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April 2016

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

D-Glucitol, 1-deoxy-1-(methylamino)-, *N*-C_{8-10} acyl derivs. (INCI Name: Capryloyl/Caproyl 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:

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Director
NICNAS

TABLE OF CONTENTS

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/1565	Clariant (Australia) Pty Ltd	D-Glucitol, 1-deoxy-1-(methylamino)-, *N*-C_{8-10} acyl derivs. (INCI Name: Capryloyl/Caproyl Methyl Glucamide)	Yes	< 20 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*
Acute toxicity, oral (Category 4)	H302 – Harmful if swallowed
Acute toxicity, inhalation (Category 4)	H332 – Harmful if inhaled
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(s):

R22: Harmful if swallowed
R20: Harmful by inhalation

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:
  - H302: Harmful if swallowed
  - H332: Harmful if inhaled
  - 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.

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:
  - Coveralls
  - Eye protection
  - Impervious gloves
  - 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.

- Formulators should take into account the potential for the notified chemical to cause serious eye damage when manufacturing consumer products containing the notified chemical.

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 3% in rinse-off cosmetic products or 5% 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 Clear (product containing the notified chemical at ~50% concentration)
GlucoPure Wet (product containing the notified chemical at ~50% concentration)

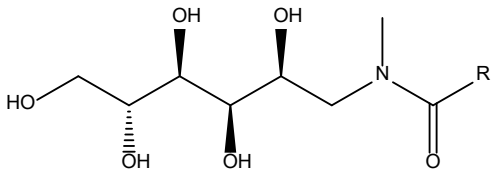
CAS NUMBER
1591782-62-5

CHEMICAL NAME
D-glucitol, 1-deoxy-1-(methylamino)-, *N*-C_{8-10} acyl derivs.

OTHER NAME(S)
Capryloyl/Caproyl Methyl Glucamide (INCI Name)

MOLECULAR FORMULA
Unspecified

STRUCTURAL FORMULA



Where R = C7 or C9 alkyl group

MOLECULAR WEIGHT
321.4 to 349.5 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 85%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: white powder

Property	Value	Data Source/Justification
Melting Range	59 – 64 °C	Measured
Boiling Point	Decomposes without boiling	Measured
Density	1,160 kg/m^3 at 20.6 °C	Measured
Vapour Pressure	1.1 × 10^{-9} kPa at 25 °C	Measured
Water Solubility	1.86 ± 0.23 g/L at pH 9.36 at 20 °C 1.75 ± 0.22 g/L at pH 9.36 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 = 1.43 at 20 °C	Calculated from measured solubilities in n-octanol and water; expected to partition to phase boundaries based on surfactant properties
Surface Tension	31.32 nM/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
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 Clear and GlucoPure Wet, at a concentration of approximately 50% in aqueous solution.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	< 20	< 20	< 20	< 20	< 20

PORT OF ENTRY
Sydney, Melbourne and Brisbane

TRANSPORTATION AND PACKAGING
The products (GlucoTain Clear and GlucoPure Wet) containing the notified chemical at ~50% concentration will be imported in 200 kg or 1,000 kg PE drums and 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 ≤ 3% concentration and in household cleaning products (such as dishwashing liquids and hard surface cleaners) at ≤ 5% concentration. The finished products containing the notified chemical will not be applied by spray.

OPERATION DESCRIPTION
The imported products containing the notified chemical, GlucoTain Clear and GlucoPure Wet, 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 Clear or GlucoPure Wet 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 ≤ 5% 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 50% concentration, only in the unlikely event of an 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 ≤ 50% 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 ≤ 5% concentration may occur in professions where the services provided involve the application 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 ≤ 5% concentration through the use of rinse-off cosmetic and 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). 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 (eńHealth, 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	3	0.01	100	0.0038
Shampoo	10,460	3	0.01	100	0.0490
Conditioner	3,920	3	0.01	100	0.0184
Shower gel	18,670	3	0.01	100	0.0875
Hand wash soap	20,000	3	0.01	100	0.0938
Total					**0.2524**

