File No: STD/1433

December 2013

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

L-Arginine hydrogen carbonate (INCI name: Arginine Bicarbonate)

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of the Environment.

For the purposes of subsection 78(1) of the Act, this Public Report may be inspected at our NICNAS office by appointment only at Level 7, 260 Elizabeth Street, Surry Hills NSW 2010.

This Public Report is also available for viewing and downloading from the NICNAS website or available on request, free of charge, by contacting NICNAS. For requests and enquiries please contact the NICNAS Administration Coordinator at:

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Director
NICNAS

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SUMMARY

The following details will be published in the NICNAS *Chemical Gazette:*

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1433	Colgate-Palmolive Pty Ltd	L-Arginine hydrogen carbonate (INCI name: Arginine Bicarbonate)	ND*	≤ 20 tonnes per annum	Component of toothpaste products

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

Human health risk assessment
Under the conditions of the occupational settings described, the notified chemical is not considered to pose an unreasonable risk to the health of workers.

When used at ≤ 11% concentration in toothpaste products the notified chemical is not considered to pose an unreasonable risk to public health.

Environmental risk assessment
On the basis of the PEC/PNEC ratio and the assessed use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES
Occupational Health and Safety

- No specific engineering controls, work practices or personal protective equipment are required for the safe use of the notified chemical itself. However, these should be selected on the basis of all ingredients in the formulation.

  Guidance in selection of personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

- A copy of the (M)SDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation should be in operation.

Disposal

- The notified chemical should be disposed of to landfill.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by physical containment, collection and subsequent safe disposal.

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(1) of the Act; if
- the notified chemical is introduced in a form other than toothpaste products at ≤ 11%;
- the concentration of the notified chemical exceeds or is intended to exceed 11% in toothpaste products;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a component of toothpaste products, or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

The Director will then decide whether a reassessment (i.e. a secondary notification and assessment) is required.

(Material) Safety Data Sheet
The (M)SDS of the product containing the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the (M)SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Colgate-Palmolive Pty Ltd (ABN 79 002 792 163)
Level 14, 345 George St
Sydney NSW 2000

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: analytical data, degree of purity, impurities, additives/adjuvants and import volume

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: all physico-chemical and ecotoxicological endpoints, acute dermal toxicity, skin sensitisation, repeated dose toxicity and genotoxicity

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
EU

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Arginine bicarbonate

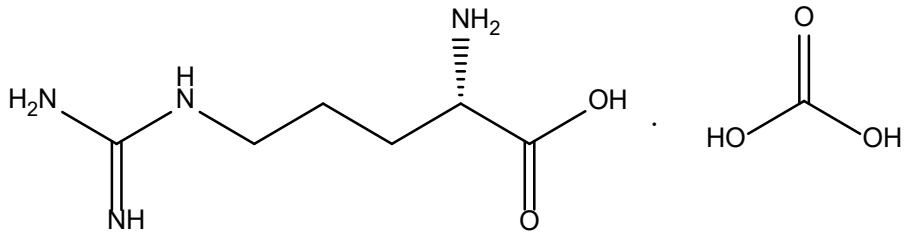
CHEMICAL NAME
L-Arginine hydrogen carbonate

OTHER NAME(S)
Arginine Bicarbonate (INCI name)

CAS NUMBER
Not assigned

MOLECULAR FORMULA
$C_6H_{14}N_4O_2.CH_2O_3$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
236 Da

ANALYTICAL DATA
Reference IR spectrum was provided.

3. COMPOSITION

DEGREE OF PURITY > 90%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: clear solution (the notified chemical is manufactured as an aqueous solution, containing < 70% notified chemical, and is not isolated)

Property	Value	Data Source/Justification
Melting Point/Freezing Point	Not determined	Manufactured as an aqueous solution and introduced in formulated products only.
Boiling Point	Not determined	Manufactured as an aqueous solution and introduced in formulated products only.
Density	1,270 kg/m^3 at 20 °C	Calculated value based on the aqueous solution containing the notified chemical.
Vapour Pressure	Not determined	Expected to be low
Water Solubility	182 g/L	Measured for arginine (US EPA, 2012a). The notified chemical is expected to be highly water soluble.
Hydrolysis as a Function of pH	Not determined	No hydrolysable functionality

