CORRIGENDUM – issued November 2015
Public report for STD/1435

Page 11, in Section 6.2 “Human Health Effects Assessment”, under the subsection “Observations on Human Exposure”, make the following changes:
* First sentence – replace “9 volunteers” with “50(49) volunteers”
* Third sentence – change the beginning of the sentence from “A larger scale repeated insult patch test” to “Another repeated insult patch test”

Page 20, In “Section B8 – Skin Sensitisation – Human Volunteers”, make the following changes:
* Induction procedure – replace “9 volunteers” with “50(49) volunteers”
* Induction procedure – replace “applications of about 48 hours” to “applications at intervals of about 48 hours”
* Rest period – replace “15 weeks” by “15 days”
* Challenge procedure – replace “50 volunteers” with “50(49) volunteers”
* Challenge procedure – remove duplicated phrase “in each application”

File No: STD/1435

March 2014

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

D-Glucopyranose, oligomeric, 12-hydroxyoctadecyl glycosides (INCI Name: Hydroxystearyl Glucoside)

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

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

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

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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/1435	Bronson & Jacobs Pty Ltd	D-Glucopyranose, oligomeric, 12-hydroxyoctadecyl glycosides (INCI Name: Hydroxystearyl Glucoside)	ND*	≤ 3 tonnes per annum	Component of cosmetic products

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

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

When used 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 assessed 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 isolation and engineering controls to minimise occupational exposure to the notified chemical during reformulation processes:
  - Enclosed, automated processes, where possible
  - Ventilation system including local exhaust ventilation

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

- 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, impervious gloves, goggles

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

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

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

Disposal

- The notified chemical should be disposed of to landfill.

Emergency procedures

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

Regulatory Obligations

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

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

1. Under Section 64(1) of the Act; if
   - The notified chemical is proposed to be used at a concentration > 5% in cosmetic products;

or
2. Under Section 64(2) of the Act; if
   - the function or use of the chemical has changed from component of cosmetic products, or is likely to change significantly;
   - the amount of chemical being introduced has increased from ≤ 3 tonnes per annum, 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.

No additional secondary notification conditions are stipulated.

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Bronson & Jacobs Pty Ltd (ABN: 81 000 063 249)
70 Marple Avenue
VILLAWOOD NSW 2163

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, structural formula, molecular weight, analytical data, degree of purity, impurities, additives/adjuvants, manufacture/import volume and identities of analogue chemicals.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: All physico-chemical and toxicological endpoints.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Simulgreen 18-2 (containing ≤ 20% notified chemical)

CAS NUMBER
1200736-34-0

CHEMICAL NAME
D-Glucopyranose, oligomeric, 12-hydroxyoctadecyl glycosides

OTHER NAME(S)
Hydroxystearyl Glucoside (INCI name)

MOLECULAR FORMULA
Unspecified

MOLECULAR WEIGHT
> 400 Da

ANALYTICAL DATA
Reference IR and UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
Part of an inseparable mixture

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 ºC AND 101.3 kPa: white solid pellets (Product containing ≤ 20% notified chemical)

Property	Value*	Data Source/Justification
Melting Point/Freezing Point	59.5 ± 0.5 °C	Measured
Boiling Point	310.9 ± 0.5 °C at 101.3 kPa	Measured
Density	984 kg/m^3 at 20.5 °C	Measured
Vapour Pressure	9.9 x 10^{-8} kPa at 20 °C	Measured. The chemical itself is expected to have a low vapour pressure.
Water Solubility	3.192 × 10^{-4} g/L at 20 °C	Calculated for notified chemical (WSKOW v1.41; US EPA, 2011). Due to potential surface activity, the notified chemical is expected to disperse in water.
Hydrolysis as a Function of pH	Not determined	Contains no hydrolysable functional groups
Partition Coefficient (n-octanol/water)	log Pow = 4.3 at 20 °C	Calculated for the most representative species of the notified chemical (KOWWIN v1.10; US EPA, 2011). Calculated results may not adequately characterise the partitioning behaviour of the notified chemical due to potential surface activity. Nevertheless, the notified chemical is expected to partition to phase boundaries.
Adsorption/Desorption	log Koc = 2.31 at 25 °C	Calculated for the most representative species of the notified chemical (KOCWIN v2.00; US EPA, 2011). Calculated results may not adequately characterise the partitioning behaviour of the notified chemical due to potential surface activity. Nevertheless, the notified chemical is expected to partition to phase boundaries.
Dissociation Constant	Not determined	Not expected to dissociate under environmental conditions (pH 4–9) given no dissociable functionality.
Particle Size	> 1 mm	(M)SDS
Flash Point/Flammability	Not highly flammable	Measured
Autoignition Temperature	Not determined	Not expected to autoignite under normal conditions of use
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

*All studies conducted on a product containing ≤ 20% notified chemical

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 product containing ≤ 20% notified chemical is not recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported into Australia as a component (≤ 20%) of Simulgreen 18-2 and as a component of finished cosmetic products. Simulgreen 18-2 will be present in the finished products at ≤ 5%

concentration.

