Butanoic acid: Human health tier II assessment

22 March 2013

CAS Number: 107-92-6

Preface

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

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

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

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

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

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

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

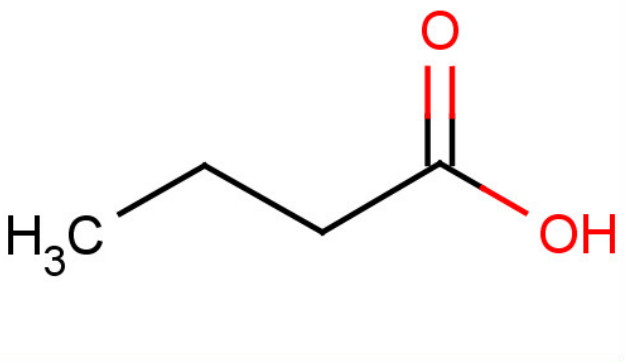
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Butyric acid Ethylacetic acid 1-Propanecarboxylic acid Butanic acid
Structural Formula	
Molecular Formula	C4H8O2
Molecular Weight (g/mol)	88.11
Appearance and Odour (where available)	Colourless clear liquid with a foul suffocating odour
SMILES	C(=O)(O)CCC

Import, Manufacture and Use

Australian

The following Australian industrial use was reported under previous mandatory and/or voluntary calls for information (NICNAS Calls For Information 1991-2008).

The chemical has reported commercial use including:

- in the flavours manufacturing sector.

International

The following international uses have been identified via 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, the European Commission Cosmetic Ingredients and Substances (CosIng) database, United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use:

- as a masking agent in cosmetic products; and
- as a fragrance ingredient.

The chemical has reported domestic use including:

- in varnishes and detergents.

The chemical has reported commercial uses including:

- as a leather tanning agent; and
- in the manufacture of varnishes and detergents.

The chemical has reported site-limited uses including:

- in the manufacture of cellulose acetate butyrate (CAB);
- as an intermediate for pharmaceuticals, emulsifiers, and disinfectants;
- as a sweetening agent in gasolines;
- to make butyroperoxides;
- in the manufacture of esters; and
- in the synthesis of butyrate ester perfumes.

The chemical is also reported to be used as a food additive and to preserve grains from fungal deterioration.

Butyric acid is listed by the US Food and Drug Administration (FDA) as a synthetic flavoring substance that is generally recognised as safe (GRAS) for its intended use (21 CFR 182.60) (US Occupational Safety & Health Administration (OSHA)).

Restrictions

Australian

Butyric acid used in insect lures is listed in Schedule 6 of the Poisons Standard (the Australian Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)). Schedule 6 chemicals are labelled with 'POISON'. These are substances with

a moderate potential for causing harm, the extent of which can be reduced through using distinctive packaging with strong warnings and safety directions on the label.

International

No known restrictions have been identified.

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):

C; R34 (Corrosive).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following are identified (Galleria Chemica):

US DOE Temporary Emergency Exposure Limits (TEELs) = 15 ppm (TEEL-0), 40 ppm (TEEL-1) and 250 ppm (TEEL-2 and TEEL-3);

Bulgaria Occupational Exposure Limits (15 min OEL); and

Latvia Occupational Exposure Limit Values (8 hour OELV) and Russia Maximum Allowed Concentrations (PDK) = 10 mg/m³.

Health Hazard Information

Toxicokinetics

The chemical has been reported to be rapidly metabolised when administered via intravenous route in rats.

Following intravenous administration of n-butyric acid (up to 0.28 mmol/kg doses in rat), target blood collection times were 0, 0.5, 1.5, 3, 6, 8, 10, and 15 minutes post dosing. Analysis of these blood samples showed n-butyric acid peak levels (1.0 µmol/g blood) at 0.5 minutes (the earliest time point tested). n-Butyric acid levels were at or near background levels by 10 minutes. The half time for n-butyric acid was less than one minute. This study demonstrates rapid metabolism of n-butyric acid (OECD, 2003).

Because increased blood levels of n-butryic acid have been demonstrated following administration of the metabolic precursors of butyric acid (n-butyl actetate and n-butanol), hazard identification studies using either n-butyl acetate or n-butanol exposures have been accepted to identify the hazards associated with systemic exposure to n-butyric acid (OECD, 2003).

Acute Toxicity

Oral

The chemical has low acute toxicity via the oral route.

Rat oral LD50 = 8,790 mg/kg bw in female rats and 2,940 mg/kg bw in male rats. No toxic effects were reported (OECD, 2003).

Rat oral LD50 = 2,000 mg/kg bw (ChemIDPlus).

Dermal

The chemical has low acute toxicity via the dermal route.

Rabbit dermal LD50 = 6,350 mL/kg bw (6,077 mg/kg bw) (OECD, 2003).

Inhalation

The chemical has low acute toxicity via the inhalation route.

Rat inhalation LD50 is >2,200 ppm. There were no deaths among rats exposed to saturated vapour. Based on the vapour pressure, the maximum concentration achievable at ambient temperatures is approximately 2,200 ppm (OECD, 2003).

