Tetrabutylammonium salts: Human health tier II assessment

12 December 2019

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1-Butanaminium, N,N,N-tributyl-, chloride	1112-67-0
1-Butanaminium, N,N,N-tributyl-, bromide	1643-19-2
1-Butanaminium, N,N,N-tributyl-, sulfate (2:1)	2472-88-0
1-Butanaminium, N,N,N-tributyl-, phosphate (1:1)	5574-97-0

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

Grouping Rationale

The chemicals in this group are tetrabutylammonium compounds including of tetrabutylammonium halides (chloride and bromide) and other salts with anions of low toxicity (NICNAS). These chemicals share the same tetrabutylammonium cation which drives the toxicity of these chemicals. They have similar uses as phase transfer catalysts and are expected to have similar hazard profiles.

The following acronyms and their corresponding CAS numbers will be used in this assessment:

- TBAC (CAS No. 1112-67-0);
- TBAB (CAS No. 1643-19-2);
- TBAS (CAS No. 2472-88-0); and
- TBA-DHP (CAS No. 5574-97-0).

Import, Manufacture and Use

Australian

The National Pollutant Inventory (NPI) holds data for all sources of these chemicals 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; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR), the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and World Health Organisation (IPCS) document (IPCS, 1999).

The chemical, TBAB has reported cosmetic uses as a antimicrobial and antistatic agent.

These chemicals have reported commercial use in oil and water based hydraulic fracturing fluids.

These chemicals have reported site-limited uses, including:

- as phase-transfer catalysts; and
- in ion pair chromatography.

Restrictions

Australian

These chemicals are 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, TBAC is listed on Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist') (Galleria Chemica).

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

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Chemicals Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified for some of the chemicals in this group (Galleria Chemica):

Temporary Emergency Exposure Limit (TEELs) defined by the US Department of Energy (DOE) for TBAB and TBA-DHP are reported as:

TEEL-1 = 6–30 mg/m^3;

TEEL-2 = 66–330 mg/m^3; and

TEEL-3 = 390–2000 mg/m^3.

Health Hazard Information

The toxicity of the tetrabutylammonium salts in this assessment is considered to be due to the presence of the tetrabutylammonium cation. The anion components are not considered to contribute to the toxicity of the chemicals.

Limited data are available for the chemicals in this group. Therefore, unless specifically stated, toxicity study data for TBAB is used and should be read-across for all chemicals in this group to represent the toxicity of the tetrabutylammonium cation.

Toxicokinetics

No data are available for specific chemicals in this group; however, quaternary ammonium compounds are known to be poorly absorbed by the oral route. Dermal absorption is also very low. Dermal absorption can occur through damaged skin (IPCS, 1999).

Acute Toxicity

Oral

The chemicals have low to moderate acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) for TBAB was in the range of 300–2000 mg/kg bw, warranting hazard classification.

In a study based on OECD Test Guideline (TG) 423, female Wistar rats (n=9/dose) were given a single dose, 10 mL of TBAB in distilled water by gavage at concentrations of 300 or 2000 mg/kg bw and were observed for 14 days post-treatment. Mortality recorded was 0/3 at 300 mg/kg bw (group1); 0/3 at 300 mg/kg bw (group 2) and 3/3 at 2000 mg/kg bw (group 3). Observed clinical signs at 2000 mg/kg bw included mild tremors, mild to moderate abdominal breathing, moderate salivation and sternal recumbency followed by mortality. While no gross pathological changes were reported in animals treated at 300 mg/kg bw, all 3 animals at 2000 mg/kg bw were observed to have severe red discolouration of lung lobes and the chemical was observed in the stomach and intestines. An LD50 >300 to ≤ 2000 mg/kg bw was determined (REACH)

Dermal

The chemicals have moderate acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) for TBAB >2000 mg/kg bw.

In an acute dermal toxicity study (OECD TG 402) in Wistar rats (n=10/sex), 2000 mg/kg bw of TBAB in 0.2 mL of distilled water was occlusively applied to intact skin and the animals were observed for 14 days. No mortality was recorded. Observed effects in male animals included vocalisation (at 1 hour post-exposure), mild to moderate erythema, mild to moderate scaling (at 7 to 14 days post-exposure); while females showed vocalisation, moderate to severe erythema, and scab formation. No other gross pathological changes were observed. A LD50 of >2000 mg/kg bw was determined (REACH).

