1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-coco acyl derivatives, hydroxides, inner salts: Human health tier II assessment

25 November 2016

CAS Number: 61789-40-0

Preface

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

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

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

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

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

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

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

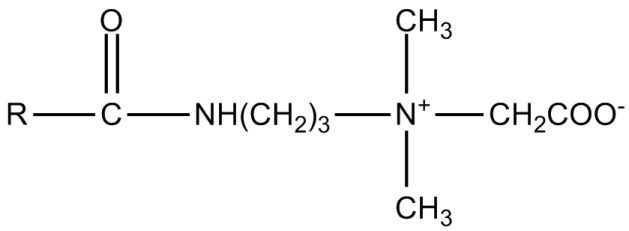
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Cocamidopropyl betaine Cocoamidopropylbetaine Coconut oil, amidopropyl betaine N-(3-Cocoamidopropyl)-N,N-dimethyl-N-carboxymethyl betaine N-(Cocoamidopropyl)-N,N-dimethyl-N-carboxymethyl ammonium, betaine
Structural Formula	
Molecular Formula	Unspecified
Molecular Weight (g/mol)	342-398
Appearance and Odour (where available)	Clear pale yellow liquid with slight fatty odour
SMILES	C(=O)(CCCCCCCCCCC)NCCCN(C)(C)CC(=O)O

Import, Manufacture and Use

Australian

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

The cocamidopropyl betaine has reported cosmetic use in:

- shampoo;
- shower gel; and
- bubble bath formulations.

The chemical has reported domestic use in surface-active agents.

International

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

The chemical has reported cosmetic use in:

- shampoos;
- bath foams; and
- shower gels.

The chemical has reported domestic use in:

- cleaning/washing agents;
- colouring agents;
- fillers;
- flame retardants and extinguishing agents;
- odour agents;
- paints, lacquers and varnishes; and
- surface treatment.

The chemical has reported commercial use in:

- foaming agents;
- lubricants and additives; and
- viscosity adjusters.

The chemical has reported site-limited use including in stabilisers.

The chemical has reported non-industrial use including in:

- non-agricultural pesticides and preservatives; and
- pharmaceuticals.

Restrictions

Australian

Cocamidopropyl betaine is a quaternary ammonium compound. Quaternary ammonium compounds are listed in the *Poisons Standard* (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP, 2014)) in Schedules 5 and 6. However, cocamidopropyl betaine is a zwitterionic compound, and therefore does not have the severe irritant properties of cationic surfactants (NICNAS, 2014), the main group covered by this entry.

International

Cocamidopropyl betaine is on the United Kingdom (UK) and Oslo and Paris Convention (OSPAR) of lists of candidates for substitution (Galleria Chemica).

Cocamidopropyl betaine is on the Canadian Environmental Protection Act (CEPA) Environmental Registry substance Lists - lists of Substances on the Domestic Substances List (DSL) that are inherently toxic and persistent (Galleria Chemica).

Cocamidopropyl betaine is not listed on any of the Annexes of the European Union (EU) Cosmetics Regulation.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia, 2014).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are identified.

Health Hazard Information

Toxicokinetics

No specific information is available on the toxicokinetics, metabolism or distribution of cocamidopropyl betaine. Generally, amphoteric surfactants are easily absorbed by the oral route and are excreted partly unchanged via the faeces. Metabolisation to short-chained fatty acids; and carbon dioxide also occurs.

Acute Toxicity

Oral

Acute oral toxicity of cocamidopropyl betaine (30–35.5% aqueous solution) was low in rats, with the median lethal dose (LD50) >5000 mg/kg bw (>1500 mg active substance/kg bw). Observed sub-lethal effects included lethargy, changes in motor activity, salivation, collapse and coma (OECD, 2006).

Dermal

The chemical had low acute dermal toxicity in rats. The dermal LD50 for the 30–35.5% aqueous suspension was >2000 mg/kg bw (>600 mg/kg bw for the active substance) (OECD, 2006).

Inhalation

No studies were available for respiratory exposure.

Corrosion / Irritation

Respiratory Irritation

No data are available.

