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April 2016

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

D-Glucitol, 1-deoxy-1-(methylamino)-, *N*-coco acyl derivs. (INCI Name: Cocoyl Methyl Glucamide)

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (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.

This Public Report is 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:

Street Address:	Level 7, 260 Elizabeth Street, SURRY HILLS NSW 2010, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL:	+ 61 2 8577 8800
FAX:	+ 61 2 8577 8888
Website:	www.nicnas.gov.au

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/1566	Clariant (Australia) Pty Ltd	D-Glucitol, 1-deoxy-1-(methylamino)-, *N*-coco acyl derivs. (INCI Name: Cocoyl Methyl Glucamide)	Yes	< 25 tonnes per annum	Component of rinse-off cosmetic and household cleaning products

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard classification	*Hazard statement*
Serious eye damage/eye irritation (Category 1)	H318 – Causes serious eye damage

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrase:

R41: Risk of serious eye damage

The environmental hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS) is presented below. Environmental classification under the GHS is not mandated in Australia and carries no legal status but is presented for information purposes.

Hazard classification	*Hazard statement*
Acute Category 2	H401 – Toxic to aquatic life

Human health risk assessment
Provided that the recommended controls are being adhered to, 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 in the proposed manner, 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 reported use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - H318: Causes serious eye damage

The above should be used for products/mixtures containing the notified chemical, if applicable, based on the concentration of the notified chemical present and the intended use/exposure scenario.

- The Delegate (and/or the Advisory Committee on Chemicals Scheduling) should consider the notified chemical for listing on the SUSMP.

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical during reformulation processes:
  - Enclosed, automated processes, where possible
  - Adequate general ventilation and local exhaust ventilation

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure to the notified chemical during reformulation processes:
  - Avoid contact with eyes
  - Avoid formation of mists/aerosols

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical during reformulation processes:
  - Eye protection
  - Respiratory protection if mist/aerosol formation is expected

  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 of 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.

Public Health

- Product formulators should exercise due care when using the notified chemical in cosmetic products given its potential ability to enhance the dermal penetration of other chemicals in the formulation.

- Consumer products containing the notified chemical should be labelled with a warning against eye contact, and directions on first aid measures if the product contacts the eyes (e.g. avoid contact with eyes; in case of contact with eyes, rinse immediately with plenty of water and seek medical advice).

Disposal

- Where reuse or recycling are not appropriate, dispose of the notified chemical in an environmentally sound manner in accordance with relevant Commonwealth, state, territory and local government legislation.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by containment, physical 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 concentration of the chemical is intended to exceed 8% in rinse-off cosmetic products or 10% in household cleaning products;
- the chemical is intended to be used in products involving spray applications;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a component of rinse-off cosmetic and household cleaning 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 products containing the notified chemical provided by the notifier were 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
Clariant (Australia) Pty Ltd (ABN: 30 069 435 552)
Level 3, 3 Acacia Place
296 - 324 Ferntree Gully Road
NOTTING HILL VIC 3168

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: other names, 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: hydrolysis as a function of pH, adsorption/desorption, particle size, flash point, explosive properties, and oxidising properties

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
GlucoTain Care (product containing the notified chemical at ~40% concentration)
GlucoPure Foam (product containing the notified chemical at ~40% concentration)

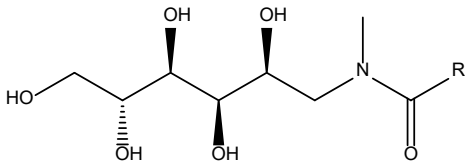
CAS NUMBER
1591783-13-9

CHEMICAL NAME
D-glucitol, 1-deoxy-1-(methylamino)-, *N*-coco acyl derivs.

OTHER NAME(S)
Cocoyl Methyl Glucamide (INCI Name)

MOLECULAR FORMULA
Unspecified

STRUCTURAL FORMULA



Where R = C7-C17 alkyl group or C17 alkenyl group

MOLECULAR WEIGHT
321.4 to 461.7 Da

ANALYTICAL DATA
Reference NMR, IR and UV-Vis spectra were provided

3. COMPOSITION

DEGREE OF PURITY
> 75%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: white waxy solid

Property	Value	Data Source/Justification
Melting Point	70 – 71 °C	Measured
Boiling Point	Decomposes without boiling	Measured
Density	1,110 kg/m^3 at 20 °C	Measured
Vapour Pressure	< 1 × 10^{-4} kPa at up to 110 °C	Measured
Water Solubility	0.061 ± 0.015 g/L at pH 6.13 at 20 °C 0.049 ± 0.012 g/L at pH 6.13 at 20 °C (active content)	Measured
Fat (or n-octanol) Solubility	47 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Contains no hydrolysable functionalities
Partition Coefficient (n-octanol/water)	log Pow = 2.90 at pH 6.13 at 20 °C	Calculated from measured solubilities in n-octanol and water; expected to partition to phase boundaries based on surfactant properties
Surface Tension	32.9 mN/m at 20 °C	Measured. The notified chemical is surface active
Adsorption/Desorption	Not determined	Expected to adsorb strongly to soil and sediment based on surfactant properties
Dissociation Constant	pKa_1 = -1.31 to 0.12; pKa_2 = 13.24 to 13.64	Calculated for all homologues in the C8 to C18 range using I-Lab v2.0
Particle Size	Not determined	Introduced as a paste
Flash Point	Not determined	Estimated to be high based on flammability
Flammability	Not highly flammable	Measured
Autoignition Temperature	> 400 °C	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidative properties

DISCUSSION OF PROPERTIES
For full details of tests on physical and chemical properties, refer to Appendix A.

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

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System of 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 not be manufactured within Australia. It will be imported into Australia as a component of the products, GlucoTain Care and GlucoPure Foam, at ~ 40% concentration as a paste.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	< 15	< 25	< 25	< 25	< 25

PORT OF ENTRY
Sydney and Melbourne

TRANSPORTATION AND PACKAGING
The products (GlucoTain Care and GlucoPure Foam) containing the notified chemical at ~40% concentration will be imported in 1 tonne IBCs. The imported containers will be transported from the wharf to the warehouses for storage and distribution.

USE
The notified chemical will be used in rinse-off cosmetic products at ≤ 8% concentration and in household cleaning products (such as dishwashing liquids and hard surface cleaners) at ≤ 10% concentration. The finished products containing the notified chemical will not be applied by spray.

OPERATION DESCRIPTION
The imported products containing the notified chemical, GlucoTain Care and GlucoPure Foam, will be distributed to formulators for reformulation of rinse-off cosmetic and household cleaning products.

