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December 2016

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

D-Glucitol, 1,4:3,6-dianhydro-, mixed esters with octanoic acid and sorbitan

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 and Energy.

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

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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/1583	Clariant (Australia) Pty Ltd	D-Glucitol, 1,4:3,6-dianhydro-, mixed esters with octanoic acid and sorbitan	No	≤ 3 tonnes per annum	Component of cosmetic and household products

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

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 3	H402: Harmful to aquatic life

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

Based on the available information, when used at < 5% concentration in cosmetic and household products, the notified chemical is not considered to pose an unreasonable risk to public health.

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

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical during reformulation:
  - Avoid skin contact

  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.

- 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 notified chemical exceeds, or is intended to exceed, 5% in cosmetic and household products;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a component of cosmetic and household 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 notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the (M)SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT
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, use details, import volume, residual monomers/impurities and identity of manufacturer.

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, dissociation constant, flammability, autoignition temperature and acute dermal toxicity.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME
Velsan SC

OTHER NAMES
Sorbitan Caprylate (INCI name)

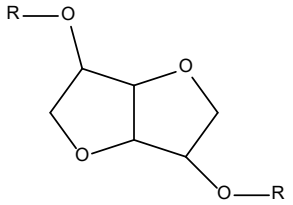
CAS NUMBER
1956326-43-4

CHEMICAL NAME
D-Glucitol, 1,4:3,6-dianhydro-, mixed esters with octanoic acid and sorbitan

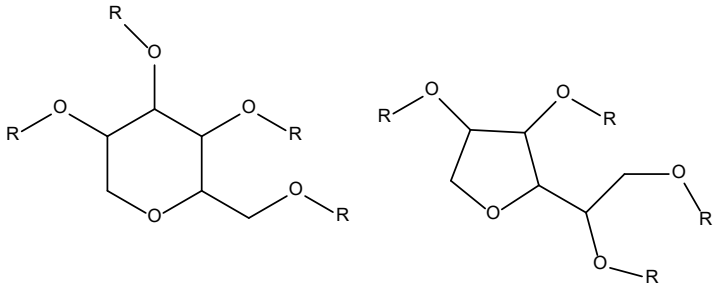
MOLECULAR FORMULA
Unspecified

STRUCTURAL FORMULA
Following are representative structures of the notified chemical (stereochemistry not shown).

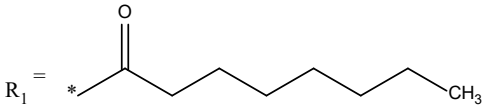
Octanoate esters derived from sorbitan



Octanoate esters derived from 1,4:3,6-dianhydro-D-glucitol



R = H or



Note: For each structure above at least one R is equal to R_1

MOLECULAR WEIGHT
272.34 - 668.94 Da

ANALYTICAL DATA
Reference IR, GC, UV and NMR spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 75%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 25 °C AND 101.3 kPa: clear amber coloured liquid

Property	Value	Data Source/Justification
Melting Point	-10 ± 3 °C	Measured
Boiling Point	Decomposes on boiling at 317 ± 13 °C at 101.3 kPa	Measured
Density	1,124.8 kg/m^3 at 20 °C	Measured
Vapour Pressure	7.63 x 10^{-6} kPa at 25 °C	Measured
Water Solubility	2.7 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Contains hydrolysable functionalities

Property	Value	Data Source/Justification
Partition Coefficient (n-octanol/water)	log Pow = 2.55 at 23 °C	Measured; expected to partition to phase boundaries based on surface activity
Surface Tension	29.1 ± 0.1 mN/m at 20 °C	Measured
Kinematic Viscosity	501 ± 13 mm^2/s at 20 °C	Measured
Adsorption/Desorption	Not determined	Expected to adsorb to soil and sediment
Dissociation Constant	Not determined	Contains no dissociable functionalities
Flash Point	> 200 °C at 101.7 kPa (closed cup)	Measured
Flammability	Not determined	Not expected to be flammable based on measured flash point
Autoignition Temperature	> 385 °C	(M)SDS
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 in Australia. The notified chemical will be imported into Australia in the neat form (at > 75%) as a liquid.

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

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

PORT OF ENTRY
Melbourne and Sydney

TRANSPORTATION AND PACKAGING
The notified chemical will be imported into Australia in 50 kg PE Packs. The notified chemical will be transported from the port of entry by road to the notifier's warehouse facilities for storage in its original packaging until transportation to the customer site. Alternatively, the notified chemical will be shipped directly from the port of entry to the customer site. The finished cosmetic products containing the notified chemical at < 5% concentration will be packaged in 250 mL, 500 mL, 750 mL, 1 L and 5 L plastic bottles.

USE
The notified chemical will be used as an emulsifier in cosmetic (including wet wipes) and household products (such as hand dishwashing liquid) at < 5% concentration. The finished products containing the notified chemical will not be applied by spray.

OPERATION DESCRIPTION
The notified chemical will be distributed to formulators for reformulation of cosmetic and household products.

Reformulation
At the customer facilities, the procedures for incorporating the notified chemical into end-use products will likely vary depending on the nature of the products formulated, and may involve both automated and manual

transfer steps. In general it is expected that the reformulation processes will involve mixing and blending operations that will be highly automated and occur in a fully enclosed systems or under conditions designed not to create aerosols or to generate airborne dusts, followed by automated filling of the reformulated products into containers of various sizes.