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	5	1980	0.01	0.01	0.007	100	0.0015
Dishwashing liquid	3	5	1980	0.009	0.01	0.03	100	0.0125
All-purpose cleaner	1	5	1980	1	0.01	0.007	100	0.1083
Total								**0.1224**

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	5	0.95	10	100	0.1707
Fabric softener	90	5	0.95	10	100	0.0668
Total						**0.2375**

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 0.6123 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 = 500 mg/kg bw; harmful
Rat, acute oral toxicity*	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity**	1 mg/L/ 4 h < LC50 < 5 mg/L/4 h; harmful
Skin irritation (*in vitro*)	non-irritating
Eye irritation (*in vitro*)	severely irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 250 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

*Test substance 50% notified chemical in water/propylene glycol
**Test substance 50% notified chemical in water

Toxicokinetics

No toxicokinetic data was provided for the notified chemical. The notified chemical has a molecular weight of 321.4 to 349.5 Da and a log Pow of 1.43 at 20 °C, indicating potential for absorption. The notified chemical is a surfactant and therefore may have the ability to enhance dermal penetration of other chemicals in the formulations.

Acute toxicity

Based on acute toxicity studies in rats the notified chemical is harmful via the oral route but is of low toxicity via the dermal route. In an acute inhalation toxicity study in rats the notified chemical at 50% concentration in water was found to be harmful. In the study, three out of six rats died within 3 days of post-treatment at an exposure concentration of 5.1 mg/L. No deaths occurred at an exposure concentration of 1.1 mg/L. Based on the results of this study, the notified chemical is at least harmful via inhalation.

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. However, an *in vitro* study on eye irritation using bovine corneal opacity and permeability test method demonstrated that the notified chemical is likely to be a severe eye irritant.

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

Repeated dose toxicity

A 28-day repeated dose oral toxicity study on the notified chemical in rats was provided. Mortality occurred at a dose level of 500 mg/kg bw/day in 5 of 20 test animals. The causes of the deaths were unclear. Toxicity of the notified chemical at this dose level was reflected in slightly attenuated body weight development, increased neutrophil and decreased lymphocyte rates, macroscopic findings in gastrointestinal tract and histopathological findings in stomach, trachea, lung, spleen, thymus and bone marrow. No treatment related adverse effects were observed at the lower doses. Based on microscopic findings in the stomach, trachea, lung, spleen, thymus and bone marrow, the NOAEL was established at 250 mg/kg bw/day by the study authors for the notified chemical.

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***
Acute toxicity, oral (Category 4)	H302 – Harmful if swallowed
Acute toxicity, inhalation (Category 4)	H332 – Harmful if inhaled
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(s):

R22: Harmful if swallowed
R20: Harmful by inhalation

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Based on the studies provided, the notified chemical is harmful via the oral route and if inhaled, and is severely irritating to eyes.

Reformulation

Dermal, ocular and potentially inhalation exposure to the notified chemical at up to 50% 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 ≤ 5% 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 ≤ 5% 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. ≤ 3%) and use in rinse-off cosmetics only, significant eye irritation effects are not expected.

Risk of repeated exposure

Members of the public may experience repeated exposure to the notified chemical up to 5% concentration through the use of a range of rinse-off cosmetics 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 0.6123 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 250 mg/kg bw/day established in a 28 day oral repeat dose toxicity study on the notified chemical, the margin of exposure (MoE) was calculated to be 408. 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, the risk to the public from use of the notified chemical at ≤ 3% in rinse-off cosmetics and ≤ 5% 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 a biodegradability study, the notified chemical is considered to be readily biodegradable (76-93% in 28 days). 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 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	20,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	20,000	kg/year
Days per year where release occurs	365	days/year

Daily chemical release:	54.49	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:	12.116	µg/L
PEC - Ocean:	1.212	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 12.116 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 the 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

The results from ecotoxicological investigations conducted on the notified chemical 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 > 100 mg/L	Not acutely harmful to fish
Daphnia	48 h EC50 > 100 mg/L	Not acutely harmful to *Daphnia*
Algae	72 h E_rC50 > 100 mg/L	Not acutely harmful to algae
Inhibition of Bacterial Respiration	3 h IC50 > 1000 mg/L	Not inhibitory to bacterial respiration
Chronic toxicity		
Fish	9 d NOEC = 200 mg/L	Not chronically harmful to fish
Daphnia	21 d NOEC = 50 mg/L	Not chronically harmful to *Daphnia*
Algae	72 h E_rC10 > 100 mg/L	Not chronically harmful to algae