At the reformulation sites, metering pumps will be used to transfer either GlucoTain Care or GlucoPure Foam from the original containers into vats where they will be blended with other raw materials. Blending will be carried out in enclosed and automated systems. Once blending is complete, quality assurance (QA) workers will take aliquots of samples for laboratory analysis. An automated and metered process will be applied to dispense the finished products into individual consumer size packaging.

The finished rinse-off cosmetic and household cleaning products containing the notified chemical at ≤ 10% concentration will be distributed nationwide for retail and consumer use.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Stevedores	2-3	10-15
Transport workers	6	260
Warehousing workers	6	260
Reformulation process workers	4	260
Quality assurance workers	4	260
Maintenance workers and cleaners	1	260

EXPOSURE DETAILS
Transportation and storage
Stevedores, transport and warehouse workers may come into contact with the notified chemical at up to 40% concentration, only in the event of an unlikely accidental rupture of containers.

Reformulation
During reformulation into cosmetic and household cleaning products, dermal, ocular and inhalation exposure of workers to the notified chemical at ≤ 40% concentration may occur. Exposure is expected to be minimised through the use of exhaust ventilation and/or automated/enclosed systems as well as through the use of personal protective equipment (PPE) such as coveralls, eye protection, impervious gloves and respiratory protection (as appropriate).

End-use
Exposure to the notified chemical in end-use products at ≤ 10% concentration may occur in professions where the services provided involve the applications of cosmetic products to clients (e.g. hair dressers and workers in beauty salons) or in the cleaning industry. Spray applications involving the use of the notified chemical are not expected as indicated by the notifier. The main route of exposure is therefore expected to be dermal, while ocular exposure is also possible. Such professionals may use some PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or less extent than that experienced by consumers using the same products containing the notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical at ≤ 10% concentration through the use of rinse-off cosmetic or household cleaning products. The principal route of exposure will be dermal, while ocular exposure is also possible.

For the purposes of the exposure assessment via the dermal route, data on typical use patterns of product categories in which the notified chemical may be used are shown in the following tables (SCCS, 2012; Cadby et al., 2002; ACI, 2010; Loretz et al., 2006). Australian use patterns for the various product categories are assumed to be similar to those in Europe. A lifetime average female body weight (BW) of 64 kg (enHealth, 2012) was used for the calculations. In the absence of dermal absorption data, a dermal absorption (DA) of 100% was assumed for the notified chemical (ECHA, 2014).

Direct dermal exposure
Cosmetic products

Product type	*Use Amount (mg/day)*	*C (%)*	*RF*	*DA (%)*	*Daily Systemic Exposure (mg/kg bw/day)*
Facial cleanser	800	8	0.01	100	0.0100
Shampoo	10,460	8	0.01	100	0.1308
Conditioner	3,920	8	0.01	100	0.0490
Shower gel	18,670	8	0.01	100	0.2334
Hand wash soap	20,000	8	0.01	100	0.2500
Total					**0.6731**

Daily systemic exposure = (Use amount × C × RF × DA)/BW, where C = Use concentration, RF = Retention factor, DA = Dermal absorption rate, BW = Average bodyweight

Household cleaning products

Product type	*Frequency (use/day)*	*C (%)*	*Contact Area (cm^2)*	*Product Use C (g/cm^3)*	*Film Thickness (cm)*	*Time Scale Factor*	*DA (%)*	*Daily systemic exposure (mg/kg bw/day)*
Laundry liquid	1.43	10	1980	0.01	0.01	0.007	100	0.0031
Dishwashing liquid	3	10	1980	0.009	0.01	0.03	100	0.0251
All-purpose cleaner	1	10	1980	1	0.01	0.007	100	0.2166
Total								**0.2447**

Daily systemic exposure = (Frequency × C × Contact area × Product Use C × Film thickness × Time scale factor × DA)/BW, where C = concentration, DA = Dermal absorption rate, BW = Average bodyweight

Indirect dermal exposure (from wearing clothes)
Household cleaning products

Product type	*Amount (g/use)*	*C (%)*	*PR (%)*	*PT (%)*	*DA (%)*	*Daily systemic exposure (mg/kg bw/day)*
Laundry liquid	230	10	0.95	10	100	0.3414
Fabric softener	90	10	0.95	10	100	0.1336
Total						**0.4750**

Daily systemic exposure = (Amount × C × PR × PT × DA)/BW, where C = Use concentration, PR = Retained product rate, PT = Percentage transfer, DA = Dermal absorption rate

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemical. This would result in a combined internal dose of 1.393 mg/kg bw/day.

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 of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 cut-off = 2,500 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Skin irritation (*in vitro*)	non-irritating
Eye irritation (*in vitro*)	unable to predict
Rabbit, eye irritation	severely irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL = 750 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian cell gene mutation test	non genotoxic
Genotoxicity – *in vivo* mammalian erythrocyte micronucleus test	non genotoxic

Toxicokinetics

No toxicokinetic data was provided for the notified chemical. The notified chemical has a molecular weight of 321.4 to 461.7 Da and a log Pow of 2.90 at 20 °C, indicating potential for absorption. The notified chemical is to be used a surfactant and therefore may have the ability to enhance dermal penetration of other chemicals in the formulations.

Acute toxicity

Based on studies conducted in rats, the notified chemical is of low acute oral and dermal toxicity. However, a similar chemical (D-glucitol, 1-deoxy-1-(methylamino)-, *N*-C_{8-10} acyl derivs., CAS No. 1591782-62-5; STD/1565) has been found to be harmful if inhaled. Therefore the potential of the notified chemical to cause toxicity effects through inhalation cannot be ruled out.

Irritation and sensitisation

An *in vitro* study on skin irritation using a reconstituted three-dimensional human epidermis model showed that the notified chemical is not expected to be irritating to the skin.

An *in vitro* study on eye irritation using bovine corneal opacity and permeability test method indicated that the notified chemical may have potential for eye irritation, but no prediction could be made from the test results. However, a subsequent *in vivo* eye irritation study in rabbits demonstrated that the notified chemical is severely irritating to eyes.

A guinea pig maximisation test on the notified chemical at up to 5% concentration did not reveal any evidence of skin sensitisation properties for the notified chemical.

Repeated dose toxicity

In a 28 day repeated dose oral toxicity study on the notified chemical, no treatment-related adverse effects were observed in the test animals at any dose tested. The No Observed Adverse Effect Level (NOAEL) was therefore established at 750 mg/kg bw/day based on the highest dose level tested.