End-use
The finished cosmetic and household products containing the notified chemical at < 5% concentration will be used by consumers and professionals (such as beauticians and hairdressers). Depending on the nature of the product, application of products could be by hand or through the use of an applicator.

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	6	260
Warehousing	6	260
Reformulation	9	260
Retail workers	1	260
End users (professionals)	1	260

EXPOSURE DETAILS
Transport and storage
Transport and storage workers may come into contact with the notified chemical, only in the event of accidental rupture of containers.

Reformulation
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at < 100% concentration) may occur during weighing and transfer stages, blending, quality control, and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of enclosed systems and/or engineering controls designed not to create aerosols or to generate airborne dust, and through the use of appropriate PPE.

End-use
Exposure to the notified chemical (at < 5% concentration) in end-use products may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hair dressers, workers in beauty salons). The principal route of exposure will 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
Public exposure to the notified chemical is expected to be widespread and frequent through daily use of cosmetic and household products containing the notified chemical at < 5% concentration. The principal route of exposure will be dermal, while ocular exposure is also possible. As the notified chemical is not proposed to be used in spray products, inhalation exposure is not anticipated.

Data on typical use patterns of product categories in which the notified chemical may be used are shown in the following tables (SCCS, 2012; ACI, 2010). A lifetime average female body weight (BW) of 64 kg (eńHealth, 2012) was used for calculation purposes.

For the purposes of the exposure assessment via the dermal route, Australian use patterns for the various product categories were assumed to be similar to those in Europe. In the absence of dermal absorption data, a dermal absorption (DA) of 100% was assumed for the notified chemical (ECHA, 2014).

Cosmetic products (dermal exposure)

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Face cream	1540	5	1	1.2031
Make-up remover	5000	5	0.1	0.3906
Shampoo	10460	5	0.01	0.0817
Conditioner	3920	5	0.01	0.0306
Shower gel	18670	5	0.01	0.1459
Hand soap	20000	5	0.01	0.1563
Total				2.0082

C = concentration (%); RF = retention factor.
Daily systemic exposure = (Amount × C × RF × dermal absorption)/body weight

Household products (Direct dermal exposure)

Product type	Frequency (use/day)	C (%)	Contact Area (cm^2)	Product Use C (g/cm^3)	Film Thickness (cm)	Time Scale Factor	Daily systemic exposure (mg/kg bw/day)
Dishwashing liquid	3	5	1980	0.009	0.01	0.03	0.0125

Daily systemic exposure = (Frequency × C × Contact area × Product Use Concentration × Film Thickness on skin × Time Scale Factor x dermal absorption)/body weight

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above table that contain the notified chemical. This would result in a combined internal dose of 2.0207 mg/kg bw/day.

Exposure to the notified chemical from use in wet wipes is expected to be low as only a small percentage of liquid from the wet wipe is expected to be left residual on the skin. Therefore, aggregate exposure from use of the above cosmetic and household products, which assumes a conservative 100% absorption rate, is expected to be sufficiently protective to cover exposure to the notified chemical from use in wet wipes.

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 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	non-irritating
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL = 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* chromosome aberration test	inconclusive
Genotoxicity – *in vitro* gene mutation test	non-genotoxic
Genotoxicity – *in vivo* micronucleus test	non genotoxic
Rat, reproductive and developmental toxicity	NOAEL = 1000 mg/kg bw/day

Toxicokinetics, metabolism and distribution

Given the molecular weight range of the notified chemical (272.34 - 668.94 Da), there is potential for absorption across biological membranes; however, dermal absorption may be limited by the relatively high water solubility (2.7 g/L) and surfactant properties of the notified chemical.

The metabolism and kinetics of the notified chemical was evaluated by a lipase assay (BSL, 2013). The study demonstrated that the notified chemical undergoes enzymatic hydrolysis with porcine pancreatic lipase to liberate free acid at a rate 2.4 times faster than that of olive oil. The notified chemical is therefore expected to undergo ready hydrolysis in the gut to release octanoic acid and anhydrides of sorbitol.

Acute toxicity

The notified chemical was found to be of low acute oral toxicity in a study conducted in rats.

No acute dermal toxicity studies were provided for the notified chemical. Although there is potential for dermal absorption of the notified chemical based on its molecular weight, it is expected to be limited by its relatively high water solubility and surfactant properties. If absorbed the notified chemical may undergo hydrolysis to release octanoic acid and anhydrides of sorbitol, which are expected to be of low toxicological concern. Given the limited potential for dermal absorption, low toxicity of metabolites and low toxicity observed in acute and repeated dose oral toxicity studies, the notified chemical is expected to be of low acute dermal toxicity.

Irritation and sensitisation
Based on studies conducted in rabbits, the notified chemical is slightly irritating to skin but non irritating to eyes. In the skin irritation study, very slight erythema was observed in all animals. All signs of irritation were resolved at the 7 day observation period.

In a mouse local lymph node assay, the notified chemical did not show evidence of skin sensitisation when tested up to 50% concentration.

Repeated dose toxicity
In a 28-day repeated dose oral toxicity study in rats the No Observed Adverse Effect Level (NOAEL) for the notified chemical was established as 1000 mg/kg bw/day based on no test substance related adverse effects at any of the doses tested.