Partition Coefficient (n-octanol/water)	log Pow = -4.2	Measured for arginine (US EPA, 2012a). The notified chemical is expected to partition to the aqueous phase.
Adsorption/Desorption	log K_{oc} = -2.25	Calculated for arginine (US EPA, 2012b). Likely to sorb to organic matter based on potential cationicity. Bicarbonate is expected to be mobile.
Dissociation Constant	pKa = 1.82, 8.99, 12.48 (Arginine; Aylward & Findlay, 2002) pKa = 6.33, 10.33 (Bicarbonate; OECD, 2002)	The notified chemical is a salt. The notified chemical is expected to dissociate and its constituents are expected to be ionised under environmental conditions (pH 4-9).
Particle Size	Not determined	Manufactured as an aqueous solution and introduced in formulated products only.
Flash Point/Flammability	Not determined	Manufactured as an aqueous solution and introduced in formulated products only. Not expected to be flammable under the conditions of use.
Autoignition Temperature	Not determined	Manufactured as an aqueous solution and introduced in formulated products only. Not expected to autoignite under the conditions of use.
Explosive Properties	Not determined	Not expected to have explosive properties, based on the chemical structure.
Oxidising Properties	Not determined	Not expected to have oxidising properties, based on the chemical structure.

DISCUSSION OF PROPERTIES

Reactivity

The notified chemical is expected to be stable under normal conditions of use.

Physical hazard classification

Based on the limited submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS

The notified chemical will be introduced as a component (≤ 11%) of toothpaste.

MAXIMUM INTRODUCTION VOLUME OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	5-10	10-20	10-20	10-20	10-20

PORT OF ENTRY

Melbourne and Sydney

IDENTITY OF RECIPIENTS

Colgate-Palmolive Pty Ltd

TRANSPORTATION AND PACKAGING

The toothpaste products containing the notified chemical (at ≤ 11%) will be imported in tubes/containers suitable for retail sale and will be distributed within Australia by road.

USE
The notified chemical will be used as a component of toothpaste at ≤ 11% concentration.

OPERATION DESCRIPTION
The notified chemical will not be manufactured or reformulated in Australia. Toothpaste products containing the notified chemical at ≤ 11% will be imported and distributed to retailers for sale to the general public.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure
Transportation, storage and retail workers will only come into contact with the notified chemical (at ≤ 11% in end use products), in the event of accidental rupture of containers.

6.1.2. Public Exposure
There will be widespread and repeated exposure of the public to the notified chemical through the use of toothpastes (containing ≤ 11% notified chemical). The principal route of exposure will be oral. The notified chemical will be present in toothpastes intended for use by adults and also by children.

Data on typical use patterns of toothpaste are shown in the following table. For the purposes of the exposure assessment, Australian use patterns for toothpaste are assumed to be similar to those in Europe. As the products are intended for use by children as well as adults, and the systemic exposure level is expected to be significantly higher in children, average values for usage by 2 - 4 year olds, body weight (12kg) and retention factor (RIVM 2006) have been used as a worst case scenario. In addition, 100% systemic exposure has been assumed based on buccal and/or gastrointestinal absorption. Using this data, the systemic exposure is estimated to be 9.775 mg/kg bw/day notified chemical.

Product type	**Amount** (mg/day)	**C** (%)	**RF**	**Daily systemic exposure** (mg/kg bw/day)
toothpaste	1720	11	0.62*	9.775

C = concentration; RF = retention factor; assumed brushing twice daily
Daily systemic exposure = Amount × C × RF × absorption/body weight
*Based on 75th percentile of amount orally ingested

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the following table. For full details, refer to Appendix A.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity (25% suspension in corn oil)	LD_{50} = 8900 mg/kg bw; low toxicity

Additional information on the expected health effects of the notified chemical is based on published literature for the two chemical components arginine and sodium bicarbonate and/or studies conducted on products containing them (WHO 2006, The EFSA Journal 2007, OECD 2002, Visek 1986, Tsubuku 2004). As sodium bicarbonate is expected to dissociate upon ingestion, repeat dose data will be primarily based on the effects noted for arginine.

Notified chemical

Acute toxicity
Albino rats were treated with 1, 5 or 10g/kg notified chemical (25% suspension in corn oil) in a range finding test and 6.3, 7.06, 7.94, 8.93 and 10g/kg in the main test. There were numerous deaths at doses ≥ 7.94 g/kg. Clinical signs, which included depression, mucoid diarrhoea and matted and unkept hair, were noted in all treatment groups in the main test. However, all effects in surviving animals recovered after 14 days post dosing indicating reversibility. At necropsy, animals showed gastrointestinal effects including distended, blanched and/or reddened GI tract and stomach. The notified chemical was determined to be of low acute oral toxicity to rats with a LD_{50} of 8900mg/kg (8400 – 9430mg/kg, 95% confidence limits).