Mutagenicity/Genotoxicity

The notified chemical tested negative in a bacterial reverse mutation assay and an *in vitro* mammalian cell gene mutation test using Chinese Hamster V79 cells. The notified chemical also tested negative in an *in vivo* mouse bone marrow micronucleus test via the oral route.

Health hazard classification

Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard classification	*Hazard statement*
Serious eye damage/eye irritation (Category 1)	H318 – Causes serious eye damage

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrase:

R41: Risk of serious eye damage

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Based on the available information, the notified chemical causes serious eye damage and the potential for the chemical to cause acute inhalation toxicity cannot be ruled out.

Reformulation

Dermal, ocular and potentially inhalation exposure to the notified chemical at up to 40% concentration may occur during reformulation. The stated use by the notifier of PPE such as coveralls, eye protection, impervious gloves and respiratory protection (as appropriate) and engineering controls including automated/enclosed processes and local exhaust ventilation should minimise the risk for workers.

Provided that control measures stated by the notifier are in place to minimise worker exposure, including the use of automated processes and PPE, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

End-use

Cleaners and beauty care professionals may come into contact with products containing the notified chemical at ≤ 10% concentration. These products will also be available to the public. The risk to workers who regularly use these products is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical (for details of the public health risk assessment, see Section 6.3.2).

6.3.2. Public Health

Cosmetic and household cleaning products containing the notified chemical at ≤ 10% concentration will be available to the public. The main route of exposure is expected to be dermal with some potential for accidental ocular or oral exposure.

Irritation

The notified chemical is a severe eye irritant. The main risk of irritation will be expected from use of cosmetic products containing the notified chemical. Given the low proposed use concentration in cosmetics (i.e. ≤ 8%) and use in rinse-off cosmetics only, significant eye irritation effects are not expected. The eye irritation risk associated with use of the notified chemical in consumer products may be further minimised by the inclusion of appropriate labelling and directions for use to warn against eye contact.

Risk of repeated exposure

Members of the public may experience repeated exposure to the notified chemical up to 10% concentration through the use of a range of rinse-off cosmetic and household cleaning products.

Estimation of repeated dose toxicity potential of the notified chemical using the worst case exposure scenario from the use of multiple products would result in a combined internal dose of 1.393 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 750 mg/kg bw/day established in a 28 day oral repeat dose toxicity study on the chemical, the margin of exposure (MoE) was calculated to be 538. A MoE value greater than or equal to 100 is generally considered acceptable to account for intra- and inter-species differences.

Therefore, based on the available information and with appropriate labelling regarding risks associated from eye contact, the risk to the public from use of the notified chemical at ≤ 8% in rinse-off cosmetics and ≤ 10% in household cleaning products 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 raw material for reformulation into finished cosmetic products and household cleaning products. There is unlikely to be any significant release to the environment from transport and storage, except in the case of accidental spills and leaks. In the event of spills, the product containing the notified chemical is expected to be collected with inert material, and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve transfer of the raw material containing the notified chemical into blending vessels using metering pumps, followed by blending operations that will be highly automated that is expected to occur within a fully enclosed environment. Therefore, significant release of the notified chemical from this process to the environment is not expected. The process will be followed by automated filling of the formulated products into end-use containers of various sizes. Wastes containing the notified chemical generated during reformulation include equipment wash water, spilt materials, and empty import containers. Wastes are not expected to be released to sewer and are expected to be collected and disposed of to landfill in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE

The majority of the notified chemical is expected to be released to sewer across Australia as a result of its use in various cosmetic formulations and household cleaning products, which will be washed off the hair and skin of consumers, or disposed of following cleaning activities to the sewer. A small proportion of the notified chemical is expected to be disposed of to landfill as residue in empty end-use containers.

RELEASE OF CHEMICAL FROM DISPOSAL

A small proportion of the notified chemical may remain in end-use containers once the consumer products are used up. Wastes and residues of the notified chemical in empty containers are likely either to share the fate of the container and be disposed of to landfill, or to be released to sewer when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in cosmetic and household cleaning formulations, the majority of the notified chemical is expected to enter the sewer system, before potential release to surface waters nationwide. Based on the results of biodegradability studies conducted on two suitable analogues, the notified chemical is considered to be readily biodegradable (76-93% in 28 days for Analogue 1; 83.7-85.2% in 28 days for Analogue 2). For details of the environmental fate studies, please refer to Appendix C. Based on its low water solubility and surfactant properties, the notified chemical is expected to bind strongly to sludge and sediment. The notified chemical is expected to partition to phase boundaries based on its surfactant properties, and along with its expected ready biodegradability, is therefore not expected to be bioaccumulative. In surface waters, the notified chemical is expected to adsorb to soil and sediment, and eventually degrade through biotic and abiotic processes to form water and oxides of carbon and nitrogen.

The majority of the notified chemical will be released to sewer after use. A proportion of the notified chemical may be applied to land when effluent is used for irrigation, or when sewage sludge is used for soil remediation, or disposed of to landfill as collected spills and empty container residue. The notified chemical residues in landfill, soil and sludge are expected to eventually degrade to form water and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated to assume a worst case scenario, with 100% release of the notified chemical into sewer systems nationwide and no removal within sewage treatment plants (STPs).

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	25,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	25,000	kg/year

Days per year where release occurs	365	days/year
Daily chemical release:	68.49	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	15.145	µg/L
PEC - Ocean:	1.515	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 15.145 µg/L may potentially result in a soil concentration of approximately 101.0 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of the notified chemical in the applied soil in 5 and 10 years may be approximately 504.8 µg/kg and 1,010.0 µg/kg, respectively.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemical and an accepted analogue (Analogue 2) are summarised in the table below. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Acute toxicity		
Fish*	96 h LC50 = 7.5 mg/L	Acutely toxic to fish
Daphnia	48 h EC50 = 5.91 mg/L[#]	Acutely toxic to *Daphnia*
Algae	72 h E_rC50 = 60.1 mg/L[#]	Acutely harmful to algae
Inhibition of Bacterial Respiration	3 h IC50 = 171 mg/L	Not inhibitory to bacterial respiration
Chronic toxicity		
Daphnia	21 d NOEC = 3.24 mg/L	Not chronically harmful to *Daphnia*
Algae	72 h E_rC10 = 8.88 mg/L[#]	Not chronically harmful to algae

* Analogue data
[#] Concentration based on the active components.