Mutagenicity/Genotoxicity
The notified chemical tested negative in a bacterial reverse mutation assay and negative in an *in vitro* mammalian cell gene mutation test, however the result from an *in vitro* chromosomal aberration assay was inconclusive. Although a positive response was obtained there was no dose-response relationship. In particular, a biologically relevant increase in aberrant cells at the highest dose was not obtained in both tests, with and without metabolic activation. The study authors considered the inconsistency of the results may be due to the nature of the test substance and its solubility.

The notified chemical was negative in an *in vivo* mouse micronucleus assay; however there was no evidence to indicate the test substance had reached the bone marrow. However the notified chemical and/or its metabolites are expected to be bioavailable, therefore the negative test result is considered relevant.

Based on the weight of evidence, the notified chemical is not expected to be genotoxic.

Toxicity for reproduction
In a reproductive and developmental toxicity screening test in rats, the NO(A)EL was established as 1000 mg/kg bw/day for both general toxicity and reproductive toxicity, based on no test substance related adverse effects at any of the doses tested.

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

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
The notified chemical is expected to be of low hazard presenting only as a slight skin irritant.

Reformulation
During reformulation, workers may be exposed to the notified chemical at < 75% concentration via dermal, ocular and, to a lesser extent, inhalation routes. The notifier anticipates that worker exposure will be limited through the use of engineering controls such as enclosed systems, automated processes and ventilation designed not to create airborne particulates and/or aerosols. The use of appropriate PPE (coveralls, imperious gloves and eye protection) will also be used to limit worker exposure.

End-use
Workers involved in professions where the services involve application of cosmetic products containing the notified chemical to clients (*e.g.*, hairdressers, beauty salon workers) may be exposed to the notified chemical at < 5% concentration. Dermal, and to a lesser extent, ocular exposure may occur. PPE may be employed by

workers to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, the risk to such workers is expected to be of a similar or lesser extent than that for consumers using the various products containing the notified chemical.

Therefore, under the occupational settings described, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

6.3.2. Public Health

Cosmetic and household products containing the notified chemical at < 5% concentration will be available to the public. Widespread and frequent exposure to the notified chemical through daily use of these products is anticipated. The main route of exposure is expected to be dermal with some potential for accidental ocular and oral exposure.

Local effects

The notified chemical is slightly irritating to skin. Given the low proposed use concentration (< 5%) irritation effects are not expected.

Systemic effects

The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products of 2.0207 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 1000 mg/kg bw/day derived from a 28 day repeated dose oral toxicity study and a reproductive/developmental toxicity study, the margin of exposure was estimated to be 495. A MoE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences.

Overall, based on the information available, the risk to the public associated with use of the notified chemical at < 5% concentration in cosmetic and household 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 neat into Australia for reformulation into finished cosmetic and household 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 notified chemical is expected to be collected with adsorbents, and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve transfer of the notified chemical into blending vessels, followed by blending operations that will be highly automated, and 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, residues in import containers, and spilt materials. These, along with empty import containers, are expected to be collected for disposal by licensed waste management services, in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE

The notified chemical is expected to be released to the aquatic compartment through sewers during its use in various cosmetic and household products.

RELEASE OF CHEMICAL FROM DISPOSAL

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

7.1.2. Environmental Fate

Following its use in cosmetic and household products in Australia, 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 ready biodegradability study, the notified chemical is considered readily biodegradable (86-90% in 28 days). For details of the environmental fate study, please refer to Appendix C. Based on its surfactant properties, release to surface waters is unlikely to occur as partitioning to sludge and sediment is expected under environmental pH. The notified chemical is not expected to be bioaccumulative, due to its surfactant properties and ready biodegradability. Therefore, in surface waters the notified chemical is expected to disperse and degrade through biotic and abiotic processes to form water and oxides of carbon.

The majority of the notified chemical will be released to sewer after use. A small 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. The notified chemical may also be applied to land when disposed of to landfill as collected spills and empty container residue. Residues of the notified chemical in landfill, soil and sludge are expected to eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

Based on the reported use in cosmetic and household products, it is assumed that 100% of the total import volume of the notified chemical will be released to the sewer. The release is assumed to be nationwide over 365 days per year. It is conservatively assumed that none of the notified chemical will be removed during sewage treatment plant (STP) processes.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	3,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	3,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	8.22	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:	1.817	µg/L
PEC - Ocean:	0.182	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1,000 L/m2/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 1,500 kg/m3). Using these assumptions, irrigation with a concentration of 1.82 µg/L may potentially result in a soil concentration of approximately 12.12 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 60.58 µg/kg and 121.2 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*
Fish Toxicity	96 h LC50 > 100 mg/L	Not harmful to fish
Daphnia Toxicity	48 h EC50 = 40.1 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	72 h E_rC50 = 79.8 mg/L	Harmful to algae
Inhibition of Bacterial Respiration	3 h IC50 = 1,696 mg/L	Not inhibitory to microbial respiration