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

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

PORT OF ENTRY
Melbourne and Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
Bronson and Jacobs Pty Ltd

TRANSPORTATION AND PACKAGING
Simulgreen 18-2 (≤ 20% notified chemical) will be imported in drums/containers on pallets and will be transported by road to a central warehouse and/or reformulation sites.

Finished products containing the notified chemical will be imported in containers suitable for retail sale (≤ 500 mL). These containers will be packed in cardboard cartons and will be transported by road to a central warehouse and/or to retail distribution centres.

USE
Simulgreen 18-2 (≤ 20% notified chemical) will be used at ≤ 5% concentration in various rinse-off and leave-on cosmetic products (e.g. body lotions/creams and products for use on the lips and around the eyes).

OPERATION DESCRIPTION
The notified chemical will be imported as a component of Simulgreen 18-2 (≤ 20%) and as a component of finished cosmetic products.

Reformulation processes are expected to involve transferring the necessary quantities of Simulgreen 18-2 into a separate container, then adding it directly to a mixing tank for blending into finished products (process may involve heating). Mixing and dispensing of the finished product into end-use containers is expected to be carried out using automated processes and in a closed system, or in a system designed to prevent the creation of aerosols or dust hazards. Quality Assurance chemists will sample for quality assurance using a scoop.

The finished products containing the notified chemical may be used by consumers and professionals, such as workers in beauty salons. Depending on the nature of the product, these could be applied in a number of ways, such as by hand or using 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)*
Transport and Storage	4	12
Professional compounder	8	12
Chemist	3	12
Packers (dispensing and capping)	8	12
Store persons	4	12
Salon Workers	Unspecified	Unspecified

EXPOSURE DETAILS
Transport & Storage
Transport and storage workers may come into contact with the notified chemical, as a component of the product Simulgreen 18-2 (≤ 20% concentration) or end-use products (≤ 5% Simulgreen 18-2), only in the event

of an accidental rupture of containers.

Reformulation
During reformulation, dermal and ocular exposure of workers to the notified chemical (at ≤ 20% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. Inhalation exposure to the notified chemical is not expected during reformulation processes. Exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems and through the use of personal protective equipment (PPE) such as coveralls, safety glasses and impervious gloves.

End use
Exposure to the notified chemical in end-use products (at ≤ 5% Simulgreen 18-2) may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hair dressers, workers in beauty salons). 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 lesser extent than that experienced by consumers using products containing the notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical through the use of the rinse-off and leave-on cosmetic products. The principal route of exposure will be dermal, while ocular and oral exposure is also possible, particularly if using products applied to the lips or around the eyes.

Data on typical use patterns of cosmetic products in which the notified chemical may be used are shown in the following table (SCCS, 2010; Cadby et al., 2002). The systemic exposure estimate is based on use of the imported product containing the notified chemical, Simulgreen 18-2, which is intended to be used in cosmetic products at ≤ 5% concentration. For the purposes of the exposure assessment via the dermal route, Australian use patterns for the various product categories are assumed to be similar to those in Europe. In the absence of dermal absorption data, the default dermal absorption of 100% was assumed for calculation purposes (European Commission, 2003). An adult bodyweight of 60 kg was used for calculation purposes.

Product type	Amount (mg/day)	C (%)	RF	Daily systemic exposure (mg/kg bw/day)
Body lotion	7820	5	1	6.52
Face cream	1540	5	1	1.28
Eyeliner	5	5	1	0.004
Makeup remover	5000	5	0.1	0.42
Facial cleanser	800	5	0.01	0.01
Shower gel	18670	5	0.01	0.16
Shampoo	10460	5	0.01	0.087
Hair conditioner	3920	5	0.01	0.033
Total				**8.503**

C - concentration; RF - retention factor.
Daily systemic exposure = Amount × C × RF × 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 tables that contain the notified chemical. This would result in a combined internal dose of 8.50 mg/kg bw/day Simulgreen 18-2. The notified chemical is also proposed to be used in lipstick/gloss products. For these, exposure is mainly through the oral route. The data is shown below (SCCS, 2012). A conservative 100% ingestion rate was assumed for calculation purposes.