Based on the above acute ecotoxicological endpoints for the notified chemical, it is expected to be toxic to fish and aquatic invertebrates, and harmful to algae. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the notified chemical is formally classified as "Acute Category 2; Toxic to aquatic life". Based on the above chronic ecotoxicological endpoint for the notified chemical and its ready biodegradability, the notified chemical is not expected to be harmful to aquatic life on a long term basis, and is therefore not formally classified under the GHS for chronic toxicity.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive chronic ecotoxicological endpoint for daphnia. A safety factor of 50 was used given acute endpoints for three trophic levels and two chronic endpoints are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
NOEC (*Daphnia*, 21 d)	3.24	mg/L
Assessment Factor	50	
Mitigation Factor	1.00	
PNEC:	64.80	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) has been calculated based on the predicted PEC and PNEC.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	15.145	64.80	**0.234**

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - Ocean	1.515	64.80	**0.023**

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters, based on its maximum annual importation quantity. Based on analogue data, the notified chemical is readily biodegradable, and is expected to have a low potential for bioaccumulation. On the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic formulations and household cleaning products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point 70 – 71 °C

Method	OECD TG 102 Melting Point/Melting Range. EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature.
Remarks	Differential scanning calorimetry (DSC) and capillary method
Test Facility	Siemens AG (2013a)

Boiling Point Decomposes without boiling

Method	OECD TG 103 Boiling Point. EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks	DSC and capillary method. The test substance decomposed before boiling
Test Facility	Siemens AG (2013a)

Relative Density 1,110 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids. EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks	Gas comparison pycnometer method
Test Facility	Siemens AG (2013b)

Vapour Pressure $< 1 \times 10^{-4}$ kPa at up to 110 °C

Method	OECD TG 104 Vapour Pressure. EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks	Vapour pressure balance (Effusion method)
Test Facility	Siemens AG (2013c)

Water Solubility 0.061 ± 0.015 g/L at pH 6.13 at 20 °C
0.049 ± 0.012 g/L at pH 6.13 at 20 °C (active content)

Method	ISO 4311
Remarks	Water solubility as the determination of critical micelle concentration via surface tension by the plate method
Test Facility	Clariant (2013a)

Fat (or n-octanol) Solubility 39 g/L at 20 °C

Method	OECD TG 105 Flask Method
Remarks	Flask method adapted for n-octanol
Test Facility	Clariant (2013b)

Partition Coefficient (n-octanol/water) log Pow = 2.90 at pH 6.13 at 20 °C

Method	OECD TG 105 and ISO 4311
Remarks	Calculated from the individual solubilities of the notified chemical in n-octanol and water
Test Facility	Clariant (2013c)

Surface Tension 32.9 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions. EC Council Regulation No 440/2008 A.5 Surface Tension.
Remarks	Concentration: 51.7 mg/L
Test Facility	Siemens AG (2013d)

Flammability Not highly flammable

Method EC Council Regulation No 440/2008 A.10 Flammability (Solids)
Test Facility Siemens AG (2013e)

Autoignition Temperature > 400 °C

Method EC Council Regulation No 440/2008 A.16 Relative Self-Ignition Temperature for Solids.
Remarks The test substance showed an endothermic effect in the range of 50 – 110 °C. No autoignition temperature was observed up to the maximum test temperature of 401 °C.
Test Facility Siemens AG (2013f)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method EC Council Regulation No 440/2008 B.1 tris Acute Oral Toxicity – Acute Toxic Class Method
Species/Strain	Rat/WISTAR Crl: WI(Han)
Vehicle	Sterile water
Remarks - Method	No significant deviation of protocol was noted. The purity of the test substance was reported as 81%. The test substance was administered at a single dose by gavage using feeding tube.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
Step 1	3 F	2,000	0/3
Step 2	3 F	2,000	1/3

LD50	LD50 cut-off = 2,500 mg/kg bw
Signs of Toxicity	One animal treated with the test substance at a dose of 2,000 mg/kg bw was found dead on day 2. All remaining animals survived until the end of the study showing signs of toxicity. The most relevant clinical findings in the animals treated with the test substance were reduced spontaneous activity, moving the bedding, bradykinesia, ataxia, kyphosis, prone position, wasp waist, piloerection and eyes half closed. All symptoms recovered within 3 days after the treatment. The weight gain of the surviving animals was within the normal range.
Effects in Organs	At necropsy, no treatment-related macroscopic findings were observed in the test animals survived the treatment. Necropsy of the animal found dead revealed a stomach filled with fluid consisting of residual test substance solution.
Remarks - Results	Under the conditions of the study, a single oral application of the test substance to rats at a dose of 2,000 mg/kg bw was associated with signs of toxicity and mortality.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	BSL (2015a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal) – Limit Test
Species/Strain	Rat/WISTAR Crl: WI(Han)
Vehicle	Sterile water (for moistening only)
Type of dressing	Semi-occlusive
Remarks - Method	No significant deviation of protocol was noted. The purity of the notified chemical was reported as 81%.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	5 M	2,000	0/5
2	5 F	2,000	0/5

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	Irritation signs including erythema, oedema, desquamation and crust were observed in test animals. All signs were reversible within the observation period.
Signs of Toxicity - Systemic	No treatment-related effects were observed.
Effects in Organs	No treatment-related effects were observed.
Remarks - Results	Under the conditions of the test, the notified chemical was not associated with mortality and signs of systemic toxicity, although local irritation effects were recorded.

CONCLUSION The notified chemical is of low toxicity via the dermal route.

TEST FACILITY BSL (2015b)

B.3. Irritation – skin (*in vitro*)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 439 *In Vitro* Skin Irritation: Reconstructed Human Epidermis Test Method
EC Commission Regulation No 640/2012 B.46. *In Vitro* Skin Irritation: - Reconstructed Human Epidermis Test Method

Vehicle	Distilled water
Remarks - Method	No significant deviation of the protocol was noted. The EPISKIN-Standard Model™ (EPISKIN-SM™), a reconstituted three-dimensional human epidermis model, was used in the test. The purity of the test substance was reported as 81%.

RESULTS

Test material	*Mean OD_{570} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	0.814	100	5.0
Test substance	0.660	81.1	8.5
Positive control	0.062	7.6	5.8

OD = optical density; SD = standard deviation

Remarks - Results The relative mean tissue viability after 15 minutes of exposure and 42 hours post incubation was > 50%.

CONCLUSION The notified chemical was a non-irritant under the conditions of the test.