Based on the above ecotoxicological endpoints for the notified chemical, it is not expected to be harmful to aquatic life. Therefore, the notified chemical is not formally classified under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009) for acute and chronic toxicities.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive chronic ecotoxicological endpoint for daphnids. A safety factor of 10 was used given acute and chronic endpoints for three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
NOEC (*Daphnia*, 21 d)	50	mg/L
Assessment Factor	10	
Mitigation Factor	1.00	
PNEC:	5,000	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	12.116	5,000	**0.002**
Q - Ocean	1.212	5,000	**< 0.001**

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. 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 Range 59 – 64 °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) 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 without boiling
Test Facility	Siemens AG (2013a)

Relative Density 1,160 kg/m^3 at 20.6 °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 5.5×10^{-10} kPa at 20 °C
1.1×10^{-9} kPa at 25 °C
2.2×10^{-8} kPa at 50 °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 1.86 ± 0.23 g/L at pH 9.36 at 20 °C
1.75 ± 0.22 g/L at pH 9.36 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 47 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 = 1.43 at pH 9.36 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 31.32 nM/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: 998 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 45 – 80 °C. No autoignition temperature was observed up to the maximum test temperature of 403 °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 report as 93.9%. 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	3/3
Step 2	3 F	300	0/3
Step 3	3 F	300	0/3

LD50	LD50 cut-off was determined at 500 mg/kg bw.
Signs of Toxicity	All animals of step 1 treated at the dose level of 2,000 mg/kg bw were found dead 4 to 6 hours after the treatment. The most relevant clinical findings in these animals were prone position, increased (later reduced) spontaneous activity, salivation, moving the bedding, wasp waist, eyes half closed, piloerection, respiratory sounds, tremor, lacrimation and clonic convulsions. All animals in steps 2 and 3 treated at the dose level of 300 mg/kg bw survived. The most relevant clinical findings in these animals were reduced spontaneous activity and piloerection. All symptoms were recovered by up to day 2 of the treatment.
Effects in Organs	Necropsy of the animals treated at 2,000 mg/kg bw revealed fluid content in the stomach, large size and abnormal content (gaseous distension, fluid filled) in duodenum, jejunum and ileum, discoloured and pale lungs with smooth consistency and red or uncoloured nasal discharge.
Remarks - Results	No treatment-related macroscopic findings were observed in the animals treated at 300 mg/kg bw.
CONCLUSION	The notified chemical is harmful via the oral route.
TEST FACILITY	BSL (2013a)

B.2. Acute toxicity – oral (2)

TEST SUBSTANCE	Notified chemical (50% in water/propylene glycol)
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 concentration of the notified chemical in the test substance was reported as 50%. 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	0/3

LD50	> 2,000 mg/kg bw (equivalent to > 1,000 mg/kg bw for the notified chemical)
Signs of Toxicity	All animals in steps 1 and 2 treated at the dose level of 2,000 mg/kg bw (equivalent to 1,000 mg/kg bw of the notified chemical) survived showing treatment related signs of toxicity on the day of administration in all animals. The clinical signs of toxicity remained up to 2 days post-treatment in 1 of the 6 test animals. The most relevant clinical findings were persistence in a fixed body posture, reduced spontaneous activity, prone position, moving the bedding, slow movements, kyphosis (hunched appearance), wasp waist, piloerection, eyes half closed and respiratory noise. Symptoms recovered within 24 hours in 5 of the 6 test animals and lasted for 3 days in the remaining rat.
Effects in Organs	At necropsy, no treatment-related macroscopic findings were observed in the animals treated with the test substance.
Remarks - Results	Throughout the 14-day observation period, the body weight gain of the test animals was within the normal range of variation.

CONCLUSION The notified chemical at 50% concentration in water/propylene glycol is of low toxicity via the oral route.

TEST FACILITY BSL (2014a)

B.3. 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 93.9%.