No acute dermal toxicity data was provided; however, based on the relatively high molecular weight of the

notified chemical, limited dermal absorption is expected.

No acute inhalation data was provided; however, given the low vapour pressure of the notified chemical, significant inhalation exposure is not expected.

Irritation
There was no data provided on the irritation potential of the notified chemical. However, while skin and eye irritation from exposure to the notified chemical cannot be excluded, based on the information available for arginine and sodium bicarbonate, the notified chemical is not expected to be irritating to the skin and eyes at 11% concentration in toothpaste.

There was no data provided on the sensitisation potential of the notified chemical. However, while sensitisation cannot be ruled out, there are no structural alerts that would imply sensitisation potential and based on the information available for arginine and sodium bicarbonate, the notified chemical is not expected to be a sensitiser.

Some information was provided on the components of the notified chemical: arginine and sodium bicarbonate, and they are summarised below.

Arginine (amino acids)

Toxicokinetics, metabolism and distribution
Amino acids, including arginine, are absorbed readily through the intestinal mucosa, distributed through the bloodstream and transported into cells by a variety of carrier systems. The D-isomers and those amino acids that are not needed for new protein synthesis undergo catabolism, primarily in the liver. There is no mechanism for storage of amino acids in humans. Amino acids undergo oxidative deamination, in which amino acids are deaminated to yield α-ketoacids that are either completely oxidised to carbon dioxide (CO_2) and water, or provide three or four carbon units that are converted via gluconeogenesis to yield glucose, or undergo ketogenesis to yield ketone bodies (WHO 2006).

Acute toxicity
The oral LD_{50} value was reported to be 12,400 mg/kg bw for arginine (WHO 2006). The lower LD_{50} for the notified chemical is likely due to local effects attributed to sodium bicarbonate which are not seen in studies treating animals with arginine alone.

Irritation and sensitisation
Toothpaste containing 1.5% arginine, at 25% dilution, was found to be slightly irritating when applied to intact and abraded skin of rabbits, to the eyes of rabbits and to cheek pouch buccal mucosa in hamsters (Consumer Product Testing 2003). However, the role of arginine in any effects noted is unknown and given the low concentration, unlikely.

In separate efficacy studies, arginine did not produce any adverse effects in rats, guinea pigs, or mouse skin models (WHO 2006). Similarly, HRIPT studies of many products containing amino acid ingredients concluded that these ingredients were not dermal irritants or sensitisers.

In general, supplementary arginine is well tolerated by adults and children with no indications of irritation. Therefore, based on the information available, arginine is not expected to be irritating to the skin. While eye irritation potential cannot be ruled out, significant adverse effects from accidental exposure are not expected.

Repeated dose toxicity
In a 13 week continuous feeding study (followed by 5 week recovery), male and female Sprague-Dawley rats were treated with arginine at doses of 1.25, 2.5 and 5.0% (w/w) in a standard diet (Tsubuku et al., 2004). Elevated plasma glucose, haemoglobin, and erythrocytes were noted in high dose males; however, the degrees of change were either within the physiological range, or recovered prior to the end of the observation period, and thus considered toxicologically insignificant by the study authors. There were no dose-related changes observed in clinical signs, body weight, food consumption, ophthalmologic examination, haematology, organ weights or any abnormalities noted at necropsy. The no-observed-adverse-effect level (NOAEL) for arginine was estimated at 3.3 ± 0.1 g/kg/day (males) and 3.9 ± 0.2 g/kg/day (females).

The results are supported by the findings of a 28 day gavage study where rats were treated with one of two

arginine products (containing minimum 98% arginine) at 2000mg/kg bw/day (The EFSA Journal 2007). Prevalence of alkalised (pH9) urine and positive protein reaction increased in treatment groups of both sexes. Local effects of slight hyperplasia of the squamous epithelium at the limiting ridge in the stomach were also observed in both sexes. Changes mostly recovered by the end of the two-week recovery period, indicating that effects seen in this study were reversible. There were no dose-related clinical signs or changes in body weight, food consumption, ophthalmologic examination, haematology, organ weights or other abnormalities noted at necropsy (The EFSA Journal 2007).

Genotoxicity
The mutagenicity of arginine was investigated in multiple studies at 100% concentration. In one study, it was found to be negative when tested using the bacterial reverse mutation assay in three separate tests performed in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2*uvr*A$^-$ at up to 5000 µg/plate arginine, with and without microsomal enzyme activation (The EFSA Journal 2007). Absence of any reproducible effects between the three tests provided adequate reassurance on the lack of genotoxicity of arginine in this study.