TEST FACILITY BSL (2015c)

B.4. Irritation – eye (*in vitro*)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants

Vehicle	Physiological saline (0.9% sodium chloride in water)
Remarks - Method	No significant deviation of the protocol was noted. The purity of the test substance was reported as 81%.

RESULTS

Test material	*Mean opacity of triplicate tissues*	*Mean permeability of triplicate tissues (OD_{490})*	*IVIS*
Vehicle control	0.72	0.016	0.96
*Test substance**	4.64	1.939	33.73
*Positive control**	80.88	2.014	111.09

IVIS (*in vitro* irritancy score) = mean opacity value + (15 × mean permeability OD_{490} value)
*Corrected for background values

Remarks - Results	The IVIS of the test substance was between 3 and 55. No prediction could be made. Further testing may be required.
CONCLUSION	No prediction could be made for the notified chemical under the conditions of the test.
TEST FACILITY	BSL (2015d)

B.5. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion EC Council Regulation No 440/2008 B.5 Acute Toxicity (Eye Irritation)
Species/Strain	Rabbit/New Zealand White, Crl:KBL (NZW)
Number of Animals	3 males
Observation Period	21 days post-application
Remarks - Method	No significant deviations of protocol were noted. The active components of the test substance were report as 81%.

RESULTS

Lesion	*Mean Score** *Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.67	2.00	2.00	2	> 21 d	1
Conjunctiva: chemosis	0.00	1.67	1.33	2	> 21 d	1
Conjunctiva: discharge	0.00	2.00	1.33	2	< 6 d	0
Corneal opacity	0.00	0.67	0.33	2	> 21 d	1
Iridial inflammation	0.00	0.00	0.00	0	0	0

* Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal.

Remarks - Results	Under the conditions of the test, a single ocular application of the notified chemical produced irritant effects that were not fully reversible within 21 days post-application in 2 of 3 test animals.
CONCLUSION	The notified chemical is severely irritating to the eye.
TEST FACILITY	BSL (2015e)

B.6. Skin sensitisation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 406 Skin Sensitisation – Guinea Pig Maximisation Test EC Commission Regulation 440/2008 B.6 Skin Sensitisation – Guinea Pig Maximisation Test
Species/Strain	Guinea pig/Albino, Dunkin Hartley
PRELIMINARY STUDY	Maximum Non-irritating Concentration: Intradermal 0.1%

	Topical	5%
MAIN STUDY		
Number of Animals	Test Group: 10 F	Control Group: 5 F
Vehicle	Water	
Positive control	Not conducted in parallel with the test substance, but provided as a separate reliability check previously conducted in the test laboratory using α-hexylcinnamaldehyde	
INDUCTION PHASE	Induction Concentration:	
	Intradermal	1%
	Topical	5%
Signs of Irritation	Signs of necrosis and erythema (grade 3) on intradermal injection were observed in all test animals. Signs of erythema (grade 1) were noted in 4 test animals after topical induction.	
CHALLENGE PHASE	Topical	5%
Remarks - Method	The purity of the test substance was reported as 76.5%. In the main study, ten animals were intradermally injected with 1% and epidermally exposed to 5% of the test substance. Five control animals were similarly treated with vehicle. Two weeks after the epidermal application all test and control animals were challenged with 5% test substance and the vehicle respectively.	

RESULTS

Animal	*Challenge Concentration (%)*	*Number of Animals Showing Skin Reactions after Challenge* *24 h*	*48 h*
Test Group	5	0	0
Control Group	5	0	0

Remarks - Results	No signs of irritation were noted at challenge with the test substance at 5% concentration.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	WIL (2013)

B.7. Repeat dose toxicity (14 day dose range finding study)

TEST SUBSTANCE	Notified chemical
METHOD	14-Day dose range finding study according to: OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents EC Council Regulation No 440/2008 B.7 Repeated Dose (28 Days) Toxicity (Oral)
Species/Strain	Rat/Wistar Crl: WI(Han)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 14 days Dose regimen: 7 days per week Post-exposure observation period: none
Vehicle	Water
Remarks - Method	The purity of the substance was reported as 76.5%.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	3 M/3 F	0	0/6
Low Dose	3 M/3 F	120	0/6
Mid Dose	3 M/3 F	300	0/6
High Dose	3 M/3 F	750	0/6

Mortality and Time to Death
No mortality occurred at any dose level during the study.

Clinical Observations
Animals in the high dose group treated at 750 mg/kg bw/day showed treatment-related clinical signs, predominantly including slight piloerection, slight salivation, moderate salivation, and moving the bedding.

During the study, body weights of all groups were within the normal range. No considerable effect on food consumption was found.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Clinical Biochemistry
At the end of the treatment, mean values of alkaline phosphatase in the male test animals were dose-dependently increased. However, the increased values were in the range of historical control data. In the female animals, aspartate-aminotransferase, alanine-aminotransferase and alkaline phosphatase mean values of the low dose group (120 mg/kg bw/day) were slightly increased when compared to the control group. These findings were assumed incidental by the study authors. A slight decrease in creatinine of the females in the high dose group (750 mg/kg bw/day) was recorded. The toxicological meaning of this decrease was not clear.

Haematology
At the end of the treatment period, amount of red blood cells was slightly increased in male animals of the high dose group (750 mg/kg bw/day) in parallel with the slightly increased amount of haemoglobin and percentage of haematocrit. This increase was not assumed to be toxicologically relevant by the study authors. In females of the same group, amount of platelet count was slightly increased; however, this increase was not assumed to be of toxicological relevance by the study authors.

Effects in Organs
In the high dose group (750 mg/kg bw/day), absolute and relative mean weights of prostate of the male animals were decreased. Absolute and relative mean organ weights of adrenals and ovaries of the female animals were also clearly decreased in this group.

Remarks – Results
Under the conditions of the study, the repeated oral application of the test substance in rats at doses of 120, 300 and 750 mg/kg bw/day for 14 days was associated with slight signs of toxicity. Clinical symptoms were mostly noted in the high dose group, together with slightly decreased male prostate and female adrenal and ovary weights.

CONCLUSION
Based on the observations in the study, dose levels of 120, 300 and 750 mg/kg bw/day were suggested for the subsequent 28-day repeated dose oral toxicity study (see Appendix B.7).