Cosmetic products (Oral exposure):

Product type	Amount (mg/day)	C (%)	Daily systemic exposure (mg/kg bw/day)
Lipstick/gloss	57	5	0.048

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 8.55 mg/kg bw/day.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical as well as three structurally similar analogues 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
Rat, acute dermal toxicity***	LD50 >2000 mg/kg bw, low toxicity
Skin irritation (in vitro)	non-irritating
Rabbit, skin irritation**	non-irritating
Eye irritation (in vitro)	non-irritating
Rabbit, eye irritation**	slightly irritating
Guinea pig, skin sensitisation – adjuvant test.	no evidence of sensitisation
Human, skin sensitisation – RIPT (5%)*	no evidence of sensitisation
Human, skin sensitisation – RIPT (5%)**	limited evidence of sensitisation
Rat, repeat dose (gavage) toxicity – 28 days*	NOAEL= < 100 mg/kg bw/day
Rat, repeat dose (gavage) toxicity – 90 days*	NOAEL= 1000 mg/kg bw/day
Rat, repeat dose (gavage) toxicity – 90 days***	NOAEL= 250 mg/kg bw/day
Genotoxicity – in vitro bacterial reverse mutation	non genotoxic
Genotoxicity – in vitro cytogenetics assay***	non genotoxic
Rat, development toxicity*	NOAEL for maternal and developmental toxicity = 1000 mg/kg bw/day
Rat, reproductive and developmental toxicity**	NOAEL for parental toxicity = 1000 mg/kg bw/day; NOEL for reproductive performance = 1000 mg/kg bw/day; NOEL for progeny = 1000 mg/kg bw/day

*Analogue 1; ** Analogue 2; *** Analogue 3

Toxicokinetics, metabolism and distribution.
Whilst absorption of the notified chemical may occur (molecular weight > 400 Da), the extent of absorption through the skin or gastrointestinal tract is expected to be limited, based on its low water solubility (3.19×10^{-4} g/L at 20 °C) and relatively high log Pow (4.3 at 20 °C).

Acute toxicity.
No acute toxicity data were provided for the notified chemical. Analogue 2 was found to be of low acute oral toxicity with an LD50 > 2000 mg/kg bw. Analogue 3 was found to be of low acute dermal toxicity with an LD50 > 2000 mg/kg bw.

Based on the data obtained on analogues 2 and 3, the notified chemical is expected to be of low toxicity via the oral or dermal routes.

Irritation and sensitisation.
The notified chemical at 5% concentration was found to be non-irritating in an in vitro skin irritation study and an in vitro eye irritation study. Analogue 2 at up to 1% concentration was found to be non-irritating to the skin of rabbits and slightly irritating to the eye. Discharge from the conjunctiva was noted in all three animals but was not present after 24 hours. In addition, slight redness of the conjunctiva was observed in all three animals after one hour and in one animal up to 48 hours. The potential for irritation effects at higher concentrations cannot be ruled out.

The notified chemical (5% induction concentration; 2% challenge concentration) was not a skin sensitiser in guinea pigs under the conditions of the adjuvant skin sensitisation test.

The incidences of (hyper)salivation in the repeated dose studies with analogues 1 and 2, including a dose-dependent response with analogue 1 in the 90 day repeated dose study, provide some evidence that the analogue chemicals may be oral irritants. This effect cannot be ruled out for the notified chemical.

Based on the data obtained on the notified chemical and analogues 1 and 2 (at the concentrations tested), the notified chemical is not expected to be irritating to the skin or eyes and is not considered a skin sensitiser.

Repeated Dose Toxicity.
There are no repeat dose toxicity studies for the notified chemical. A 28 day repeat dose toxicity study was

conducted with analogue 1 in rats and was administered by oral gavage at doses of 100, 300 and 1000 mg/kg bw/day. Males and females treated with 300 and 1000 mg/kg/day had higher triglyceride levels with the highest dose group also exhibiting higher urea and cholesterol levels. Additionally, epididymal sperm count and the percentage of morphologically normal sperm was decreased for all groups treated with the analogue chemical resulting in a no observed adverse effect level (NOAEL) of < 100 mg/kg bw/day. Although the repeat dose study for analogue 1 was performed on a mixture, it has been demonstrated that the effects on spermatogenic processes are unlikely to be due to long-chain fatty alcohols acting in isolation (Sanderson et al., 2009).