Based on the above ecotoxicological endpoints for the notified chemical, it is expected to be harmful to aquatic invertebrates and algae, but is not expected to be harmful to fish. 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 3; Harmful to aquatic life”. Based on the acute toxicity, ready biodegradability and low bioaccumulation potential of the notified chemical, it is 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 endpoint for aquatic invertebrates. A safety factor of 100 was used given acute endpoints for three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Daphnia, 48 h)	40.1	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	401	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	1.817	401	**0.005**
Q - Ocean	0.182	401	**< 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 considered 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 and household products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point -10 ± 3 °C

Method	OECD TG 102 Melting Point/Melting Range.
Remarks	No meting point was observed using DSC method suggesting that the sample solidifies in a glassy state. Therefore, a pour point test was carried out. The melting point of the notified chemical, determined as pour point, was -10 ± 3 °C.
Test Facility	Clariant (2012a)

Boiling Point 317 ± 13 °C at 101.3 kPa

Method	OECD TG 103 Boiling Point.
Remarks	Determined using Differential Scanning Calorimetry (DSC). The notified chemical decomposes on boiling.
Test Facility	Clariant (2012b)

Density 1,124.8 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids
Remarks	Determined using the vibrating U-tube method.
Test Facility	Clariant (2012c)

Kinematic Viscosity 501 ± 13 mm^2/s at 20 °C

Method	OECD TG 114 Viscosity of Liquids.
Remarks	Determined using a rotational viscometer.
Test Facility	Clariant (2012d)

Vapour Pressure 7.63 x 10^{-6} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure. EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks	Effusion method
Test Facility	Siemens (2012)

Water Solubility 2.7 g/L at 20 °C

Method	OECD TG 105 Water Solubility.
Remarks	Flask Method
Test Facility	Clariant (2011a)

Partition Coefficient (n-octanol/water) log Pow = 2.55 at 23 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks	Shake Flask Method
Test Facility	Clariant (2011b)

Surface Tension 29.1 ± 0.1 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions.
Remarks	Concentration: 1g/L
Test Facility	Clariant (2012e)

Flash Point > 200 °C at 102.1 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	The Pensky-Martens method showed that the flash point was > 200 °C at 102.1 kPa, but

	failed to replicate an exact value. Therefore, an additional test with the Setaflash method was performed where a flash point of > 200 °C at 101.7 kPa was observed. This result is consistent with the Pensky-Martens measurement.
Test Facility	Clariant (2012f)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method (17 December, 2001).
EC Council Regulation No 440/2008 B.1 tris Acute Oral Toxicity – Acute Toxic Class Method (30 May 2008).

Species/Strain	Rats/HanRcc:WIST (SPF)
Vehicle	Polyethylene glycol 300 (PEG 300)
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3	2000	0/3
2	3	2000	0/3

LD50	> 2000 mg/kg bw
Signs of Toxicity	None
Effects in Organs	None
Remarks - Results	No clinical signs or mortality was observed during the study period. Animal body weights were within normal range for their strain and relevant age. No macroscopic abnormalities were recorded during post mortem examination.

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

TEST FACILITY: Harlan (2009a)

B.2. Irritation – skin

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 404 Acute Dermal Irritation/Corrosion (April 24, 2002).
EC Council Regulation No 440/2008 B.4 Acute Toxicity (Skin Irritation, 30 May, 2008).

Species/Strain	Rabbits/New Zealand White
Number of Animals	3
Vehicle	None
Observation Period	7 days
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0	0.67	1.00	1.00	< 7 days	0
Oedema	0	0	0	0	-	0

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

Remarks - Results: One hour after treatment with the test substance, a very slight erythema was noted in all animals. At the 24-hour reading, no abnormal findings were noted on the skin of one animal. A very slight erythema was still

observed in the other two test animals, which persisted up to the 48- and the 72-hour reading, respectively. These effects were reversible and were no longer evident 7 days after treatment. No oedema, staining, corrosive effects or clinical signs were observed at all observation time points following treatment. No signs of systemic toxicity were observed in the animals during the study. No mortality occurred.

CONCLUSION The notified chemical is slightly irritating to the skin.

TEST FACILITY Harlan (2009b)

B.3. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion (24 April, 2002).
EC Council Regulation No 440/2008 B.5 Acute Toxicity (Eye Irritation, 20 May 2008).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Observation Period	72 hours
Remarks - Method	No significant protocol deviations

RESULTS

Remarks - Results

No abnormal findings were observed in the cornea or iris of any animal during the course of the study. Slight reddening of the conjunctiva and the sclera was noted in all animals at the 1 hour observation period. Furthermore, slight swelling of the conjunctiva was observed in one animal and slight discharge was noted in the treated eyes of all animals. All signs of irritation were resolved at the 24 hour observation period, except for only slight reddening of the sclera in one animal. No abnormal findings were observed in the treated eye of any animal 48 and 72 hours after the treatment.

The body weights of all rabbits were within the normal range. No clinical signs of systemic toxicity were observed in the animals during the study and no mortality occurred.

CONCLUSION The notified chemical is non-irritating to the eye.

TEST FACILITY Harlan (2009c)

B.4. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (24 April, 2002).

Species/Strain	Mice/CBA/CaOlaHsd
Vehicle	Acetone:olive oil (4:1)
Preliminary study	Yes
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde in acetone:olive oil (4:1) using CBA/CaOlaHsd mice (July 2008).