Skin Irritation

In a skin irritation study conducted in accordance with OECD guidelines, cocamidopropyl betaine (about 80 % active ingredient, spray-dried) was applied semi-occlusively to rabbit skin for four hours as a moistened paste. The test substance showed no signs of erythema or oedema in any rabbit at any observation time (OECD, 2006). In two further studies following OECD TG 404, 30 % active cocamidopropyl betaine showed minimal irritation after four hours of semi-occlusive exposure (HERA, 2005).

Eye Irritation

In several eye irritation studies in rabbits, conducted according to OECD TG 405, the chemical was found to be moderately to highly irritating. Aqueous 30 % solutions of cocaimidopropyl betaine and the spray-dried cocamidopropyl betaine powder induced irreversible corneal and/or iris damage in rabbits; 14–15 % solutions of the chemical were highly irritating (HERA, 2005); the results for the ≤10 % active compound varied between mildly and moderately eye irritating, with symptoms that were reversible after 14 days (Stepan Chemicals Corporation 1982; OECD, 2006).

Observation in humans

Cocamidopropyl betaine at a concentration of 0.52 % in a formulation applied to the skin of up to 12 individuals via occlusive patches for five days indicated that the formulation was non-irritating (Elder, 1991).

Cumulative skin irritation studies in humans are available. Occlusive patches of a soap formulation containing 1.9 % cocamidopropyl betaine were applied 23 hours per day to the skin of 10 individuals for 21 consecutive days. Irritation scores showed that the test formulation was a primary irritant, with the median irritation time of two days (Hill Top Research, 1980). The chemical was a skin irritant in humans under leave-on conditions at a 1.9 % concentration from cumulative irritation tests.

Sensitisation

Respiratory Sensitisation

No data are available.

Skin Sensitisation

The chemical is not considered to be a skin sensitiser in animals.

Four adjuvant tests (two maximisation tests according to Magnusson and Kligman, one Draize and one modified Draize test) are available for cocamidopropyl betaine. Three of the studies gave no indication of the chemical's sensitising potential. The fourth study, a guinea pig maximisation test (GPMT) (Magnusson & Kligman; Induction: 0.1 % intracutaneous injection, 10 % patch; Challenge: 10 % patch), gave ambiguous results. These studies were not conducted in full compliance with the current OECD TG and no information on the purity of the test materials was available.

A local lymph node assay (LLNA) with cocamidopropyl betaine was positive for sensitisation (Basketter et al., 1999), but no other details were provided.

Observation in humans

No data are available.

Repeated Dose Toxicity

Oral

Cocamidopropyl betaine is not considered to cause serious damage to health from repeated exposure to below acutely toxic doses. In a 28-day oral study, conducted in accordance with OECD TG 407, Sprague Dawley (SD) rats were given a formulation containing 30 % cocamidopropyl betaine by gavage at 0, 250, 500, or 1000 mg/kg bw/day. At the highest dose, clinical signs of irritation of the gastrointestinal tract such as salivation, and effects on the forestomach such as acanthosis of mucosa, oedema of submucosa, multiple ulcerations and hyperplasia were reported. The effects were worse in females than males, and were completely reversible in the recovery group. There were no effects observed in the low and mid-dose groups (US EPA, 2010). The no observed adverse effect level (NOAEL) for local effects was 500 mg/kg bw/day (150 mg/kg bw/day cocamidopropyl betaine) based on histopathological changes in the forestomach at the lowest observed adverse effect level (LOAEL) of 1000 mg/kg bw/day (300 mg/kg bw/day cocamidopropyl betaine).

In a 90-day study conducted in accordance with OECD TG 408, SD rats were administered a 30 % aqueous solution of cocamidopropyl betaine by gavage at 0, 250, 500, or 1000 mg/kg bw/day. Stomach ulceration at the fundus and cardiac regions was seen at the highest dose. Forestomach gastritis with squamous hyperplasia, submucosal oedema, and inflammatory cell infiltration was observed at the mid and high doses. There were no other treatment-related effects (US EPA, 2010). The NOAEL for local effects was 250 mg/kg bw/day (75 mg/kg bw/day cocamidopropyl betaine) based on forestomach effects at the LOAEL of 500 mg/kg bw/day (150 mg/kg bw/day cocamidopropyl betaine). A NOAEL for systemic effects was established at the highest dose in this study.