Based on these data a 90-day repeated dose toxicity study was also conducted with analogue 1 which included histopathological examination of the spermatogenic system. There were no statistically significant differences in clinical parameters or other organs. Exposure to the analogue chemical resulted in slightly lower measures of the spermatogenic system but there were few statistically significant differences and no biologically significant effects. This evidence supports analogue 1 as not adversely affecting the spermatogenic system in a biologically significant manner when the exposure is over an interval greater than the duration of spermatogenesis. The NOAEL was, therefore, established as 1000 mg/kg bw/day in this study, based on no test item related effects at this dose level.

A 90 day repeat dose toxicity study was conducted with analogue 3 in rats. A NOAEL of 250 mg/kg bw/day was established based on acanthosis, subepithelial inflammatory oedema, and hyperkeratosis (females only) of the forestomach observed at higher dose levels. However, only the study summary was available for review.

Mutagenicity/Genotoxicity.
The notified chemical was not mutagenic in a bacterial reverse mutation assay and analogue 3 was found to be non-mutagenic in a cytogenetics assay.

Toxicity for reproduction.
There are not reproduction and developmental studies available for the notified chemical. A prenatal developmental toxicity study was conducted with analogue 1 in rats. There were no treatment related mortalities or effects on pregnancy parameters. There were no treatment related foetal malformations and no statistically significant foetal variations. The NOAEL was established at 1000 mg/kg bw/day for maternal and developmental toxicity.

A combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was conducted with analogue 2 in rats. No animals showed any treatment related effects on mating or fertility. The number of corpora lutea, implantation and live pups born were similar to control group levels. The NOAEL for parental toxicity was established as 1000 mg/kg bw/day in this study, based on no observed adverse effects at this dose level. The no observed effect level (NOEL) for reproductive performance was 1000 mg/kg bw/day and the NOEL for progeny was 1000 mg/kg bw/day.

Observations on Human Exposure.
A repeated insult patch test was conducted with analogue 1 at 5% concentration in 9 volunteers. The Mean Irritation Index (MII) obtained during induction was equal to 0.03 indicating that the test substance was non-sensitising. A larger scale repeated insult patch test was conducted with analogue 2 in 50 volunteers at 1%, 2.5% and 5% concentrations. The mean irritation index for all subjects during the induction phase was 0.06 and no subject showed a response that was considered positive for sensitisation.

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

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Beauty care professionals will handle the notified chemical at ≤ 20% concentration in cosmetic products, similar to public use. Therefore, the risk for beauty care professionals who regularly use products containing the notified chemical is expected to be of a similar or lesser extent than that experienced by members of the public who use such products on a regular basis. For details of the public health risk assessment, see Section 6.3.2.

Compounders and laboratory staff involved in the formulation of cosmetic products may come in contact with the neat notified chemical. Exposure is expected to be limited during product formulation by the engineering controls and PPE used, and the enclosed and automated processes. Under the proposed occupational settings and provided that formulation control measures are being adhered to, the notified chemical is not considered to pose an unreasonable risk to workers.

Based on the information available, the risk to workers associated with use of the notified chemical at ≤ 20% concentration in cosmetic products is not considered to be unreasonable.

6.3.2. Public Health

At the proposed use concentration of ≤ 5% notified chemical in cosmetic products, acute toxicity effects are not expected. The repeated dose toxicity effects of the notified chemical have not been determined. However, these studies were performed for analogue 1 and 2 of the notified chemical.

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 of 8.55 mg/kg bw/day (see Section 6.1.2) and the NOAEL of 1000 mg/kg bw/day, which was established in a 90 day toxicity study on analogue 1. Analogue 1 was considered the most representative analogue chemical for estimation of the NOAEL due to the completeness and quality of the available study data and the structural similarity to the notified chemical. A MoE value ≥ 100 is considered acceptable to account for intra- and inter-species differences. Using the abovementioned NOAEL, a MoE of 117.0 was estimated. Thus, the risk to the public from use of the notified chemical at ≤ 5% concentration in cosmetic products, including facial cleansers, shampoos, conditioners, shower gels, makeup removers and lip 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 finished cosmetic products and will also be imported as a component of Simulgreen 18-2 for use in reformulation of cosmetic products. Approximately 1% of the Simulgreen 18-2 product is expected to remain in the raw material container after manufacture, which will be disposed of to landfill or be washed to sewer when containers are rinsed before recycling. Accidental spills during transport are expected to be collected with inert material and disposed of to landfill. Residues of the notified chemical may be released to sewer during equipment cleaning where reformulation takes place.

