydroxide (1:1)
Structural Formula	
Molecular Formula	C16H36N.HO
Molecular Weight (g/mol)	259.4
Appearance and Odour (where available)	odourless, colourless liquid
SMILES	C(CCC)N{+}(.O{-})(CCCC)(CCCC)CCCC

Import, Manufacture and Use

Australian

The National Pollutant Inventory (NPI) holds data for all sources of the chemical in Australia.

Safety data sheets (SDS) indicate that the chemical has Australian site-limited uses, including as a:

- chemical intermediate; and
- phase-transfer catalyst.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; and the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR).

The chemical has reported commercial use in oil and water based hydraulic fracturing.

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

- butylation agent; and
- phase transfer catalyst.

Restrictions

Australian

This chemical is covered by the group entry for QUATERNARY AMMONIUM COMPOUNDS in Schedules 5 and 6 of the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2019):

Schedule 6:

'QUATERNARY AMMONIUM COMPOUNDS except:

a) when separately specified in these Schedules;

b) when included in Schedule 5;

c) dialkyl or dialkoyl quaternary ammonium compounds where the alkyl or alkoyl groups are derived from tallow or hydrogenated tallow or similar chain length (C16/C18) sources; or

d) in preparations containing 5 per cent or less of such quaternary ammonium compounds.'

Schedule 5:

'QUATERNARY AMMONIUM COMPOUNDS in preparations containing 20 per cent or less of quaternary ammonium compounds except:

a) when separately specified in these Schedules;

b) dialkyl or dialkoyl quaternary ammonium compounds where the alkyl or alkoyl groups are derived from tallow or hydrogenated tallow or similar chain length (C16/C18) sources; or

c) in preparations containing 5 per cent or less of such quaternary ammonium compounds.'

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, 2019).

Schedule 5 chemicals are described as '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.' Schedule 5 chemicals are labelled with 'Caution' (SUSMP, 2019).

International

The chemical is listed on the United Arab Emirates (UAE) Restricted Chemicals List (Galleria Chemica).

Quaternary ammonium compounds are listed in the Canada Identification of Risk Assessment Priorities (IRAP) as substances recommended for further scoping/problem formulation (Galleria Chemica).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified for the chemical (Galleria Chemica):

Temporary Emergency Exposure Limit (TEELs) defined by the United States (US) Department of Energy (DOE) for the substance is reported as:

TEEL-1 = 1.2 mg/m^3;

TEEL-2 = 13 mg/m^3; and

TEEL-3 = 79 mg/m^3.

Health Hazard Information

Tetrabutylammonium hydroxide ($(C_4H_9)_4OH$), also known as TBAH, is a quaternary ammonium compound containing a tetrabutylammonium cation ($(C_4H_9)_4N^+$) and a hydroxide anion (OH^-). The chemical has a base dissociation constant (pK_b) of -0.56 in solution and is, therefore, expected to be strongly basic. Due to the its low vapour pressure (1.96E-12 mmHg, at 25 °C), the chemical is not expected to be a concern through the inhalation route in the form of inhalable dust, mist or vapour (REACHa).

Limited data are available for the chemical, thus analogue data based on structurally-related tertbutylammonium (TBA) salts are considered relevant for read-across in order to address the toxicity of the tetrabutylammonium cation (NICNASa).

The caustic nature and corrosive effects of the hydroxide ion and its key health hazards (corrosive to the skin, eyes and gastrointestinal and respiratory tracts) are identified and addressed in the NICNAS IMAP Tier II Human Health assessments of sodium hydroxide (NICNASb), tetramethylammonium hydroxide (TMAH) (NICNASc), and tetraethylammonium hydroxide (TEAH) (NICNASd).

This report should be read in conjunction with the IMAP Human health Tier II reports for tetrabutylammonium (TBA) salts and sodium hydroxide at **http://www.nicnas.gov.au**

Toxicokinetics

No data are available for the chemical. Quaternary ammonium compounds are reported to have poor dermal and oral absorption (NICNASa).

Concentrated hydroxide solutions are able to penetrate the skin and gastrointestinal tract by causing burns to the tissue (NICNASb).

Acute Toxicity

Oral

Based on the limited available data, the chemical is expected to have low to moderate acute oral toxicity, and warrants hazard classification (see **Recommendation** section).

In a non-guideline acute oral toxicity study with the chemical, a median lethal dose (LD50) of >300 to ≤2000 mg/kg bw was found. The chemical was administered orally to Wistar rats (n=3/dose) at doses of 300 and 2000 mg/kg bw. At the highest dose, test animals died and the following clinical signs were observed: mild tremors, moderate abdominal breathing, moderate salivation, and sternal recumbency. Gross pathology findings included severe red discolouration of all lung lobes and observation of the chemical (TBAH) in the stomach and intestine (REACHa).

Dermal

Based on the available analogue data on other tetraalkylammonium hydroxide salts (TMAH and TEAH), the chemical is expected to have moderate dermal toxicity, warranting hazard classification (see **Recommendations** section) (NICNASc; NICNASd).