A Chromosomal Aberration Test (OECD 473) was performed with arginine using cultured human lymphocytes both with and without microsomal enzyme activation up to the 10 mM limit dose of 1740 µg/mL. The test substance showed no evidence of increased chromosome aberrations with or without activation and was therefore considered to be non-clastogenic to human lymphocytes under the conditions of the test (The EFSA Journal 2007).

Studies in humans
An epidemiological study was conducted over 10 years on 806 men (64-84 years) which indicated daily intake of > 4.65 g/day arginine resulted in no increased risk of coronary heart disease (Oomen 2000). General health checks and multiple covariates were included. While the outcome of this study is not relevant for the risk assessment, it does indicate that doses of dietary arginine of > 4.65 g/day are well tolerated in a human population. This is supported by other published literature that indicates a daily intake of 3-6 g/day dietary arginine is common for healthy individuals (Visek 1986).

An epidemiological study conducted in 109 children 7-13 years old indicates that daily dietary intake of arginine is up to 3.2 g/day with no adverse effects (van Vught 2013). In addition, it is estimated that children aged 2 – 6 years consume at least approximately 600 mg/day of arginine from dietary sources (using the recommended daily consumption of dairy foods as an estimate) with no adverse effects. The latter can be considered as an estimate of the tolerable dose for a child for the purposes of a risk assessment.

In addition, three clinical dental studies (twice or three times daily brushing for ≥ 6 months) have been conducted with products containing 1.5% arginine in adults and children (Study 1: 450 participants age 8-21; Study 2: 360 participants aged ≥ 18 years; Study 3: 726 participants aged 11-12). No adverse effects were recorded by participants, or noted in the oral cavity from dental examination. While this data is not sufficient for determining a NOAEL, it is useful when considering a weight of evidence approach for determining the risk of local effects. The absence of oral irritation and sensitization support the use of arginine at low concentrations in the oral cavity (Consumer product testing 2003).

While there are some studies linking high arginine intake to adverse outcomes such as cardiac events and reproductive performance, these are either small case report data, or are contradicted in more well conducted studies (Shao 2008).

<u>Sodium bicarbonate</u>
For sodium bicarbonate, oral LD50 values were > 4,000 mg/kg bw. An inhalation study in rats using a concentration of 4.74 mg/L inhalable dust produced no deaths (OECD 2002).

There are no directly relevant studies on repeated dose exposure; however, knowledge of prior use and available literature does not indicate any adverse effects following long-term exposure via any route. In vitro bacterial and mammalian cell tests showed no evidence of genotoxic activity. As with other sodium salts, high doses of sodium bicarbonate promote carcinoma formation in rat urinary bladder after pre-exposure to initiator or broad-band noise. However, when rats were only exposed to sodium bicarbonate no carcinogenic effect on the urinary bladder was found. Based on the available information there are no indications that sodium bicarbonate has carcinogenic effects.

Sodium bicarbonate has a long history of use in foodstuff, feed and industrial processes. The bicarbonate ion is a normal constituent in vertebrates, as the principal extracellular buffer in the blood and interstitial fluid is the bicarbonate buffer system. Excess sodium and bicarbonate ions are readily excreted in the urine. It is therefore assumed that normal handling and use will not have any adverse effects. The consequences of accidental or excessive oral ingestion have been described in a number of publications. Acute oral ingestion by the patients may result in a ruptured stomach due to excessive gas development. Acute or chronic excessive oral ingestion may cause metabolic alkalosis, cyanosis and hypernatraemia. These conditions are usually reversible, and will not cause long term adverse effects (OECD 2002).

While local irritant effects from excessive ingestion of sodium bicarbonate cannot be ruled out based on the information available, these effects are not anticipated from small volume ingestion at low concentrations in children or adults.

Health hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
As exposure to the notified chemical will be limited to accidental exposure of transport and storage workers, the risk to workers associated with use of the notified chemical at ≤ 11% concentration in toothpastes is not considered to be unreasonable.

6.3.2. Public Health
The notified chemical is proposed for use by adults and children at ≤ 11% concentration in toothpaste. The notified chemical is not considered to be harmful via the oral route and is not expected to cause irritation at the concentration proposed. Exposure in a 2 - 4 yr old child is considered the worst case scenario and thus is the basis for the risk assessment.