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

No data are available.

Genotoxicity

There is no evidence for genotoxic potential of the alkylamidopropyl betaines category.

In Ames tests performed in accordance with OECD TG 471 with 29–31 % aqueous solutions of cocamidopropyl betaine in *Salmonella typhimurium* strains TA 98, 100, 1535, 1537 and 1538 with and without metabolic activation, no evidence of mutagenicity was reported. All positive controls gave the expected results (OECD, 2006). In vitro tests in mammalian cells (mouse lymphoma test) showed no genotoxicity for the 30 % aqueous solution of cocamidopropyl betaine. A mouse micronucleus test with 27 % active cocamidopropyl betaine showed no evidence of clastogenicity in vivo at non-toxic dose-levels of 200 mg/kg bw/day (highest tested dose; corresponding to 54 mg active substance/kg bw) (Goldschmidt France, 1987).

Based on the available data, cocamidopropyl betaine is not considered to be genotoxic.

Carcinogenicity

No valid carcinogenicity data for the chemical are available.

An aqueous solution of a non-oxidative hair dye formulation containing 0.09 % cocamidopropyl betaine was examined for carcinogenicity. The formulation was applied to Swiss Webster mouse skin thrice weekly for 20 months. There were no adverse effects on body weight gains, survival, haematological or urinalysis values, and the incidence of neoplasms in dosed animals was not different from that in the control group (Jacobs et al, 1984).

Cocamidopropyl betaine is not considered to be carcinogenic based on lack of genotoxicity.

Reproductive and Developmental Toxicity

No data are available on the effects of the chemical on the reproductive system. In the 90-day repeated oral toxicity study (US EPA, 2010), no effects were reported on the male and female reproductive organs of SD rats treated with 30 % cocamidopropyl betaine. The chemical is not expected to cause effects on fertility.

In a prenatal developmental toxicity study following OECD TG 414, female pregnant CD rats (25/group) were administered 0, 95, 286, or 950 mg/kg bw/day of cocamidopropyl betaine by gavage on gestation days 5–19. Maternal effects observed at 286 and 950 mg/kg bw/day included decreased bodyweight gain and stomach changes (thickened mucosa, discoloration, and ulcers). The decreased bodyweight is considered an effect caused by the local irritation in the stomach. Clinical signs such as abdominal position, piloerection, and reduced motility were also seen in the dams at the highest dose. Developmental effects, observed at the highest dose only, were embryotoxicity consisting of an increased number of resorptions, a decreased number of viable foetuses, and decreased foetal bodyweight (US EPA, 2010). The NOAEL for maternal toxicity was 95 mg/kg bw/day based on local effects at the LOAEL of 286 mg/kg bw/day. The NOAEL for developmental toxicity was >950 mg/kg bw/day as the post-implantation loss and decreased mean foetal bodyweight were considered to be secondary to maternal toxicity.

The chemical is not considered to cause developmental effects.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include no or slight skin irritation and moderate to severe eye irritation.

Public Risk Characterisation

The public may be exposed to cocamidopropyl betaine through cosmetic and domestic use. Provided that normal precautions are taken to avoid eye contact, use of cosmetic and domestic products containing cocamidopropyl betaine is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure may occur, particularly where manual or open processes are used. These may 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 health effects, the chemical could pose an unreasonable risk to workers, unless adequate control measures to minimise dermal and ocular exposure to the chemicals are implemented, particularly at high concentrations. 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 appropriate controls. The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation** section) for these chemicals.

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 chemical should be labelled in accordance with state and territory legislation. The report will be provided to the Delegate for Poisons Scheduling for consideration as to whether the chemical should be excluded from the entry for quarternary ammonium compounds based on its low skin irritation effects.

Work Health and Safety

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Irritating to eyes (Xi; R36)	Causes serious eye irritation - Cat. 2A (H319)

[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 instruction on the label.

Advice for industry

Control measures

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

Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

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

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

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals— Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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