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, eschar, necrosis, wounds, white coloured macules and dark macules were observed in test animals. All signs were reversible within the observation period except for 2 males and 1 female.
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 toxicity, although local irritation effects were recorded.

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

TEST FACILITY BSL (2013b)

B.4. Acute toxicity – inhalation

TEST SUBSTANCE Notified chemical (50% in water)

METHOD OECD TG 436 Acute Inhalation Toxicity – Acute Toxic Class Method
Species/Strain Rat/Crl:WI(Han)
Vehicle Water
Method of Exposure Nose-only exposure
Exposure Period 4 hours
Physical Form Liquid aerosol (nebulised)
Particle Size (MMAD) 2.85 μm at 5 mg/L
2.6 μm at 1 mg/L
Remarks - Method No significant deviation of protocol was noted. The concentration of the notified chemical in the test substance was reported as 50%.

RESULTS

Group	*Number and Sex of Animals*	*Concentration (mg/L)*		*Mortality*
		Nominal	*Actual*	
1	3 F/3 M	9.1	5.1 ± 0.13	3/6
2	3 F/3 M	1.9	1.1 ± 0.03	0/6

LC50 1 mg/L/ 4 hours < LC50 < 5 mg/L/4 hours
Signs of Toxicity At 5 mg/L, 2 males and 1 female were found dead within 3 days post-treatment. The animals in the treatment group showed slow breathing and one animal was restless during the exposure. After exposure, lethargy, hunched posture, abnormal gait, laboured respiration, rales, chromodacryorrhoea and/or ptosis was noted for the animals between Days 1 and 9. One female showed hunched posture up to Day 14.

At 1 mg/L, no death of the test animals occurred during the study. No clinical signs were noted during exposure. After exposure, hunched posture was seen in all animals between Days 1 and 4. One male showed laboured respiration and ptosis between Days 1 and 2.
Effects in Organs Macroscopic post mortem examination of the males found dead revealed several dark red foci on the lungs or foamy contents in the lungs. Examination of the female found dead and of the surviving animals at termination did not reveal any abnormalities.
Remarks - Results For all test animals, overall body weight gain was within the range expected during the study.

CONCLUSION The notified chemical at 50% concentration in water is harmful via inhalation.

TEST FACILITY WIL (2014)

B.5. 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 93.9%.

RESULTS

Test material	*Mean OD_{550} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	0.621	100	7.5
Test substance	0.622	100.2	17.6
Positive control	0.177	28.5	2.9

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 (2013c)

B.6. 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 at 93.9%.

RESULTS

Test material	*Mean opacity of triplicate tissues*	*Mean permeability of triplicate tissues (OD490)*	*IVIS*
Vehicle control	1.00	0.011	1.17
*Test substance**	99.67	2.087	130.97
*Positive control**	207.33	1.938	236.40

IVIS (in vitro irritancy score) = mean opacity value + (15 × mean permeability OD490 value)
*Corrected for background values

Remarks - Results IVIS of the test substance was greater than 55, the cut-off value for identifying test chemicals as inducing serious eye damage (GHS Category 1).

CONCLUSION The notified chemical was a severe eye irritant under the conditions of the test.

TEST FACILITY BSL (2013d)

B.7. Skin sensitisation

TEST SUBSTANCE Notified chemical

METHOD OECD TG 406 Skin Sensitisation – Guinea Pig Maximisation Test
EC Directive 96/54/EC 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 Control Group: 5

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 0.5% Topical 5%
Signs of Irritation	Signs of necrosis and erythema (grade 3) on intradermal injection were observed in all test animals. No signs of irritation were noted in test animals after topical induction.
CHALLENGE PHASE	Topical 5%
Remarks - Method	The purity of the test substance was reported as 85.5%. In the main study, ten animals were intradermally injected with 0.5% 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	0	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.8. Repeat dose toxicity

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	Water
Remarks - Method	No significant deviation of the protocol was noted. The purity of the substance was reported at 93.9%.