Rat and mouse inhalation LC50 values are reported as >500 mg/m³ with structural or functional change in trachea or bronchi (ChemIDPlus).

Corrosion / Irritation

Corrosivity

The chemical is currently classified as hazardous with the risk phrase 'Causes burns' (C; R34) (Safe Work Australia). The data available support this classification.

Corrosive effects were reported after topical exposure in rats and mice (skin and appendages) (TNPKV, 1961).

The chemical is also reported as a moderately strong irritant in both modified Draize and skin patch tests in rabbits (OECD, 2003).

Sensitisation

Skin Sensitisation

No data are available. There are no structural indications of sensitisation potential.

Repeated Dose Toxicity

Oral

No repeat dose oral toxicity studies are available for the chemical. Based on the information available for n-butanol and butyrin (glyceryl tributyrate), butyric acid is not expected to have high repeat dose oral toxicity.

Lesions in the forestomach such as acanthosis, oedema of the lamina propria (a type of connective tissue) and increased numbers of mitotic figures (chromosome aggregation during mitosis) were reported after oral administration of butyric acid (4%) in the diet for rats, mice and hamsters for seven days. For rats, acanthosis, epithelial vacuolation (a fluid cavity in a skin cell) and ulceration (with associated marked epithelial hyperplasia (increased cell production)) were the main observed lesions. Rats reported to be the most sensitive of the three tested species. The formation of lesions in the gastro-intestinal tract caused by the oral application of butyric acid was expected due to the acidic nature (corrosivity) of the chemical (ECHA, Galleria Chemica).

Considering the rapid and complete metabolism of n-butanol to butyric acid, via butyraldehyde, the studies available on n-butanol were considered appropriate to use as analogue data for butyric acid for this hazard indicator (hazard directly related to the systemic blood levels in the absence of gastric corrosive effects).

In a 90 day gavage study, rats were exposed to n-butanol at 0, 30, 125 or 500 mg/kg bw/day. There were no dose-related differences observed between treatment or control rats on body or organ weight changes, food consumption or mortality. In addition, there were no dose-related differences observed in gross or histopathological examination of the eye. Ataxia and hypo activity were observed in both sexes of the high dose group (500/mg/kg bw/day) during the final six weeks of the dosing period. No treatment related signs were observed at 30 or 125 mg/kg bw/day groups (OECD, 2003).

Butyrin (or tributyrin), prepared by esterification of glycerin with excess butyric acid and metabolised by hydrolysis to butyric acid, as for other triglycerides, is on the US Food and Drug Administration's CFR Part 184 list of direct food substances affirmed as generally recognised as safe (US Food & Drug Administration).

Dermal

No data are available.

Inhalation

No data are available for the chemical. Based on the data available on n-butyl acetate, butyric acid is not expected to have high repeat dose inhalation toxicity.

No information was found regarding the health effects of chronic low-level inhalational exposure to butyric acid (US OSHA).

Considering the rapid and complete metabolism of n-butyl acetate to butyric acid, via n-butanol and butyraldehyde, studies on n-butyl acetate were considered appropriate to use as worst case analogue data for butyric acid. In a 90 day inhalation study, rats were exposed to 0, 500, 1500 or 3000 ppm doses of n-butyl acetate (corresponding to 0, 2376, 7128 or 14256 mg/m^3, respectively). Rats exposed to 1500 and 3000 ppm showed minimal transient narcosis and sedation. Repeated exposures did not exacerbate these transient effects. Reduced body weight gain and decreased feed consumption were reported at the same dose levels. There was no evidence of neurotoxicity based on functional observational battery (FOB), quantitative motor activity, neuropathy and scheduled-controlled operant behavior endpoints. Based on decreased body weight gain, the NOAEL for systemic effects is reported as 500 ppm and a NOAEL for post-exposure neurotoxicity is reported as 3000 ppm (highest dose tested) (OECD, 2003).

Genotoxicity

Based on the negative in vitro data available for the chemical and negative in vivo data available for n-butanol (analogue chemical), the chemical is not expected to be genotoxic.

In several bacterial in vitro tests (Ames) with Salmonella typhimurium test strains (TA 92, TA 94, TA 97, TA 98, TA 100, TA 102 TA 1535, TA 1537), n-butyric acid was not mutagenic with and without metabolic activation (10 mg/plate). Negative results were reported in an in vitro chromosome abberation test with cultured Chinese hamster lung fibroblast cells without metabolic activation, up to 1 mg/mL concentrations (OECD, 2003).

An in vivo mouse micronucleus test conducted with n-butanol administered once orally to male and female NMRI mice at doses up to 2000 mg/kg bw did not show any chromosome-damaging (clastogenic) effect. In addition, there were no indications of any impairment of chromosome distribution in the course of mitosis (spindle poison effect) (OECD, 2003).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

No data are available for the chemical. Although the data available on analogue chemicals (n-butanol and n-butyl acetate) reported some developmental effects in rats and rabbits at very high doses (~7000 mg/m³), the chemical is not expected to be a reproductive/developmental toxin.