RELEASE OF CHEMICAL FROM USE

The notified chemical is a component of various cosmetic products such as body lotions and creams. Therefore, it is expected that the majority of the imported quantity of the notified chemical will eventually be washed off the skin and released to sewer. Alternatively, some of the notified chemical may be physically removed and disposed of to landfill, or ingested by the user.

RELEASE OF CHEMICAL FROM DISPOSAL

Approximately 3% of the notified chemical is expected to remain in containers after use. The notified chemical in the empty end-use containers is likely either to share the fate of the container and be disposed of to landfill, or to be washed to sewer when containers are rinsed before recycling.

7.1.2. Environmental Fate

The majority of the notified chemical is expected to be released to sewer during use in cosmetic products. During waste water treatment processes in sewage treatment plants (STPs), it is estimated that 19% of the notified chemical will adsorb to sludge (European Commission, 2003), due to its likelihood to partition to phase boundaries. The notified chemical that partitions to sludge will be removed with the sludge for disposal to landfill or used on land for soil remediation. Based on its potential surface activity and water dispersibility, the notified chemical is not expected to bioaccumulate. Although study data do not support the ready biodegradation of the notified chemical (as the 10 day window requirement was not met), the test substance did exceed 60% degradation at 28 days. Published studies have found C_{8-16} alkyl polyglycosides to be readily biodegradable (Masden, 2001). Calculated QSAR data also indicates that the notified chemical itself should be readily biodegradable (BIOWIN v4.10; US EPA, 2011). Therefore, the notified chemical is expected to degrade rapidly. If released to surface waters, the notified chemical is expected to disperse and undergo degradation. Ultimately, the notified chemical is expected to degrade via biotic and abiotic processes in soil, sludge and surface waters to form water and oxides of carbon. For the details of the environmental fate studies please refer to Appendix C.

7.1.3. Predicted Environmental Concentration (PEC)

The calculation for the predicted environmental concentration (PEC) is summarised in the table below. Based on the reported use in cosmetic products, it is assumed that 100% of the notified chemical will be released to sewer on a nationwide basis over 365 days per year. Assuming a worst-case scenario of inherent biodegradability (given the absence of data to support ready biodegradability), it is estimated that 33% of the notified chemical to be degraded during STP processes, and 19% of the notified chemical will to partition to sludge (European Commission, 2003).

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	52%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.87	µg/L
PEC - Ocean:	0.087	µg/L

The SimpleTreat model may underestimate partitioning to sludge given the surface activity of the notified chemical. Nevertheless, based on the SimpleTreat estimations, partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 3.45 mg/kg (dry wt). Biosolids are applied to agricultural soils, with an assumed average rate of 10 t/ha/year. Assuming a soil bulk density of 1500 kg/m^3 and a soil-mixing zone of 10 cm, the concentration of the notified chemical may approximate 0.023 mg/kg in applied soil. This assumes that degradation of the notified chemical occurs in the soil within 1 year from application. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated biosolids application, the concentration of notified chemical in the applied soil in 5 and 10 years may approximate 0.115 mg/kg and 0.23 mg/kg, respectively.

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 0.872 µg/L may potentially result in a soil concentration of approximately 5.82 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 29.1 µg/kg and 58.2 µg/kg, respectively.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on filtered water accommodated fractions (WAFs) for a product containing ≤ 20% 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 Toxicity (96 h)	LC50 > 100 mg/L (filtered WAF)	Not harmful to fish
Daphnia Toxicity (48 h)	LC50 > 100 mg/L (filtered WAF)	Not harmful to aquatic invertebrates
Algal Toxicity (72 h)	E_rC50 > 100 mg/L (filtered WAF)	Not harmful to algae

These results indicate that the test substance is not harmful to aquatic organisms. However, as these studies were conducted on a mixture containing the notified chemical, the data presented may not accurately represent the hazard of the notified chemical itself to aquatic organisms. Alkyl polyglycosides of C_{12-14} are generally toxic to aquatic organisms, with E(L)C50 values of 2.5–12 mg/L (Masden, 2001). An analogue C_{18} non-ionic surfactant is also toxic to *Daphnia* (EC50 1.18 mg/L) (OECD, 2013), with these data suggesting that toxicity may increase with chain length. Subsequently, the notified chemical is expected to possess higher toxicity than C_{12-14} polyglycosides. The limited solubility of the notified chemical is not so low as to be capable of mitigating high toxicity. Therefore, the notified chemical may be toxic to aquatic organisms.