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	100	0/10
Mid Dose	5 M/5 F	250	0/10
High Dose	5 M/5 F	500	1/10
Control Recovery	5 M/5 F	0	0/10
High Dose Recovery	5 M/5 F	500	4/10

Mortality and Time to Death

At 500 mg/kg bw/day mortality occurred in a total of 5/20 animals (1/10 male and 4/10 female):

- One male was euthanized for animal welfare reasons on study day 12.
- One female was found dead on study day 13.
- Two females were euthanized for animal welfare reasons on study day 18.
- One female was euthanized for animal welfare reasons on study day 22.

No mortality occurred at dose levels of 100 and 250 mg/kg bw/day.

Clinical Observations

There were no clinical signs of systemic toxicity.

During the treatment period, immediately after administration, the transient behaviour of moving the nose through the bedding was observed at 100, 250 and 500 mg/kg bw/day in a dose dependent manner. At the low dose, a few animals but at the medium and high dose all animals were affected. In some animals the behaviour was associated with slight to marked salivation, more frequently and more prominently at the mid and high dose levels. The study authors considered that these findings were associated with oral gavage and were not assumed to be a sign of systemic toxicity.

At 500 mg/kg bw/day piloerection was observed in some female animals and one male animal on single or occasional days of the treatment period. At 100 mg/kg bw/day one animal was affected on a single day. The study authors considered that the piloerection was related to the local irritant effect of the test substance and was not assumed to be a sign of systemic toxicity.

Respiratory sounds were noted at all treatment dose levels in a dose-dependent manner during the treatment but were not noted during the recovery period. Abnormal breathing was observed in a single male animal treated at 500 mg/kg bw/day on a single day. The study authors considered that these findings were possibly associated with accidental inhalation of the test substance by regurgitation.

Occasionally, reduced spontaneous activity, hardened abdomen and diarrhoea were observed in dosed animals and mostly during the last treatment week, transiently over periods of a few days. The study authors assumed that these findings were not related to systemic toxicity but were possibly related to a local effect.

No test substance related body weight effect was observed at dose levels of 100 or 250 mg/kg bw/day. A tendency towards a slightly attenuated body weight gain was observed at 500 mg/kg bw/day level. At the end of the treatment period, this effect was not statistically significant. During the recovery period, the body weight effect was recovered. In correlation to the attenuated body weight gain observed at 500 mg/kg bw/day, food consumption in the group was slightly but not statistically significantly lower than that in the control group during the study.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Clinical Biochemistry

At the end of the treatment period an increased total bile acid (TBA) value of 123 µmol/L was observed in 1 male animal at the dose level of 500 mg/kg bw/day. Histopathologically, this finding was associated with minimal inflammatory foci in the liver and a relation to the treatment cannot be ruled out.

No other biologically relevant effects on parameters of clinical biochemistry were noted during the study.

Haematology and Blood Coagulation

At the dose level of 500 mg/kg bw/day, in female test animals the rate of neutrophils was slightly but statistically significantly increased and the rate of lymphocytes was slightly but statistically significantly decreased when compared to control groups at the end of the treatment period. Monocytes were also slightly but not statistically significantly increased. These effects were not observed at the end of the recovery period.

Slightly but statistically significantly higher mean corpuscular haemoglobin concentration (MCHC) in male animals of the high dose group at the end of the recovery period was observed but was assumed by the study authors to be of no biologically relevance.

Urinalysis

No significant treatment-related effects were observed on urinary parameters analysed during the study.

Effects in Organs

Pathology

Following findings were recorded for the animals that died during the study:

1. In the male euthanised on study day 12, a gaseous distention of the gastrointestinal tract and small sized thymus, testes, epididymis, prostate and seminal vesicles (including coagulating glands were noted);

2. In the female dead on study day 13, a gaseous distention of the gastrointestinal tract and small sized axillary lymph nodes, oviduct and uterus, liver, spleen and thymus were found;

3. In the female euthanised on study day 22, a gaseous distention of the gastrointestinal tract was noted;

4. In the female euthanised on study day 18, gaseous distension of the colon and rectum and small sized axillary lymph nodes, spleen and thymus were noted;

5. In the other female euthanised on study day 18, a gaseous distention of the gastrointestinal tract and small sized liver, spleen, thymus and axillary lymph nodes were noted.

Histopathologically, in all animals that died prematurely, primary and adverse test substance related findings were recorded in the forestomach and consisted of forestomach erosion, ulceration, epithelial hyperplasia, hyperkeratosis and submucosal inflammation.