TEST FACILITY BSL (2012a)

B.8. Repeat dose toxicity (28 day study)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-Day Oral Toxicity Study in Rodents EC Council Regulation No 440/2008 B.7 Repeated Dose (28 Days) Toxicity (Oral)
Species/Strain	Rat/Wistar Crl: WI(Han)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	Sterile water
Remarks - Method	No significant deviation of the protocol was noted. The purity of the substance was reported as 76.5%.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	5 M/5 F	0	0/10
Low Dose	5 M/5 F	120	0/10
Mid Dose	5 M/5 F	300	0/10
High Dose	5 M/5 F	750	0/10
Control Recovery	5 M/5 F	0	0/10
High Dose Recovery	5 M/5 F	750	0/10

Mortality and Time to Death

No mortality occurred at any dose level during the study.

Clinical Observations

No treatment-related clinical signs were observed in the test male and female animals during the study.

Predominant spontaneous clinical signs observed occasionally in the test animals especially in mid dose (300 mg/kg bw/day) and high dose (750 mg/kg bw/day) groups were moving the bedding, slight to moderate piloerection, nasal discharge and slight to severe salivation. In the absence of effects on general health parameters, these clinical signs were not considered by the study authors to be treatment-related.

Compared with the controls, statistically significant increase in mean body weight gain in the animals of the high dose group was recorded. However, the body weight gain of each treatment group was within the normal range of variation. No other statistically significant effect was observed on body weight and body weight gain in treatment groups during the study.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Clinical Biochemistry

At the end of the treatment and recovery period, no statistically significant difference was observed in the clinical biochemistry parameters in the treatment groups when compared with the controls. All clinical biochemistry parameter values in the test animals were within the normal range of variation.

Haematology and Blood Coagulation

In male test animals, at the end of the treatment, statistical analysis of haematology data revealed no significant difference when compared to the controls. However, at the end of recovery, statistically significant decrease in mean corpuscular volume, mean corpuscular haemoglobin and large unstained cells was observed in high dose recovery group. Since the decrease was marginal and not observed at the end of treatment in the non-recovery high dose group, these effects were not considered by the study authors to be adverse and biologically relevant. Blood coagulation was not affected in males by the treatment.

In female test animals, at the end of the treatment and recovery, no statistically significant difference was observed in the haematology parameters except a statistically significant increase in activated partial thromboplastin time in the mid dose group (300 mg/kg bw/day) when compared with the controls. Since this increase was within the normal range of variation and lacked dose dependency, the effect was not considered by the study authors to be of toxicological significance.

All remaining haematological parameters were remained unaffected in the test animals and were within the normal range of variation.

Urinalysis

High protein and erythrocyte levels were found in the urine of several animals including control animals. All other urinary parameters were in the normal range of variation. No conspicuous differences between the dose groups and control groups were observed.

Effects in Organs

Pathology

At necropsy of the test animals, macroscopic examination revealed several gross pathological findings including yellow spot on epididymides, decreased adrenal gland, decreased pituitary gland, and fluid distension in uterus with oviduct and cervix. These effects were assumed by the study authors to be common background and not due to a systemic toxicity related to the treatment.

Organ Weight
In male test animals, statistically significant decrease in relative heart and total testes weight in all treatment groups was observed when compared with controls. As the decrease was marginal and in the absence of histopathological findings this effect was not considered by the study authors to be adverse.

In female test animals, statistically significant increase in absolute and relative liver weights in the high dose group, decrease in absolute total adrenal weights in low dose group and decrease in relative total adrenal weights in low dose and high dose groups were observed when compared with the controls. In the absence of histopathological findings and dose dependency, these effects were not considered by the study authors to be adverse.

Absolute and relative organ weight from the female test animals sacrificed at the end of recovery period remained unaffected except statistically significant decrease in relative total ovary weight in the high dose recovery group. As this effect was not observed at the end of treatment period and in the absence of histopathological findings, the effect was not considered to by the study authors be adverse and biologically relevant.

No other toxicologically significant treatment related body weight effects were noted during the study.

Histopathology
In several males and females treated at high dose of 750 mg/kg bw/day, mild to moderate focally extensive submucosal oedema and/or minimal to mild diffuse epithelial hyperplasia were observed in the nonglandular part of the stomach. In one single female rat treated at mid dose of 300 mg/kg bw/day, the nonglandular part of the stomach showed minor submucosal oedema and diffuse submucosal mixed cell infiltration. These gastric findings were considered by the study authors to be related to local irritation effect of the test substance. These effects were resolved during the recovery period.

No other toxicologically significant treatment related histopathology effects were recorded during the study.

Remarks – Results
The study authors concluded that, under the conditions of the study, the repeated oral administration of the test substance to male and female rats was not associated with major signs of toxicity or mortality at the dose levels designated.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 750 mg/kg bw/day in this study, the highest dose level tested, based on no major signs of toxicity or mortality at all dose levels tested.

TEST FACILITY BSL (2013a)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical	
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Council Regulation No 440/2008 B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure and pre incubation procedure	
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 and TA102	
Metabolic Activation System	S9 microsomal fraction of male rat liver induced with phenobarbital and β-naphthoflavone	
Concentration Range in Main Test	a) With metabolic activation:	1.00 – 5,000 µg/plate
	b) Without metabolic activation:	0.316 – 5,000 µg/plate
Vehicle	Dimethyl sulfoxide (DMSO)	
Remarks - Method	No significant deviation of the protocol was recorded. The purity of the test substance was reported as 76.5%. Preliminary test for cytotoxicity was conducted on strains TA98 and TA100. Negative control was sterile water and solvent control was DMSO. Positive controls were: - with metabolic activation: 2-aminoanthracene	

- without metabolic activation: sodium azide (TA1535, TA100); methylmethanesulfonate (TA102); 4-nitro-o-phenylene-diamine (TA98, TA1537)

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 100	≥ 100	> 5,000	Negative
Test 2	≥ 316	≥ 31.6	> 5,000	Negative
Present				
Test 1	≥ 316	≥ 316	> 5,000	Negative
Test 2	≥ 1,000	≥ 316	> 5,000	Negative

Remarks - Results: No biologically relevant increases in revertant colony numbers of any of the five tester strains were observed during the test in either the presence or absence of metabolic activation. The positive controls induced a distinct increase of revertant colonies during the study indicating the validity of the test system.

CONCLUSION: The notified chemical was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY: BSL (2012b)

B.10. Genotoxicity – *in vitro*

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 476 *In vitro* Mammalian Cell Gene Mutation Test.
EC Commission Regulation No 440/2008 B.17 Mutagenicity - *In vitro* Mammalian Cell Gene Mutation Test.