Inhalation

No data are available for the chemicals.

Corrosion / Irritation

Skin Irritation

The chemicals in this group are reported to slightly irritate skin in animal studies. The irritation effects were not sufficient to warrant hazard classification.

In an acute dermal irritation study (OECD TG 404), 0.5 g of TBAB (powder form) was occlusively applied to the skin of New Zealand White (NZW) rabbits (n=3) for 24 hours. Slight erythema (mean score = 2.0/4 in 3/3 treated animals) was observed at 24 hours post-exposure (REACH).

Eye Irritation

Based on the available data on TBAB, the chemicals in this group are considered to cause eye irritation and warrant hazard classification (see **Recommendation** section).

In an acute eye irritation study conducted according to OECD TG 405, female NZW rabbits (n=3) were treated with 100 mg of TBAB in 1 eye and observed for 7 days following treatment. Reversible conjunctival redness and swelling; some corneal opacity; and no iris damage was observed in all 3 animals. Mean scores for corneal opacity, iris, conjunctivae and chemosis were 1.33, 0.00, 1.89 and 1.66. All effects were fully reversed by day 7 (REACH).

In another acute eye irritation study, female NZW rabbits (n=3) were treated with 0.1 g of TBAB in 1 eye and animals were observed for 21 days post instillation. Slight ocular irritation with conjunctival hyperaemia and swelling were observed at 24 hour observation. All effects subsided after 48–72 hours post treatment (REACH).

Sensitisation

Skin Sensitisation

Although limited information is available on the skin sensitisation potential of these chemicals, based on the available information, the chemicals in this group are not likely to be skin sensitisers.

In a skin sensitisation study conducted similar to OECD TG 406, TBAB was not found to be sensitising to the skin in Pirbright albino guinea pigs (n=46/group). The chemical at 4 % concentration in water was used for topical induction on day 1, day 8 and day 15. Animals were challenged with 1 % concentration in water and observed for 48 hours. Slight to well-defined erythema and slight oedema were observed after the induction phase. No reactions indicative of sensitisation were seen after the challenge (REACH).

Repeated Dose Toxicity

Oral

Although limited data are available, the chemicals in this group are not considered to cause serious damage to health following repeated exposure by the oral route.

In a 42-day combined repeated oral dose and reproductive toxicity study conducted in accordance with OECD TG 422, Sprague-Dawley (SD) rats (n=12/sex/dose) were administered TBAB at doses of 0, 60, 180 or 600 mg/kg bw/day by gavage. One male and 1 female died in the 600 mg/kg bw/day group. Clinical signs observed in the deceased male before death included fractures of incisors, soft stool, and decreased amount of faeces, while the deceased female had staining of lower abdominal fur and a staggering gait. All surviving animals at 600 mg/kg bw/day were reported to have red to light brownish urine; males showed suppressed body weights; high aspartate aminotransferase (AST); low blood urea nitrogen (BUN); decrease in absolute weights of thymus, heart, kidneys and epididymis. Females at 600 mg/kg bw/day showed increased body weight and food consumption; slight increase in red blood cell count; slight decrease in platelets; decreased fibrinogen and lymphocyte levels; increased levels of monocytes; high levels of AST; low BUN; high levels of calcium; decrease in brain and thymus absolute weights; increase in absolute weights of thyroid, heart, liver, spleen and kidney; and cell debris in rectal crypt. Changes in liver morphology; diffuse hyperplasia in the caecum mucosa and changes in the intestinal tracts were reported in treated animals at doses of 180 mg/kg bw/day and above. A no observed adverse effect level (NOAEL) of 180 mg/kg/bw/day and a lowest observed adverse effect level (LOAEL) of 600 mg/kg bw/day were proposed (REACH).