In survived animals examined macroscopically at the end of the treatment period, gaseous distension in the gastrointestinal tract was found in single animals at 100 or 250 mg/kg bw/day and in 2 female animals at 500 mg/kg bw/day. As this finding was also noted in the animals euthanized during the study, a relation to the test substance cannot be ruled out. This finding is possibly associated with histopathological findings in the stomach.

Organ Weight

At the end of the treatment period slightly and statistically significantly higher absolute thymus weight was found in male animals at 250 mg/kg bw/day dose level, when compared to controls. At a dose of 500 mg/kg bw/day, however, thymus weight of the male animals was ordinary. This was in contrast to a slightly but not statistically significantly decrease of thymus weight at 500 mg/kg bw/day in female animals. The study authors suggested that, whereas an increase of thymus weight possibly indicated activation of the immune system, a decrease of thymus weight was associated with atrophy found in histopathological examination.

Apart from the above findings, following observations were noted but not considered as adverse effects by the study authors:

1. Slightly and not statistically significantly increase of uterus weight was observed in all dose groups. The study authors assumed that, in the absence of histopathological findings, this finding was not an adverse effect;

2. A statistically significantly increase of relative pituitary gland weight in male animals at 100 mg/kg bw/day (23% above control group) was not assumed by the study authors to be toxicologically relevant as no considerable difference was seen in female test animals and at 250 and 500 mg/kg bw/day dose levels;

3. Slight but statistically significantly increase of relative liver and heart weight of the male test animals was found at 250 mg/kg bw/day but not at 500 mg/kg bw/day. Slight but statistically significantly decrease of brain weight was observed at 100 and 250 mg/kg bw/day in male test animals. These findings were not assumed by the study authors to be toxicologically relevant;

4. Relative seminal vesicles weight in animals treated with 250 mg/kg bw/day was statistically significantly lower than that of the control group. Only a tendency was found at the dose level of 500 mg/kg bw/day and in the absolute weight of seminal vesicles of all dose groups. This was not assumed by the study authors to be toxicologically relevant.

At the end of the recovery period no conspicuous differences in organ weight were observed between animals of the high dose group and controls. It was noted that due to the low number in the recovery group, a reliable evaluation of the organ weight data was not possible for the female test animals.

Histopathology
Under the conditions of this study, treatment-related findings were recorded in the stomach, trachea, lungs, spleen, thymus and bone marrow mainly in high-dose group animals that died during the study.

In the stomach, histopathological findings consisted of forestomach erosion, ulceration, epithelial hyperplasia, hyperkeratosis and submucosal inflammation. These findings were considered to be adverse and due to a local irritation by the test substance when administered orally.

Further microscopic findings consisted of tracheal epithelial necrosis, granulomatous inflammation in the lungs, basophilic foreign material in bronchioles and alveoli, bronchiolar necrosis and bronchiolar hyperplasia in high-dose animals. These findings were considered by the study authors to be most likely due to accidental inhalation of the test substance (basophilic foreign material) by regurgitation, and hence to be excluded from primary toxicity effect.

Secondary stress-related microscopic lesions were observed in spleen, thymus and bone marrow from high-dose animals. These consisted of splenic lymphoid atrophy, increased thymus atrophy and bone marrow atrophy. In the bone marrow, atrophy was accompanied by myeloid hypercellularity. This latter finding was considered by the study authors to be of secondary reactive nature as a consequence of the inflammatory/necrotic processes in stomach, trachea and lung.

None of the above microscopic findings were recorded in high-dose animals that survived to the end of the recovery period. Therefore, all effects were considered reversible after the recovery.

Remarks – Results
At a dose of 500 mg/kg bw/day, mortality was observed in 5/20 animals. Toxicity was also reflected in clinical signs, slightly attenuated body weight development, increased neutrophil and decreased lymphocyte rates, macroscopic findings in gastrointestinal tract and histopathological findings in stomach, trachea, lung, spleen, thymus and bone marrow. Female animals appeared slightly more susceptible to the toxic effects of the test item than males.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 250 mg/kg bw/day in this study, based on microscopic findings recorded in stomach, trachea, lung, spleen, thymus and bone marrow.