Considering the rapid and complete metabolism of n-butanol and n-butyl acetate to butyric acid, the studies available on n-butanol and n-butyl acetate were considered appropriate to use as analogue data for butyric acid.

In a 20 day inhalation study, a groups of 18 male Sprague-Dawley rats were exposed to 0, 3000, or 6000 ppm (0, 9096, 18192 mg/m³) n-butyl alcohol (n-butanol) for 7 hours/day for 6 weeks. The males were then mated to non-exposed female rats of the same strain. In a separate experiment, groups of 15 pregnant female rats were exposed to 0, 3000, or 6000 ppm n-butyl alcohol for 7 hours/day from gestation day 1-20. These females were then allowed to deliver. No detectable effect on pregnancy was found after either maternal or paternal exposure (OECD, 2003).

In a 90 day inhalation study rats received 0, 500, 1500 or 3000 ppm doses of n-butyl acetate (corresponding to 0, 2376, 7128 or 14256 mg/m³ respectively). There were no mortalities. There was no effect on either epididymidal or testicular sperm counts and testes histopathology was normal in the treated animals. Given the intensive investigations of testicular and epididymal structure and function in this study, the higher testicular weights in the 1500 and 3000 ppm groups were not considered indicative of testicular toxicity and instead represent a 'tissue-sparing' effect due to the reduced body weight gains in these groups. Therefore, 3000 ppm was reported as the NOAEL for reproductive toxicity (OECD, 2003).

Groups of approximately 15 pregnant Sprague-Dawley rats were exposed via inhalation to 0, 3500, 6000 or 8000 ppm (0, 10612, 18192, or 24256 mg/m³) of n-butanol vapor for 7 hours/day from gestation day 1-19. The 8000 ppm level produced narcosis in approximately one-half of the dams. No behavioural effects were noted at 6000 ppm. Two of the eighteen dams at 8000 ppm died during the exposure period. Feed consumption was decreased in the 6000 and 8000 ppm dams, but the 3500 ppm dams were similar to controls. No effect was observed on mean corpora lutea/litter, mean resorptions/litter, mean number of live foetuses/litter or sex ratio. Foetal weights were slightly decreased at 6000 and 8000 ppm groups, but the 3500 ppm group was unaffected. External foetal malformations were not observed. There were no differences in malformation rates (skeletal or visceral) or in rates of commonly observed variations. However, there was a slight increase in the percent of foetuses with any skeletal variation or malformation in the 8000 ppm group, but not in the lower two exposure groups. The study reported that high concentrations (8000 ppm) produced developmental toxicity, but it is not a strong developmental toxin. The NOEL for maternal animals and offspring was 3500 ppm (OECD, 2003).

Studies with Sprague-Dawley rats and New Zealand White rabbits have reported some foetal skeletal variations when exposed to air concentrations of n-butyl acetate at 1500 ppm (~7128 mg/m³) for 7 hr/day during the gestation period (OECD, 2003).

Risk Characterisation

Critical Health Effects

The main critical effect from exposure to the chemical is corrosivity, which may cause skin, eye and respiratory irritation at high concentrations.

Information on carcinogenicity is not available. The chemical is found naturally in vegetable oils and in animal fluids, such as sweat, tissue fluids and milk fat. It is an important metabolite of carbohydrates, fats and proteins and is formed naturally in the

human digestive system (OECD, 2003). Therefore, this chemical is not expected to be a carcinogen.

Public Risk Characterisation

The chemical is used as a masking agent and a fragrance ingredient in cosmetic products. It is also used in domestic products in varnishes and detergents. The concentrations of the chemical in these cosmetics, fragrances and domestic products are not known. The general public may be exposed to the chemical through dermal, oral and/or inhalation routes when using the products containing the chemical.

In Australia, the chemical 'in preparations for use as insect lures' is listed in the SUSMP under Schedule 6.

Currently there are no restrictions in Australia for using this chemical in cosmetics or domestic products. The chemical (with a foul suffocating odour) is not expected to be used at concentrations that may cause corrosive/irritation effects in cosmetics and domestic products. Therefore, further risk management is not required through scheduling.

Occupational Risk Characterisation

Given the corrosive effects of the chemical, the risk to workers is considered high if adequate control measures to minimise occupational exposure to the chemical are not implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU), or an employee at a workplace, has adequate information to determine appropriate controls.

NICNAS Recommendation

The chemical is sufficiently assessed and risk managed provided the recommendation for classification and labelling is followed.

Regulatory Control

Public Health

Considering the available information, no regulatory controls are recommended.

Work Health and Safety

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Causes burns (C; R34)*	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 consumers

Cosmetic and domestic products containing the chemical should be used according to the label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular or inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls: substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storage, handling and use of a hazardous chemical are dependent 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 isolation of operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- use of 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 be relied upon on its own to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selection of personal protective equipment can be obtained from Australia, 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 hazardous 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 physical hazards of the chemical has not been undertaken as part of this assessment.

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Last update 22 March 2013

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