In a 28-day study conducted according to OECD TG 407, TBAB was orally administered to SD rats (n=6/sex/dose) at 0, 250, 500 or 1000 mg/kg bw/day. No mortality was recorded. Males in the 250 mg/kg bw/day were found to have increased relative weight of adrenals. Females at 250 mg/kg bw/day and above showed increased relative liver and uterus weight. Increased relative weight of lungs was seen in females at 500 mg/kg bw/day. Pathological and histological examination showed no treatment-related adverse effects. A NOAEL of 1000 mg/kg bw/day was proposed (REACH).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available in vitro genotoxicity study, the chemicals are not considered to be genotoxic.

In a bacterial reverse mutation assay (OECD TG 471), TBAB tested in *Salmonella typhimurium* (*S. typhimurium* strains TA98, TA100, TA1535 and TA1537) and *Escherichia coli* WP2 uvrA at concentrations up to 5000 µg/plate, with and without metabolic activation, gave negative results (REACH).

Negative results were observed with TBAB in a mammalian cell gene mutation test (OECD TG 476) in Chinese hamster ovary (CHO) cells at concentrations up to 5 µM, with metabolic activation (REACH).

Negative results were observed in an in vitro mammalian chromosome aberration test (OECD TG 471) with TBAB at concentrations up to 2280 µg/mL, with and without metabolic activation (REACH).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

Based on the limited data available, the chemicals in this group do not cause specific reproductive or developmental toxicity (see **Repeat Dose Toxicity: Oral** section).

In a 42-day combined repeated dose and reproductive toxicity oral gavage study conducted in accordance with OECD TG 422, SD rats (n=12/sex/dose) were administered TBAB at doses of 0, 60, 180 or 600 mg/kg bw/day. Higher stillbirth index values were observed at 600 mg/kg bw/day. The NOAEL for maternal and developmental toxicity was proposed at 180 mg/kg bw/day (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include acute toxicity from oral exposure and eye irritation.

Public Risk Characterisation

Although use in cosmetic or domestic products in Australia is not reported, TBAB is reported to be used in cosmetic products overseas (see Import, manufacture and use section).

Considering the range of cosmetic and personal care products that may contain these chemicals, the main route of public exposure is expected to be through the skin and potential oral exposure.

The chemicals are currently listed on Schedule 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.

TBAC is listed on Health Canada -Cosmetic Ingredient 'Hotlitst' and restricted from use in cosmetic products (see **International Restrictions** section).

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

Currently, there are no restrictions in Australia on using these chemicals in concentrations below 5 %, including in cosmetics or domestic products. However, cosmetic/domestic products containing the chemicals at low concentrations (<5 %) are not considered to pose an unreasonable risk to public health.

Provided that normal precautions are taken to avoid prolonged skin contact and with available controls for quaternary ammonium compounds, cosmetic/domestic products containing the chemicals are not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

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

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

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

NICNAS Recommendation

Assessment of these chemical are 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

All chemicals in this assessment are 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)
Irritation / Corrosivity	Not Applicable	Causes eye irritation - Cat. 2B (H320)

[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 and ocular exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are 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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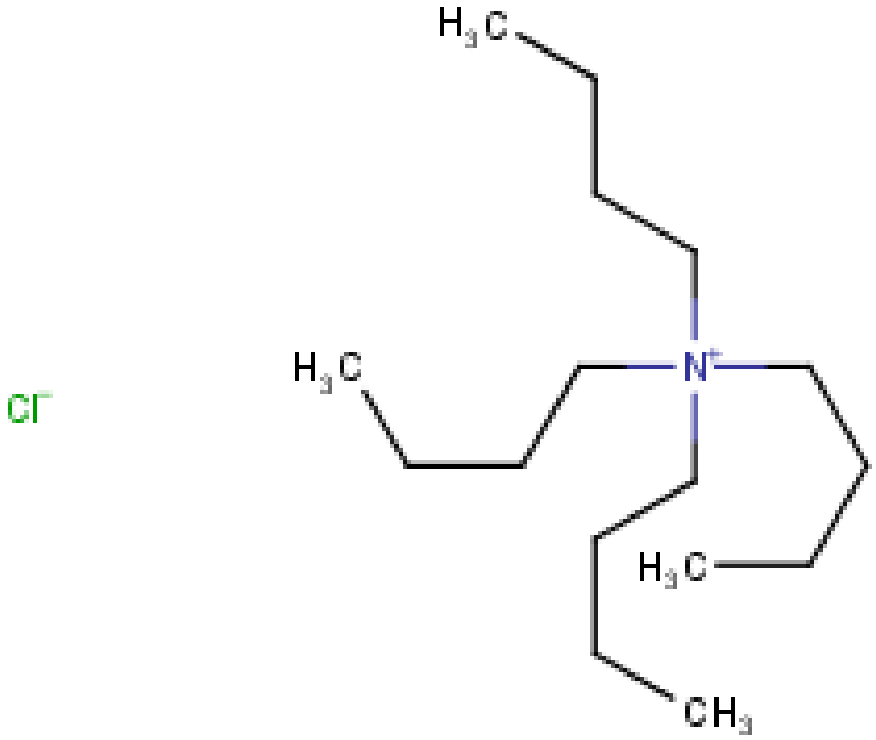
The United States (US) Environmental Protection Agency's (EPA) Aggregated Computational Toxicology Resource (ACToR). Accessed June 2019 at **https://actor.epa.gov/actor/home.xhtml**