The repeated dose toxicity effects of the notified chemical have not been determined. Arginine dietary consumption in 2 – 6 year olds is at least 600 mg/day. This value is above the exposure expected from toothpaste ingestion (see section 6.1.2) where a 2 - 4 yr old child may ingest up to 117 mg/day notified chemical. Therefore, as a known tolerable intake is higher than expected ingestion of the notified chemical from toothpaste use, significant adverse systemic effects are not expected based on epidemiological data.

In addition to epidemiological data regarding dietary arginine, results from the 13 week feeding study in rats indicate a NOAEL of the highest dose (3318 mg/kg bw/day). This dose could be considered a worst case scenario for a child and thus can be used to conduct a quantitative risk assessment.

Repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical. Using the exposure scenario for 2 - 4 year old children of 9.775 mg/kg bw/day (see section 6.1.2) and a NOAEL of 3318 mg/kg bw/day, a MoE of 339 was estimated. A MoE ≥ 100 is considered acceptable to account for interspecies and intraspecies differences. Thus the risk to young children associated with use of tooth paste products is not considered to be unreasonable.

As adults ingest even higher doses of arginine without adverse effect, and ingest less than a child from toothpaste on average, the risk to adult health is considered to be less than for a child and therefore also not considered to be unreasonable.

Therefore, given the high MoE and estimated tolerable intake, the risk to the public associated with the use of the notified chemical at ≤ 11% concentration in toothpaste is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported as a component of toothpaste. As manufacturing and reformulation will take place overseas, no release of the notified chemical will occur in Australia from these activities. Release from spills is expected to account for 1% of the total import volume. Spills are expected to be contained, collected and disposed of to landfill.

RELEASE OF CHEMICAL FROM USE

Toothpaste containing the notified chemical will be sold nationwide. The majority of the toothpaste will be used undiluted and will usually be released directly to the sewer.

RELEASE OF CHEMICAL FROM DISPOSAL

Up to 5% of the total import volume of the notified chemical will remain as residues in empty product containers. Empty containers are expected to be disposed of to landfill.

7.1.2. Environmental Fate

No environmental fate data were submitted. The majority of the notified chemical is expected to be released to sewer during use. Due to its likely high water solubility and low n-octanol/water partition coefficient, the notified chemical is expected to remain in the aqueous phase. It is also expected to dissociate and be in its ionised state in the environment. A portion of the cationic constituent of the notified chemical may sorb to sludge and be removed during sewage treatment plant (STP) processes. The bicarbonate constituent is expected to remain in the aqueous phase. In the aqueous waste stream, the notified chemical or its respective dissociated constituent ions are expected to eventually disperse and degrade. Less than 6% of the notified chemical is expected to be released to landfill due to disposal of spills and residues remaining in product containers. The dissociated constituent ions of the notified chemical are likely to leach from landfill and enter surface waters due to their high water solubility. The cationic constituent of the notified chemical may have reduced mobility in soil. Arginine is likely to be rapidly biodegradable based on modelled data (US EPA, 2012b) and biodegradation pathways for amino acids (Jones, 2005). Therefore, the notified chemical is not likely to be persistent in the environment. Upon entering surface waters, it is expected to degrade via biotic and abiotic processes to form water and oxides of carbon and nitrogen. The notified chemical is also not expected to bioaccumulate due to its low bioaccumulation factor (log BCF = -0.5; US EPA, 2011b), very low n-octanol partition coefficient (log P_{OW}) and high solubility in water.

7.1.3. Predicted Environmental Concentration (PEC)

The calculation for the predicted environmental concentration (PEC) is summarised in the table below. Based on the reported use in toothpaste, it is assumed that 100% of the notified chemical will be released to sewer on a nationwide basis over 365 days per year. It is also assumed that there is no removal of the notified chemical during STP processes.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	20000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	20000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	54.79	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1	
Dilution Factor - Ocean	10	
PEC - River:	12.12	µg/L
PEC - Ocean:	1.21	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 12.12 µg/L may potentially result in a soil concentration of approximately 80.77 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the

concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 403.9 µg/kg and 807.7 µg/kg, respectively.

7.2. Environmental Effects Assessment

No ecotoxicity data were submitted. Endpoints for the constituents of the notified chemical – arginine and sodium bicarbonate – are presented in the table below. The ECOSAR v1.00 estimations for arginine are based on the ECOSAR class of 'aliphatic amines-acid' with mitigation for the presence of the acid moiety. The estimations for the values of the endpoints appear reasonable, as arginine is a naturally occurring amino acid. It is an essential amino acid for birds, carnivores and young mammals and a conditionally essential amino acid for adults, depending on health status (Tapiero, 2002).