Remarks - Method

No deviation from the guideline was noted. A solubility experiment determined that the highest notified chemical concentration which can be used was a 50% solution in acetone:olive oil (4:1). To determine the highest non-irritant test concentration, a preliminary study was performed

on two mice at doses of 5, 10, 25, or 50 % notified chemical. The animals did not show any signs of irritation or systemic toxicity at all doses.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	4F	710.0	-
10	4F	1359.0	1.91
25	4F	1314.4	1.85
50	4F	2039.0	2.87
Positive Control[#]			
0 (vehicle control)	4	278.7	-
5	4	1461.6	5.24
10	4	2055.4	7.38
25	4	2596.4	9.32

[#]α-Hexylcinnamaldehyde (not conducted in parallel with the test substance)

Remarks - Results: No mortalities and no signs of systemic toxicity were noted in the test or control animals during the study.

The results showed that the test substance at all concentrations elicited stimulation indices < 3 hence an EC3 value could not be derived.

CONCLUSION: There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY: Harlan (2009d)

B.5. Repeat dose toxicity

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents (October 3, 2008).
EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral) (30 May, 2008).

Species/Strain: Rats/Wistar (RccHan:SPF)
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: PEG 300
Remarks - Method: No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5M/5F	0	0/10
low dose	5M/5F	40	0/10
mid dose	5M/5F	200	0/10
high dose	5M/5F	1000	0/10
control recovery	5M/5F	0	0/10
high dose recovery	5M/5F	1000	0/10

Mortality and Time to Death
All animals survived the scheduled treatment or recovery periods.

Clinical Observations
No clinical signs of toxicity were observed. There were no test substance related effects on food consumption, functional performance or on mean body weights or body weight gain during the treatment and recovery periods.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Haematology
At 1000 mg/kg/day, males showed statistically significant decreases in the mean cell haemoglobin concentration, mean white blood cell count, neutrophils, lymphocytes and monocytes compared to controls. Mean methemoglobin was increased and the activated partial thromboplastin time was significantly prolonged, compared to controls. Females displayed a significantly increased thromboplastin time, compared to controls.

At 200 mg/kg/day, the mean white cell count and lymphocyte population was significantly reduced, compared to controls. The activated partial thromboplastin time of the females was significantly shorter than controls.

At 40 mg/kg/day, the mean white cell count and mean absolute lymphocyte count was significantly reduced compared to controls.

The study authors have noted however, that all these differences seen at the end of the treatment period were either unrelated to dose, within the ranges of the historical control values, or restricted to one sex.

During the recovery period for males treated at 1000 mg/kg/day, the mean relative eosinophil count was significantly increased and the mean absolute lymphocyte count was significantly decreased. Methemoglobin levels were significantly elevated in treated males and significantly reduced in treated females. The mean platelet count was significantly decreased in previously treated females compared to controls. The authors have noted however, that differences recorded after the recovery period were within the ranges of the historical control data and/or either not already evident at the end of treatment period and therefore not considered to represent test item-related effects.

Clinical Biochemistry
At 1000 mg/kg/day, males had significantly elevated creatinine levels, reduced calcium levels and reduced phosphorus levels compared to controls. Females at this dose had significantly reduced total bilirubin levels, reduced lactate dehydrogenase activity and decreased creatine kinase activity compared to controls.

Females treated with 200 mg/kg/day displayed significantly reduced total bilirubin levels and creatine kinase activity. Lactate dehydrogenase activity was significantly decreased in both sexes when compared with the controls.

At 40 mg/kg/day, males had significantly elevations in creatinine, sodium and chloride, while females showed significantly decreased total bilirubin and increased sodium.

The authors have noted however that all statistically significant differences at the end of the treatment period or recovery period were either unrelated to dose, within the ranges of the historical control values, or restricted to one sex.

Urinalysis
Males treated with 1000 mg/kg/day displayed significantly lower urine volume than controls. In females, the urine was significantly less acidic than controls. The differences were within the range of the historical control data.

Effects in Organs
In males treated with 1000 mg/kg/day, the mean absolute and relative liver weights, and mean adrenal-to-brain weight ratio were significantly lower than controls.

In females treated with 200 mg/kg/day, the mean absolute and relative liver weights and mean absolute spleen weights were significantly elevated. The mean spleen-to-body weight and spleen-to-brain weight ratios were significantly higher in these females.

At 40 mg/kg/day, the mean absolute and relative liver weights were significantly elevated in females and the mean kidney-to-brain weight ratio of the males was significantly lower than that of the controls. The

significantly lower mean liver-to-body weight ratio in males previously treated with 1000 mg/kg/day was not considered to represent a test item-related effect as there were no commensurate microscopical changes.

There were no gross or microscopic lesions that could be attributed to treatment with the test substance. All microscopic lesions recorded were considered to be within the range of normal background alterations.

REMARKS – RESULTS
No test substance related adverse effects were noted at any dose tested.

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) was established as 1000 mg/kg bw/day in this study, based on an absence of treatment related adverse effects at the highest dose tested.