Species: Chinese Hamster
Cell Type/Cell Line: V79
Metabolic Activation System: S9 microsomal fraction of male rat liver induced with phenobarbital and β-naphthoflavone
Vehicle: Cell culture medium (MEM for 4 hour treatment and MEM with 10% FBS for 20 hour treatment)
Remarks - Method: No significant deviation of the protocol was noted. The purity of the test substance was reported as 76.5%. The V79 cells were tested with the test substance for potential to induce mutations at the HPRT locus.

Vehicle and positive controls (ethylmethanesulfonate and 7,12-dimethylbenz(a)anthracene) were run concurrently with the test substance.

Metabolic Activation	*Test Substance Concentration (μM)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test 1	2.5, 5, 10, 15, 20, 25, 32, 34, 38	4 h	48-72 h	1 week
Test 2	25, 50, 60, 70, 80, 90, 100, 110, 120, 140	20 h	48-72 h	1 week
Present				
Test 1	20, 40, 60, 80, 100, 125, 150, 175, 200, 225	4 h	48-72 h	1 week
Test 2	15, 30, 70, 110, 170, 200, 210, 220, 250	4 h	48-72 h	1 week

Note: all cultures were selected for metaphase analysis

RESULTS

Metabolic Activation	*Test Substance Concentration (μM) Resulting in: Cytotoxicity in Preliminary Test*	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 500	≥ 25	> 38	Negative
Test 2	≥ 100	≥ 90	> 140	Equivocal
Present				
Test 1	≥ 100	≥ 125	> 225	Negative
Test 2	-	≥ 170	> 250	Negative

Remarks - Results: The highest mutation rate (compared to the negative control) was recorded as 8.75 at a test concentration of 50 μM with a relative cell growth of 95.4% when exposed to the test substance for 20 hours without metabolic activation. This mutation rate, together with a few mutation rates observed in the same experiment, exceeded the critical threshold value of 3.0. The study authors stated that this was due to very low mutant values recorded for the negative controls of the experiment. The mutation frequencies observed however were within the historical data range. Therefore, these exceedances of mutation rate were not considered by the study author to be biologically relevant.

CONCLUSION: There was no clear evidence of clastogenicity for the notified chemical to Chinese Hamster V79 cells treated *in vitro* under the conditions of the test.

TEST FACILITY: BSL (2013b)

B.11. Genotoxicity – *in vivo*

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 474 Mammalian Erythrocyte Micronucleus Test
EC Council Regulation No 440/2008 B.12 Mutagenicity - Mammalian Erythrocyte Micronucleus Test

Species/Strain: Mouse/NMRI
Route of Administration: Oral – gavage
Vehicle: Sterile water
Remarks - Method: No significant deviation of the protocol was noted. The purity of the test substance was reported as 76.5%.

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Sacrifice Time (hours)*
I (vehicle control)	5 M/5 F	0	44
II (low dose)	5 M/5 F	400	44
III (mid dose)	5 M/5 F	1,000	44
IV (high dose)	5 M/5 F	2,000	44
V (positive control, CP)	5 M/5 F	40	44
VI (vehicle control)	5 M/5 F	0	68
VII (high dose)	5 M/5 F	2,000	68

CP = cyclophosphamide

RESULTS

Doses Producing Toxicity: The animals treated with doses of 400 and 1,000 mg/kg bw showed no signs of systemic toxicity.

The animals treated with a dose of 2,000 mg/kg bw showed mild signs of systemic toxicity including reduction of spontaneous activity, catalepsis, constricted abdomen, piloerection and half eyelid closure.

Genotoxic Effects: Compared with negative controls, statistically significant increases of cells with micronuclei were recorded in the females treated with 2,000 mg/kg bw for either 44 h or 68 h. However, the increased values were within the

	range of the historical negative control data and therefore not regarded by the study authors to be biologically relevant.
Remarks - Results	Cyclophosphamide at 40 mg/kg bw administered through intraperitoneal injection induced a significant increase in micronucleus frequency, demonstrating the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this *in vivo* mammalian erythrocyte micronucleus test.
TEST FACILITY	BSL (2013c)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability (Analogue 1)

TEST SUBSTANCE	Analogue 1
METHOD	OECD TG 301 B Ready Biodegradability: CO2 Evolution Test.
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Carbon Dioxide ($ThCO_2$)
Remarks - Method	No significant deviations to the test protocol were reported.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
6	4-11	6	57
14	33-48	14	85
21	60-79	21	94
29*	76-93	29*	100

* Corrected for the last gas wash

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, surpassed the threshold level of 60% by 14 days (85%). Therefore, the tests indicate the suitability of the inoculums. The percentage degradation of the toxicity control surpassed the threshold level of 25% by 6 days (37%; 90% in 28 days), showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the test substance after 28 days was 76-93%, and a degradation plateau was not achieved. As the test substance is surface active, the 10-day window is not applicable. Therefore, the test substance is considered to be readily biodegradable according to the OECD (301 B) guideline.
CONCLUSION	The test substance is readily biodegradable.
TEST FACILITY	Dr U Noack-Laboratorien (2013)

C.1.2. Ready biodegradability (Analogue 2)

TEST SUBSTANCE	Analogue 2
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Dissolved/Total Organic Carbon (DOC/TOC)
Remarks – Method	The organic carbon content was not measured at the start of the test due to analyser malfunction, and the starting measurement was taken on the second day. The starting organic carbon content should be 10 mg C/L but was measured to be 8.7 mg C/L on the second day. The deviation was not deemed to have had a significant impact on the validity or integrity of the study.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
6	21.4-21.9	6	24.5
14	64.4-64.6	14	77.1
20	77.7-78.2	20	87.3
28	83.7-84.4	28	91.6
29	84.5-85.2	29	92.3

Remarks – Results: All validity criteria for the test were satisfied. The percentage degradation of the reference compound, surpassed the threshold level of 60% by 12 days (68.2%). Therefore, the tests indicate the suitability of the inoculums. The degree of degradation of the test substance after 28 days was > 83%, and a degradation plateau was not achieved. As the test substance is surface active, the 10-day window is not applicable. Therefore, the test substance is considered to be readily biodegradable according to the OECD (301 B) guideline.

CONCLUSION: The test substance is readily biodegradable.

TEST FACILITY: LISEC (1997)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish (Analogue 2)

TEST SUBSTANCE: Analogue 2

METHOD: EC Directive 92/69/EEC Method C.1 – Semi-Static.

Species: *Brachydanio rerio* (zebrafish)
Exposure Period: 96 hours
Auxiliary Solvent: None
Water Hardness: 217 mg $CaCO_3$/L
Analytical Monitoring: None
Remarks – Method: No significant deviations to the test protocol were reported. The test was carried out as a semi-static test with daily replacement of the test solutions and with 2 × 10 fishes (duplicate test solutions) for each concentration.