TEST FACILITY	BSL (2014b)

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:	3.16 – 5,000 µg/plate
	b) Without metabolic activation:	3.16 – 5,000 µg/plate
Vehicle	Sterile water	
Remarks - Method	No significant deviation of the protocol was recorded. The purity of the test substance was reported as 85.48%. Preliminary test for cytotoxicity was conducted on strains TA98 and TA100.	

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 2,500	≥ 1,000	> 5,000	Negative
Test 2		≥ 1,000	> 5,000	Negative
Present				
Test 1	≥ 5,000	≥ 2,500	> 5,000	Negative
Test 2		≥ 2,500	> 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 (2012)

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 85.48%. The V79 cells were tested with the test substance for potential to induce mutations at the HPRT locus.

Metabolic Activation	*Test Substance Concentration (mM)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test 1	0.50, 0.75, 1.00, 1.50, 1.60, 1.90, 1.95, 2.05	4 h	48-72 h	1 week
Test 2	0.010, 0.025, 0.05, 0.10, 0.25, 0.50, 1.00, 1.50, 1.75, 2	20 h	48-72 h	1 week
Present				
Test 1	0.25, 0.5, 1.0, 2.0, 2.5, 2.7, 2.8, 2.9, 3.0, 3.1	4 h	48-72 h	1 week
Test 2	0.20, 0.40, 0.80, 1.50, 2.10, 2.35, 2.60, 2.95	4 h	48-72 h	1 week

All cultures were selected for metaphase analysis

RESULTS

Metabolic Activation	*Test Substance Concentration (mM) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 2.0	≥ 1.90	> 2.05	Negative
Test 2	≥ 2.0	≥ 1.50	> 2	Negative
Present				
Test 1	≥ 3.0	≥ 2.50	> 3.1	Negative
Test 2	-	≥ 0.80	> 2.95	Negative

Remarks - Results	No biologically relevant increase of mutants was found after treatment with the test substance and no dose-response relationship was observed.
CONCLUSION	The notified chemical was not clastogenic to Chinese hamster V79 cells treated *in vitro* under the conditions of the test.
TEST FACILITY	BSL (2013e)

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 85.48%.

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Sacrifice Time (hours)*
I (vehicle control)	5 M/5 F	0	
II (low dose)	5 M/5 F	400	48
III (mid dose)	5 M/5 F	1,000	48
IV (high dose)	5 M/5 F	2,000	48
V (positive control, CP)	5 M/5 F	40	48
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 to moderate signs of systemic toxicity including reduction of spontaneous activity, catalepsis, constricted abdomen, piloerection and half eyelid closure. In the male dose group, two mice were found dead 24 hours after the treatment. One of the dead mice was replaced with one reserve animal. After 44 hours one additional male mouse was found dead. Directly after the deaths of the three animals, autopsies were conducted. However, no abnormalities were found and the causes of the deaths remained unclear. One female mouse of the high dose group showed strong signs of gasping directly after the application, probably as a consequence of a wrong application (intratracheal). This animal was euthanized and replaced with a reserve animal.
Genotoxic Effects	No biologically relevant increase of micronuclei was found after treatment with the test substance in any of the dose groups evaluated.
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 (2013f)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
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, sodium benzoate, surpassed the threshold level of 60% by 14 days (85%). Therefore, the tests indicate the suitability of the inoculum. 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 notified chemical is readily biodegradable.
TEST FACILITY	Dr U Noack-Laboratorien (2013a)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Static.
Species	*Danio rerio* (zebrafish)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	10-250 mg $CaCO_3$/L
Analytical Monitoring	LC-MS/MS
Remarks – Method	No significant deviations to the test protocol were reported.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*				
Nominal	*Actual*		*0 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	7	0	0	0	0	0
100	103-105	7	0	0	0	0	0

LC50	> 100 mg/L at 96 hours.
NOEC	100 mg/L at 96 hours.
Remarks – Results	All validity criteria for the test were satisfied. The test solution was not renewed during the 96 h test period. The actual concentration of the test substance was measured at 0 and 96 hours during the 96 h test period. The 96 h LC50 and NOEC for fish was determined to be > 100 mg/L and 100 mg/L, respectively, based on the nominal concentration.
CONCLUSION	Under the study conditions, the notified chemical is not considered to be harmful to fish.
TEST FACILITY	Dr U Noack-Laboratorien (2013d)