Inhalation

No data are available.

Observation in humans

No data available on the chemical or related TBA salts in humans. Based on data available from sodium hydroxide, adverse effects through the oral or dermal routes are associated with corrosion.

In cases of oral ingestion of sodium hydroxide in humans, serious oesophageal and gastric injuries have been sustained. Observations included transmural necrosis, mucosal legions, pleuritis, emphysema, and mortality (NICNASb).

A dermal exposure to concentrated sodium hydroxide in an occupational accident resulted in fatal chemical burns (NICNASb).

Corrosion / Irritation

Corrosivity

Based on the strong alkaline nature (pK_b -0.56) of the chemical and available data from analogues and sodium hydroxide, the chemical is considered to be corrosive. Hazard classification is warranted (see **Recommendation** section).

The analogue sodium hydroxide is highly corrosive, and causes burns to the skin, eyes, and respiratory and gastrointestinal tracts. Exposure can lead to burns, necrosis and deep tissue breakdown (NICNASb).

In a skin irritation test on pigs, the dermal application of sodium hydroxide solution (at 8 %, 16 % and 24 %) produced blistering and severe necrosis throughout all epidermal layers, with necrosis extending to the subcutaneous tissue in the highest dose concentration. A simultaneous in vivo test on pig isolated skin flaps with sodium hydroxide (16 % and 24 %) showed severe necrosis of all epidermal cell layers (NICNASb). In a skin irritation test on rabbits, the application of sodium hydroxide (5 %) produced severe necrosis of the skin (NICNASb).

In an eye irritation test on rabbits, sodium hydroxide applied to the cornea produced mild (at 2 % concentration) and severe (at 8 % concentration) irritation over the test period (35 days) (NICNASb). In another eye irritation test on rabbits, sodium hydroxide applied to the lower conjunctival sac of the eye was considered non-irritating at 0.004 %, 0.04 % and 0.2 % concentration, irritating at 0.4 % concentration and corrosive at 1.2 % concentration (NICNASb).

Observations in Humans

In a human skin irritation test with 0.5 % sodium hydroxide applied dermally, 61 % of volunteers showed a positive skin irritation reaction after a one hour exposure. Another human skin irritation test, with sodium hydroxide (4 %) applied dermally, showed enhanced inflammatory response, decreased dermal reflectivity and increased trans-epidermal water loss in 9/34 volunteers (NICNASb).

Sensitisation

Skin Sensitisation

No data are available for the chemical. Based on the available analogue data on TBA salts and sodium hydroxide, the chemical is not considered to be a skin sensitiser.

Based on a skin sensitisation study conducted similarly to OECD TG 406 in Pirbright albino guinea pigs the TBA salts were not considered to be skin sensitisers (NICNASa).

The analogue sodium hydroxide is not considered to be a skin sensitiser. Based on a human skin sensitisation test where sodium hydroxide was applied dermally (0.063–1.0 %), a challenge dose of 1.25 % yielded no increased response (NICNASb).

Repeated Dose Toxicity

Oral

No data are available for the chemical. Based on the available data on TBA salts, the chemical is not expected to cause severe adverse health effects following repeated oral exposure (NICNASa).

Dermal

No data are available for the chemical.

Inhalation

No data are available for the chemical.

Genotoxicity

No data are available for the chemical. Based on the available data on TBA salts, the chemical is not expected to be genotoxic (NICNASa).

Carcinogenicity

No data available.

Reproductive and Developmental Toxicity

No data are available for the chemical. Based on the available data for TBA salts the chemical is not expected to cause specific reproductive or developmental toxicity (NICNASa).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are local effects (corrosive to the skin and eyes). The chemical can also cause harmful systemic effects following a single exposure through oral and dermal exposure.

Public Risk Characterisation

Given the uses identified for this chemical, direct public exposure is limited (See **Import, Use and Manufacture** section). The chemical is expected to be used under buffering conditions that avoid extremes of pH, and will not be present in the final product formulation, thus precluding any corrosive effects. Therefore, the risk to public health and exposure to the chemical is not considered to be unreasonable.

Although domestic or cosmetic uses have not been identified, the chemical is currently covered under Schedules 5 and 6 of the SUSMP for 'QUATERNARY AMMONIUM COMPOUNDS'. At concentrations greater than 5 %, a number of warning statements, first aid instructions and safety directions apply.

Currently, there are no restrictions in Australia on using this chemical in concentrations below 5 %, including in cosmetic or domestic products.

However, the risk to public health posed by cosmetic/domestic products containing the chemicals at low concentrations (<5 %) is not considered to pose a unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, oral, dermal and ocular exposure might 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 chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical acute and local health effects (severe skin burns and eye damage, and acute oral toxicity), 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.

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

NICNAS Recommendation

Assessment of the 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 and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2019).

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312)
Irritation / Corrosivity	Not Applicable	Causes severe skin burns and eye damage - Cat. 1 (H314)

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

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

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

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal 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 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 chemicals from entering the breathing zone of any worker;
- 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;
- 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 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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