TEST FACILITY Harlan (2013a)

B.6. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test (July 21, 1997).
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria (May 30, 2008).
Pre-experiment test
Plate incorporation procedure
Main test
Pre incubation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction from phenobarbital/β-napthoflavone induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 3 - 5000 µg/plate b) Without metabolic activation: 3 - 5000 µg/plate
Vehicle	DMSO
Remarks - Method	There were no deviations from the study plan. The dose range for the main test was determined from the pre-experiment test.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 1000	-	> 5000	Negative
Test 2	-	≥ 100	> 5000	Negative
Present				
Test 1	≥ 5000	-	> 5000	Negative
Test 2	-	≥ 1000	> 5000	Negative

Remarks - Results No substantial increase in revertant colony numbers of any of the five tester strains was observed following treatment with the test substance at any dose level, in the presence or absence of metabolic activation. Positive controls performed as expected, confirming the validity of the test system.

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

TEST FACILITY Harlan (2009e)

B.7. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test (21 July, 1997). EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test (30 May, 2008).
Species/Strain	Chinese hamster
Cell Type/Cell Line	Lung/V79
Metabolic Activation System	S9 fraction from phenobarbital/β-napthoflavone induced rat liver.
Vehicle	DMSO
Remarks - Method	No significant protocol deviations. A preliminary experiment was conducted to determine the dose range for the main test.

Metabolic Activation	*Test Substance Concentration (mM)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0.016, 0.031, 0.063, 0.125, 0.19, 0.25*, 0.35*, 0.50*, 0.75*, 1.0	4 h	20 h
Test 2	0.063, 0.125, 0.19, 0.25*, 0.35*, 0.50*, 0.75, 1.0	20 h	20 h
Present			
Test 1	0.063, 0.125, 0.25, 0.5, 1.0*, 2.5*, 5.0*, 7.5, 10	4 h	20 h
Test 2	0.375, 0.75, 1.5, 3.0*, 4.5*, 5.5*, 7.0, 8.5, 10	4 h	20 h

*Cultures 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	≥ 0.5	≥ 0.5	≥ 0.75	Equivocal
Test 2	-	≥ 0.5	> 0.50	Negative
Present				
Test 1	≥ 1.0	≥ 5.0	≥ 5.0	Equivocal
Test 2	-	≥ 4.5	> 5.5	Equivocal

Remarks - Results

In Test 1 without metabolic activation a biologically relevant increase of aberrant cells was observed at concentrations of 0.25 mM and 0.5 mM. With metabolic activation a biologically relevant increase of aberrant cells was observed at a concentration of 2.5 mM.

In Test 2 without metabolic activation no biologically relevant increase of the aberration rates were observed. The aberration rates were all within historical control data of the negative control. With metabolic activation a biologically relevant increase of aberrant cells was observed at concentrations of 3.0 and 4.5 mM.

Although a positive response was obtained there was no dose-response relationship. In particular, a biologically relevant increase in aberrant cells at the highest dose was not obtained in both tests, with and without metabolic activation. The study authors considered the inconsistency of the results may be due to the nature of the test substance and its solubility.

No biologically relevant increase in the frequencies of polyploidy cells was found after treatment with the test item, compared to controls.

The positive controls performed as expected, confirming the validity of the test system.

CONCLUSION Under the conditions of the study, the clastogenic potential of the notified chemical to Chinese hamster V79 cells was inconclusive.

TEST FACILITY BSL (2012a)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD OECD TG 476 In vitro Mammalian Cell Gene Mutation Test (July 21, 1997).
EC 440/2008 B.17 Mutagenicity - In vitro Mammalian Cell Gene Mutation Test (MAY 30, 2008).

Species/Strain	C
Cell Type/Cell Line	Lung/V79
Metabolic Activation System	S9 fraction from phenobarbital/β-napthoflavone-induced rat liver.
Vehicle	DMSO
Remarks - Method	No deviations from the study plan were noted. The V79 cells were tested with the test substance for potential to induce mutations at the HPRT locus. Preliminary experiments were conducted to determine the dose range for the main study.

Metabolic Activation	*Test Substance Concentration (mM)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test 1	0.25, 0.50, 1.00, 2.00, 3.00, 4.00, 4.50, 5.00, 5.50, 5.75	4 h	48-72 h	1 week
Test 2	0.005, 0.010, 0.020, 0.050, 0.075, 0.010, 0.25, 0.40, 0.55, 0.7	20 h	48-72 h	1 week
Present				
Test 1	0.50, 1.00, 2.00, 3.00, 4.00, 4.50, 5.00, 5.50, 5.75	4 h	48-72 h	1 week
Test 2	0.75, 1.50, 2.50, 3.25, 4.0, 4.2, 4.4, 4.6, 5.2, 5.6	4 h	48-72 h	1 week

All cultures were selected for metaphase analysis

Metabolic Activation	*Test Substance Concentration (mM) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 0.25	≥ 5.50	> 5.75	Negative
Test 2	≥ 1.00	≥ 0.7	> 0.7	Negative
Present				
Test 1	≥ 5.00	≥ 4.00	≥ 2.0	Negative
Test 2	-	≥ 3.25	≥ 3.25	Negative

Remarks - Results The test substance did not induce any statistically significant increases in the mutant frequency at any tested concentration in each exposure group, with and without metabolic activation.

The positive and vehicle controls gave satisfactory responses, confirming the validity of the test system.

CONCLUSION The notified chemical was not clastogenic to the HRPT locus in the V79 Chinese hamster cells treated *in vitro* under the conditions of the test.