Endpoint	*Result*	*Assessment Conclusion*
Acute (Arginine)[1]		
Fish Toxicity (96 h)	LC50 > 1000 mg/L	Not expected to be harmful to fish
Daphnia Toxicity (48 h)	LC50 > 1000 mg/L	Not expected to be harmful to aquatic invertebrates
Algal Toxicity (96 h)	EC50 > 1000 mg/L	Not expected to be harmful to algae
Acute (Sodium bicarbonate)[2]		
Fish Toxicity (*Oncorhynchus mykiss*) (96 h)	LC50 > 1000 mg/L	Not expected to be harmful to fish
Daphnia Toxicity (*Daphnia magna*) (48 h)	EC50 > 1000 mg/L	Not expected to be harmful to aquatic invertebrates
Algal Toxicity (96 h)	Not reported	Not expected to be harmful to algae*

* Sodium bicarbonate is beneficial to algal growth at 45 mg/L
[1] Calculated using ECOSAR v1.00 (US EPA, 2012b)
[2] Measured data from OECD SIDS Initial Assessment Report (OECD, 2002)

Data for the constituents of the notified chemical are considered to be reasonable in lieu of experimental data for the notified chemical. Toxicity values for the constituents are expected to closely reflect the toxicity of the notified chemical. On the basis of the calculated data for arginine and measured data for sodium bicarbonate, the notified chemical is not expected to be harmful to aquatic life. Therefore, the notified chemical is not formally classified for acute aquatic hazard under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009).

7.2.1. Predicted No-Effect Concentration

The most sensitive observed ecotoxicological endpoint for the constituents of the notified chemical was used to calculate the predicted no-effect concentration (PNEC). The 96-hour acute toxicity to fish for arginine was used as a representative value. An assessment factor of 100 was used as acute endpoints were not available for the notified chemical, but values for the constituent of the notified chemical are expected to closely reflect the toxicity of the notified chemical.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Fish, 96 h, arginine)	> 1000	mg/L
Assessment Factor	100	
PNEC:	> 10000	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	12.12	> 10000	< 0.001
Q - Ocean	1.2	> 10000	< 0.001

The Risk Quotients (Q = PEC/PNEC) have been calculated to be less than 1 for the river and ocean waters, indicating that the risk to aquatic organisms is not unreasonable. The notified chemical is not expected to pose an unreasonable risk to the environment for the assessed use pattern.

APPENDIX A: TOXICOLOGICAL INVESTIGATIONS

A.1. Acute toxicity – oral

TEST SUBSTANCE: Notified Chemical (25% concentration)

METHOD: Similar to OECD TG 401 Acute Oral Toxicity.
- Species/Strain: Rat/Wistar
- Vehicle: Corn oil
- Remarks - Method: No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
Range finding			
1	1 M	1000	0
2	1 M	5000	0
3	1 F	10000	1
Main test			
4	5 per sex	6300	0
5	5 per sex	7060	0
6	5 per sex	7940	1 M, 2F
7	5 per sex	8930	2 F
8	5 per sex	10000	4 M, 5 F

LD50: 8900 (8400-9430) mg/kg bw

Signs of Toxicity:

Range finding

Surviving animals appeared to be normal. The animal treated with 10 mg/kg bw died within 3 hours of treatment which was also the first observation point, thus, signs of toxicity prior to death were not able to be determined.

Main test

5/10 animals died at doses below the LD_{50}. Signs of toxicity were noted in animals of all dose groups (surviving and prior to death) and included degrees of activity depression (slightly to severely), mucoid diarrhoea and hair matted and unkempt which were noted in all dose groups, and in addition, muscle tremors, dehydration, convulsions, diarrhoea, laboured breathing and/or hair loss around urogenital area noted for animals treated with ≥ 7940 mg/kg bw. Effects became more severe with increasing dose but recovered by 7 days post treatment in animals of all dose groups.

Effects in Organs:

Range finding

The small and large intestine appeared distended and moderately reddened for the dead animal. No gross changes were observed for surviving animals.

Main test

Observations in animals that died (treated with ≥ 7940 mg/kg bw) included stomach, small and large intestines appearing reddened and distended, large intestine partially cannibalised, darkened liver and spleen, and a 1-2 mm hematoma on left lung (2 animals only). No gross abnormalities were noted at necropsy of surviving animals.

CONCLUSION: The test substance is of low toxicity via the oral route.

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