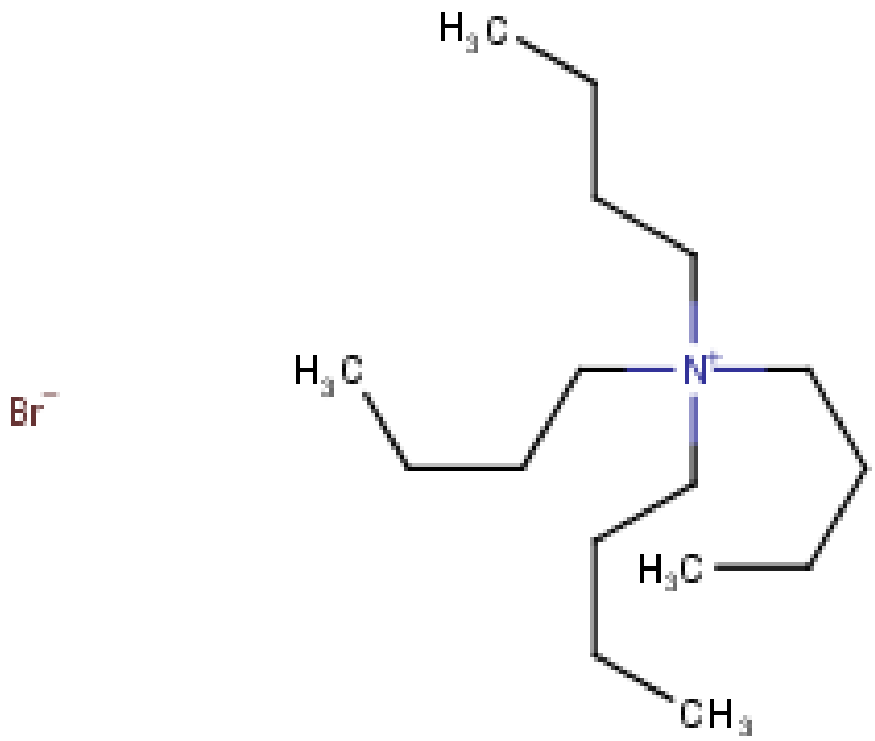
Last Update 12 December 2019

Chemical Identities

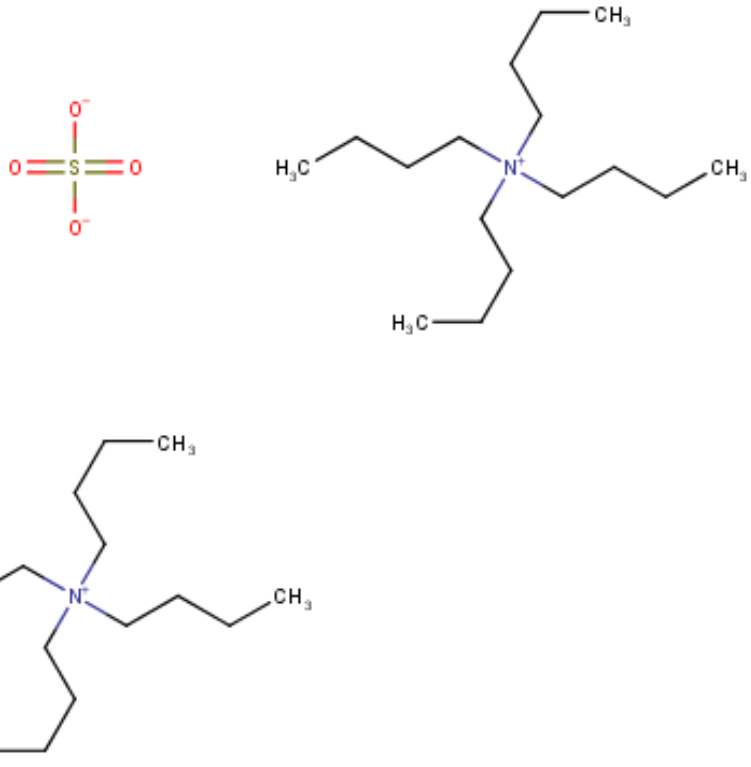
Chemical Name in the	**1-Butanaminium, N,N,N-tributyl-, chloride**

Inventory and Synonyms	tetrabutyl ammonium chloride (TBAC)
CAS Number	1112-67-0
Structural Formula	
Molecular Formula	C16H36N.Cl
Molecular Weight	277.9

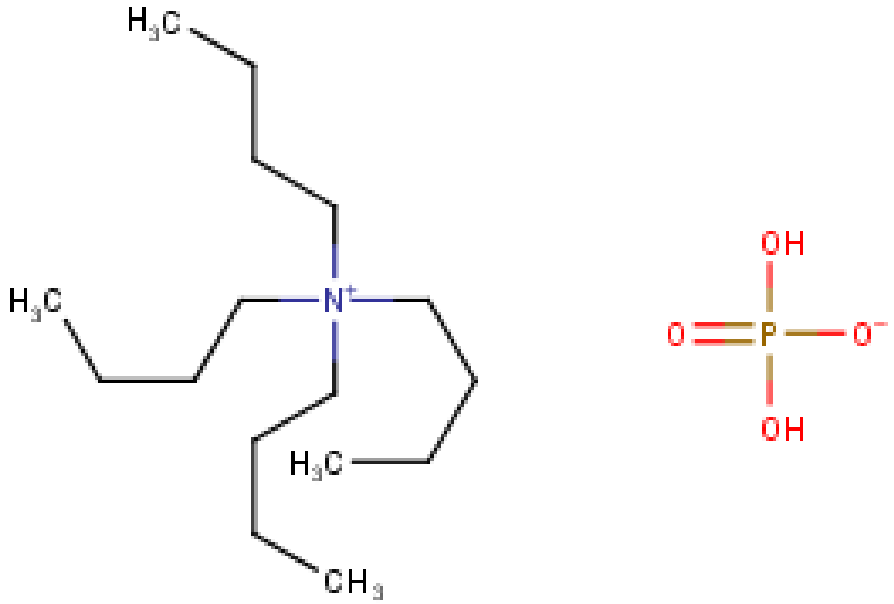
Chemical Name in the Inventory and Synonyms	**1-Butanaminium, N,N,N-tributyl-, bromide** tetrabutylammonium bromide (TBAB)
CAS Number	1643-19-2
Structural Formula	

	
Molecular Formula	C16H36N.Br
Molecular Weight	322.3

Chemical Name in the Inventory and Synonyms	**1-Butanaminium, N,N,N-tributyl-, sulfate (2:1)** bis(tetrabutylammonium) sulphate (TBA-BS)
CAS Number	2472-88-0
Structural Formula	

	
Molecular Formula	C16H36N.1/2O4S
Molecular Weight	580.9

Chemical Name in the Inventory and Synonyms	**1-Butanaminium, N,N,N-tributyl-, phosphate (1:1)** tetrabutylammonium dihydrogen phosphate (TBA-DHP)
CAS Number	5574-97-0
Structural Formula	

	
Molecular Formula	C16H36N.H2O4P
Molecular Weight	339.4

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