TEST FACILITY BSL (2012b)

B.9. Genotoxicity – in vivo

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test (July 21, 1997). E.C. 440/2008 B.12 Mutagenicity - Mammalian Erythrocyte Micronucleus Test (May 30, 2008).
Species/Strain	Mouse/NMRI Charles River
Route of Administration	Oral – gavage
Vehicle	PEG 300
Remarks - Method	No deviations from the study plan were noted. A preliminary toxicity study was carried out using 2 male and 2 female mice dosed with the test substance at 2000 mg/kg bw. No mortalities or signs of toxicity were observed.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	7M	0	24
II (high dose)	7M	2000	24
III (high dose)	7M	2000	48
IV (positive control, CP)	7M	40	24

CP=cyclophosphamide dissolved in sterile water.

RESULTS	
Doses Producing Toxicity	No clinical of toxicity were observed in the vehicle control or treated animals during the test period.
Genotoxic Effects	The test substance induced no statistically significant increases in micronucleated, polychromatic erythrocytes (PCEs) at either sampling time.
Remarks - Results	No clinical signs of toxicity or reductions in the PCE/NCE ratio (cytotoxicity) were observed with test substance treatment, so it is therefore not known if the test substance reached the bone marrow. The positive control performed as expected, confirming the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this *in vivo* mouse micronucleus test.
TEST FACILITY	Harlan (2012)

B.10. Developmental toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 421 Reproduction/Developmental Toxicity Screening Test (27 July, 1995).
Species/Strain	Rat/Wistar (RccHan:SPF)
Route of Administration	Oral – gavage
Exposure Information	Exposure: males - 4 weeks minimum (14 days prior to pairing and 14 days through the pairing) females - ~7 weeks (14 days prior to pairing, through the pairing and gestation periods until the F1 generation reached day 4 post partum) Post-exposure observation period: None
Vehicle	PEG 300
Remarks - Method	No study deviations from the protocol were noted. Dose levels were selected based on the results of a non-GLP dose range-finding study

previous conducted by the test facility (Harlan Laboratories study D57346).

RESULTS

Group	*Number of Animals*	*Dose mg/kg bw/day*	*Mortality*
1	11 per sex	0	2/22 (1M/1F)
2	11 per sex	40	2/22 (1M/1F)
3	11 per sex	200	0/22
4	11 per sex	1000	2/22 (1M/1F)

Mortality and Time to Death

At 1000 mg/kg/day, one male was found dead on Day 7 of the pre-paring period. One male treated with 40 mg/kg/day was found dead on Day 11 of the pre-pairing period. One control male was found dead on Day 1 of the pairing period. One female treated with 1000 mg/kg/day and one control female were killed on day 25 of the gestation period (four days after the scheduled litter date). One female treated with 40 mg/kg/day was found dead on day 4 of the pre-pairing period. All premature deaths were considered by the study authors to be incidental or accidental due to dosing, and were not test substance related.

Effects on Parental Animals

Females

The mean daily food consumption of the females was unaffected by treatment during the gestation and lactation periods. During the gestation period, the mean body weights of the test item-treated mated females were similar to those of the control females. During the lactation period, the mean body weights of the test item-treated females that gave birth were unaffected by treatment. No effects on fertility (% mating, fertility index and conception rate) were observed at any dose level. The duration of gestation was similar at all dose levels. The number of corpora lutea observed at all dose levels compared favourably (or exceeded that) of the controls. The implantation rate of the test item-treated and control groups compared favourably. The mean post-implantation loss of the test substance treated females was unaffected by the test substance. There were no macroscopical findings in any dam treated with 40 mg/kg/day or 1000 mg/kg/day. However, discoloration of the ovaries was noted in one female treated with 200 mg/kg/day.

Males

During the pre-pairing and pairing periods, the mean body weights of the test item-treated males were generally similar to those of the control males. Minor differences in the mean body weight gain values were noted in males at 40 mg/kg/day and 1000 mg/kg/day that occasionally attained statistical significance but these differences did not exceed 4% when compared to the body weight gain of the control males. Therefore, these differences were considered to be of no toxicological relevance.

In males, the mean absolute and relative organ weights were unaffected by the treatment with the test item. In the survivors, there were no macroscopic lesions (detected during post-mortem examination) that could be attributed to treatment with the test item. There were no test item-related effects on the testicular histomorphology, including spermatogenesis and interstitial cell structure

Effects on Foetus

When compared with the control females, the mean litter sizes were unaffected by the treatment with the test substance. Blue discoloration of the abdomen or extremity was noted in a small number of pups at 40 mg/kg/day and 1000 mg/kg/day. One pup of a dam treated with 200 mg/kg/day and two pups of a dam treated with 1000 mg/kg/day was missing the tail apex. The low incidence and type of these findings suggested incidental occurrence. The sex ratios at first litter check were within the range of typical variation. The mean body weights of the pups on day 4 post-partum were considered to be unaffected by treatment with the test substance. There were no test substance related macroscopic findings in any pup necropsied on day 4 post-partum at any dose level.

Remarks - Results

There were no effects upon mean daily food consumption or body weight development of parent animals, no effects upon mean absolute or relative organ weights of males, and no macroscopicalor microscopical findings of toxicological relevance.

No effects on mating performance, fertility, corpora lutea count, duration of gestation, implantation rate and post-implantation loss as well as litter size and post-natal loss were noted at any dose level. No test item-related findings in pups or effects on pup body weights were noted at any dose level.