RESULTS

Nominal Concentration mg/L	*Number of Fish*	*Mortality (%)*				
		0h	*24 h*	*48 h*	*72 h*	*96 h*
Control	2 × 10	0	0	0	0	0
3.2	2 × 10	0	0	0	0	0
5.6	2 × 10	0	0	0	0	0
10	2 × 10	0	100	100	100	100
18	2 × 10	0	100	100	100	100
32	2 × 10	0	100	100	100	100

LC50: 7.5 mg/L at 96 hours
NOEC: 5.6 mg/L at 96 hours
Remarks – Results: All validity criteria for the test were satisfied. The test solutions were not renewed during the 96 h test period. The 96 h LC50 and NOEC for fish were calculated to be 7.5 mg/L and 5.6 mg/L, respectively, based on the nominal concentration.

CONCLUSION: Under the study conditions the test substance is considered to be toxic to fish.

TEST FACILITY TNO (1991)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static.

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	160-180 mg $CaCO_3$/L
Analytical Monitoring	LC-MS/MS
Remarks - Method	The definitive test was conducted at the nominal concentrations of 2.5, 5, 10, 20, and 40 mg/L of the test substance, which corresponds to 2.03, 4.05, 8.1, 16.2, and 32.4 mg/L of the active components. A total of 20 daphnids (5 daphnids/replicate across 4 replicates) were used. No significant deviations to the test protocol were reported.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative Immobilised (%)*	
Nominal	*Actual*[*]		*24 h*	*48 h*
Control	Control	20	0	0
2.03	1.251	20	0	0
4.05	2.687	20	15	20
8.1	5.3	20	25	75
16.2	9.92	20	50	90
32.4	19.41	20	75	100

[*] Combined measured values for the C12- and C14-fractions

EC50	5.91 mg/L at 48 hours
NOEC	2.03 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. The test solutions were not renewed during the 48 h test period. The actual concentrations of the test substance were measured at 0 and 48 hours during the 48 h test period. The 48 h EC50 and NOEC for daphnids were determined to be 5.91 mg/L and 2.03 mg/L respectively, based on the nominal concentration of the active components.

CONCLUSION Under the study conditions, the notified chemical is considered to be toxic to aquatic invertebrates.

TEST FACILITY Dr U Noack-Laboratorien (2014a)

C.2.3. Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 211 *Daphnia magna* Reproduction Test – Semi-Static.

Species	*Daphnia magna.*
Exposure Period	21 days
Auxiliary Solvent	None
Water Hardness	160-180 mg $CaCO_3$/L
Analytical Monitoring	LC-MS/MS
Remarks - Method	The definitive test was conducted at the nominal concentrations of 0.5, 1, 2, 4, and 8 mg/L of the test substance, which corresponds to 0.405, 0.81, 1.62, 3.24, and 6.48 mg/L of the active components. A total of 20 daphnids (5 daphnids/replicate across 4 replicates) were used. No significant deviations to the test protocol were reported.

RESULTS

	Nominal Test Concentration (mg/L)					
	Control	*0.405*	*0.81*	*1.62*	*3.24*	*6.48*
Total No. of Offspring Released by Survived *Daphnia*	110 ± 8	105 ± 10	105 ± 10	111 ± 13	101 ± 17	—
Body Lengths of Surviving Adults (mm)	5.15	4.88	5.03	5.05	5.09	—
Survival (%)	100	100	100	100	80	0

NOEC 3.24 mg/L at 21 days

Remarks - Results All validity criteria for the test were satisfied. The test solutions were renewed three times per week during the 21 d test period. The actual concentrations of the test substance were measured at 0 and 21 days during the 21 d test period. No sub-lethal effects as determined by body lengths of the surviving adults were observed up to 200 mg/L concentration of the test substance. The 21 d EC50 and NOEC were determined to be 4.32 mg/L and 3.24 mg/L respectively, based on nominal concentrations.

CONCLUSION Under the conditions of the study, the notified chemical is not considered to be harmful to aquatic invertebrates on a chronic basis.

TEST FACILITY Dr U Noack-Laboratorien (2014b)

C.2.4. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test.

Species *Desmodesmus subspicatus* (green alga)

Exposure Period 72 hours

Concentration Range Nominal: 1-100 mg/L
Actual: 0.596-57.2 mg/L

Auxiliary Solvent None

Water Hardness 0.24 mmol Ca + Mg/L

Analytical Monitoring LC-MS/MS

Remarks - Method No significant deviations to the test protocol were reported.

RESULTS

Biomass		*Growth*	
E_bC50 *mg/L at 72 h*	*E_bC10* *mg/L*	*E_rC50* *mg/L at 72 h*	*E_rC10* *mg/L*
13.3	< 1	60.1	8.88

Remarks - Results All validity criteria for the test were satisfied. The test solutions were not renewed during the 72 h test period. The actual concentrations of the test substance were measured at 0 and 72 hours during the 72 h test period. The 72 h E_bC50 and E_rC50 were determined to be 13.3 mg/L and 60.1 mg/L respectively, based on the nominal concentration. The 72 h E_bC10 and E_rC10 were determined to be < 1 mg/L and 8.88 mg/L, respectively.

CONCLUSION Under the study conditions, the notified chemical is considered to be harmful to algae on both an acute or chronic basis.

TEST FACILITY Dr U Noack-Laboratorien (2015b)

C.2.5. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Activated sludge
Exposure Period	3 hours
Concentration Range	Nominal: 10-1000 mg/L Actual: Not determined
Remarks – Method	No significant deviations to the test protocol were reported. Copper (II) sulphate pentahydrate was used as the reference control. The respiration rate was determined by measurement of Biochemical Oxygen Demand during the test after 3 hours of exposure.
RESULTS	
IC50	171 mg/L
NOEC	10 mg/L
Remarks – Results	All validity criteria for the test were satisfied. No significant inhibition of respiration rates were observed at 10 and 32 mg/L concentrations of the test substance; however, > 20% inhibition was observed at 100 mg/L concentration of the test substance and higher. The 3 h EC50 was determined to be 171 mg/L based on nominal concentrations. The test substance is not considered to be inhibitory to sludge microbial activity up to the limit of its water solubility.
CONCLUSION	The notified chemical is not inhibitory to microbial activity.
TEST FACILITY	Dr U Noack-Laboratorien (2015a)

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