C.2.2. Chronic toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 212 Fish, Short-term Toxicity Test on Embryo and Sac-Fry Stages – Semi-static.
Species	*Danio rerio* (zebrafish)
Exposure Period	9 days (5 days post-hatch)
Auxiliary Solvent	None
Water Hardness	10-250 mg $CaCO_3$/L
Analytical Monitoring	LC-MS/MS
Remarks – Method	The definitive test was conducted at the nominal concentrations of 12.5, 25, 50, 100, and 200 mg/L of the test substance. No significant deviations to the test protocol were reported.

RESULTS

Concentration mg/L		*Number of Eggs*	*Mortality post-hatch day 5 (%)*
Nominal	*Actual*[*]		
Control	Control	30	7
12.5	9.94	30	3
25	21.78	30	3
50	46.5	30	3
100	96.4	30	0
200	202.2	30	17

[*] Combined measured values for the C8- and C10-fractions

NOEC	200 mg/L at 9 days.
Remarks – Results	All validity criteria for the test were satisfied. The test solutions were renewed every 48-72 hours during the 9 d test period. No significant differences in the short-term toxicity effects were observed between the control and the test substance. The 9 d NOEC for fish was determined to be 200 mg/L, based on nominal concentrations.
CONCLUSION	Under the study conditions, the notified chemical is not considered to be harmful to fish on a chronic basis.
TEST FACILITY	Dr U Noack-Laboratorien (2013e)

C.2.3. 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	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
100	97-102	20	0	0

EC50	> 100 mg/L at 48 hours
NOEC	100 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. The test solution was 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 daphnia was determined to be > 100 mg/L and 100 mg/L, respectively, based on the nominal concentration.
CONCLUSION	Under the study conditions, the notified chemical is not considered to be harmful to aquatic invertebrates.
TEST FACILITY	Dr U Noack-Laboratorien (2013c)

C.2.4. 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 25, 50, 100, 200, and 400 mg/L of the test substance. A total of 20 daphnids (5 daphnids/replicate across 4 replicates) were used. No significant deviations to the test protocol were reported.

RESULTS

	Test Concentration (nominal; mg/L)					
	Control	*25*	50	*100*	*200*	*400*
Total No. of Offspring Released by Survived *Daphnia*	98 ± 15	89 ± 9	104 ± 10	110 ± 15	55 ± 25	—
Body Lengths of Surviving Adults (mm)	5.13	5.23	5.33	5.40	5.33	—
Survival (%)	100	100	100	100	60	0

NOEC	50 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 200-400 mg/L and 50 mg/L, respectively, based on nominal concentrations.

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

TEST FACILITY Dr U Noack-Laboratorien (2014)

C.2.5. 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: 100 mg/L Actual: 93-100 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*
> 100	> 100	> 100	> 100

Remarks - Results All validity criteria for the test were satisfied. The test solutions were not renewed during the 72 h test period. The actual concentration of the test substance was measured at 0 and 72 hours during the 72 h test period. The 72 h E_bC50 and E_rC50 were both determined to be > 100 mg/L, based on the nominal concentration. The 72 h E_bC10 and E_rC10 were both determined to be > 100 mg/L.

CONCLUSION Under the study conditions, the notified chemical is not considered to be harmful to algae on both an acute or chronic basis.

TEST FACILITY Dr U Noack-Laboratorien (2013f)

C.2.6. 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: 10-10,000 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	> 1,000 mg/L
NOEC	500 mg/L
Remarks – Results	All validity criteria for the test were satisfied. No significant inhibition of respiration rates was observed at 1,000 mg/L. The 3 h IC50 was determined to be > 1,000 mg/L, based on nominal concentrations. The test substance is not considered to be inhibitory to sludge microbial activity.
CONCLUSION	The notified chemical is not inhibitory to microbial activity.
TEST FACILITY	Dr U Noack-Laboratorien (2013b)

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