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) for systemic and reproductive toxicity was established as 1000 mg/kg bw/day under the conditions of the study, based on the absence of adverse effects.

TEST FACILITY	Harlan (2013)

B.11. Metabolism

TEST SUBSTANCE	Notified chemical
METHOD	In-house method
STUDY DESIGN AND OBJECTIVE	The aim of the study was to determine if and to what extent the notified chemical is metabolised by porcine pancreatic lipase (PPL). This involved comparing the extent of PPL-mediated olive oil (a known substrate of PPL) metabolism *in vitro* with that of the notified chemical. This was conducted by comparing the amount of free fatty acid product following incubation of each substrate with PPL for 10 minutes. Both substrates were tested in triplicate. An additional sample of each substrate with PPL added after the 10 minute incubation period was used as a negative control. Free fatty acid (FFA) concentrations were measured with a commercial test kit immediately after the incubation period.
RESULTS	FFA formation occurred approximately 2.4 times faster in samples tested with the notified chemical, compared with olive oil.
CONCLUSION	The notified chemical is expected to undergo ready hydrolysis in the gut
TEST FACILITY	BSL (2013)

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 (Modified Sturm) Test.

Inoculum	Activated sewage sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Carbon Dioxide ($ThCO_2$)
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Test substance		*Toxicity control*		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*	*Day*	*% Degradation*
6	26-35	6	29	6	58
14	65-72	14	68	14	76
21	78-79	21	82	21	76
28	86-90	28	94	28	78

Remarks - Results: All validity criteria for the test were satisfied. The percentage degradation of the reference compound surpassed the threshold level of 60% by 8 days (68%). 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 (29%; 94% 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 86-90%. 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 (2009a)

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 (zebra fish)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	64 mg CaCO3/L
Analytical Monitoring	Dissolved Organic Carbon (DOC)
Remarks – Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Concentration mg/L	*Number of Fish*	*Mortality*			
Nominal		*24 h*	*48 h*	*72 h*	*96 h*
Control	7	0	0	0	0
100	7	0	0	0	0

LC50	> 100 mg/L at 96 hours.
NOEC (or LOEC)	100 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 actual concentrations of the test substance were measured at the start of the 96 h test period. As no additional measurements of the concentration of the test substance were made, the results were based on the nominal concentrations. The 96 h LC50 and NOEC for fish were determined to be > 100 mg/L and 100 mg/L, respectively, based on nominal concentrations.
CONCLUSION	The notified chemical is not considered to be harmful to fish.
TEST FACILITY	Dr U Noack-Laboratorien (2009b)

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	239 mg $CaCO_3$/L
Analytical Monitoring	Dissolved Organic Carbon (DOC)
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised (%)*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
6.25	5.67	20	0	0
12.5	9.24	20	0	0
25.0	14.6	20	0	5
50.0	28.8	20	60	80
100.0	60.8	20	80	100

LC50	40.1 mg/L (95% CI 37.1-42.3 mg/L) at 48 hours
NOEC	25.0 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 the start and end of the 48 h test period. Measured concentrations deviated from the nominal concentrations by the end of the test; however, the nominal concentrations were used. The 48 h EC50 and NOEC for daphnids were determined to be 40.1 mg/L (95% CI 37.1-42.3 mg/L) and 25.0 mg/L, respectively, based on nominal concentrations.
CONCLUSION	The notified chemical is considered to be harmful to aquatic invertebrates.

TEST FACILITY	Dr U Noack-Laboratorien (2013a)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test – Static.
Species	*Desmodesmus subspicatus* (green alga)
Exposure Period	72 hours
Concentration Range	Nominal: 6.25-100 mg/L Actual: 5.08-56.9 mg/L
Auxiliary Solvent	None
Water Hardness	0.24 mmol Ca + Mg/L
Analytical Monitoring	Total Organic Carbon (TOC)
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Biomass		*Growth*	
EC50	NOEC	EC50	NOEC
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
17.5 (95% CI 15.4-19.7)	6.25	79.8 (95% CI 74.7-84.5)	12.5

Remarks - Results	All validity criteria for the test were satisfied. Renewal of the test solutions was not specified. The actual concentrations of the test substance were measured at the start and end of the 72 h test period. Measured concentrations deviated from the nominal concentrations by the end of the test; however, the nominal concentrations were used. The 72 h EC50 and NOEC for algae were determined to be 79.8 mg/L (95% CI 74.7-84.5 mg/L) and 12.5 mg/L, respectively, based on nominal concentrations.
CONCLUSION	The notified chemical is considered to be harmful to algae.
TEST FACILITY	Dr U Noack-Laboratorien (2013b)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Analogue
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Activated sewage sludge
Exposure Period	3 hours
Concentration Range	Nominal: 100-10,000 mg/L Actual: Not determined
Remarks – Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol 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	1,696 mg/L (95% CI 1,404-2,048 mg/L) at 3 hours
NOEC	Not determined
Remarks – Results	All validity criteria for the test were satisfied. The 3 h IC50 was determined to be 1,696 mg/L (95% CI 1,404-2,048 mg/L), based on nominal concentrations.
CONCLUSION	The notified chemical is not inhibitory to microbial respiration.
TEST FACILITY	Dr U Noack-Laboratorien (1996)

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