The notified chemical cannot be formally classified under the Globally Harmonised System of Classification of Chemicals (GHS; United Nations, 2009) due to the absence of studies conducted on the notified chemical and sufficient analogue data. Although analogue data are used here to aid in characterising the toxicity of C_{18} non-ionic surfactants for risk assessment purposes, functional groups of the analogue chemical structure chain differ from that of the notified chemical. The analogue is not expected to adequately represent the toxicity of the notified chemical for purposes of GHS classification.

7.2.1. Predicted No-Effect Concentration

A worst-case, representative endpoint based on analogue data (OECD, 2013), was used to calculate the predicted no-effect concentration (PNEC). An assessment factor of 1000 was used as reliable acute ecotoxicological endpoints were not available for the notified chemical.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
Representative Endpoint	1.18	mg/L
Assessment Factor	1000	
PNEC:	1.18	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.87	1.18	0.74
Q - Ocean	0.087	1.18	0.074

The Risk Quotients (Q = PEC/PNEC) for a discharge scenario have been calculated to be < 1 for the river and ocean compartments. Although the Risk Quotient is high, the notified chemical is expected to be rapidly degradable in the environment and is not expected to bioaccumulate. Further, the representative endpoint is conservative, and the SimpleTreat model may underestimate partitioning to sludge, given the surface activity of the notified chemical. Therefore, the notified chemical is not expected to pose an unreasonable risk to the environment based on its assessed use pattern.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

All studies were conducted on products containing ≤ 20% notified chemical

Melting Point/Freezing Point 59.5 ± 0.5 °C

Method	OECD TG 102 Melting Point/Melting Range. EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature.
Remarks	Determined using the differential scanning calorimetry (DSC) method.
Test Facility	Defitraces (2011a)

Boiling Point 310.9 ± 0.5 °C at 101.3 kPa

Method	OECD TG 103 Boiling Point. EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks	Determined using the differential scanning calorimetry (DSC) method.
Test Facility	Defitraces (2011a)

Density 984 kg/m^3 at 20.5 °C

Method	OECD TG 109 Density of Liquids and Solids. EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks	Determined using the gas (helium) comparison pycnometer method.
Test Facility	Defitraces (2011b)

Vapour Pressure 9.9 x 10^{-8} kPa at 20 °C

Method	OECD TG 104 Vapour Pressure. EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks	Determined using the Knudsen cell effusion method coupled to a micro balance.
Test Facility	Defitraces (2011c)

Flammability Not highly flammable

Method	EC Council Regulation No 440/2008 A.10 Flammability (Solids).
Remarks	Determined by heating the test substance on a base plate using a gas burner and observing any ignition. The test substance was noted to have melted to afford a colourless liquid, but neither inflammation nor propagation were observed. As the preliminary test was negative for flammability, the main test was not performed.
Test Facility	Defitraces (2011d)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Analogue 2 (mixture)
METHOD	Similar to OECD TG 401 Acute Oral Toxicity – Limit Test.
Species/Strain	Rat/WISTAR
Vehicle	Liquid paraffin (1:4, Montanov 202:vehicle)
Remarks - Method	Statement of GLP. Significant protocol deviations include: 1. No pathology performed.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	5 M	2000	0/5
II	5 F	2000	0/5

LD50	> 2000 mg/kg bw (10–20% analogue chemical)
Signs of Toxicity	None.
Effects in Organs	Not applicable
Remarks - Results	There were no deaths or notified chemical related clinical signs or remarkable body weight changes during the study period.
CONCLUSION	The test substance is of low toxicity via the oral route.
TEST FACILITY	COSMEPAR (1996a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Analogue 3
METHOD	Unspecified in summary report.
Species/Strain	Rabbit
RESULTS	
Remarks - Results	LD50 > 2000 mg/kg
CONCLUSION	The test substance is of low toxicity via the dermal route.
TEST FACILITY	USEPA (2005)

B.3. Irritation – skin (in vitro)

TEST SUBSTANCE	Simulgreen 18-2 (5% notified chemical)
METHOD	Similar to OECD TG 439 *In Vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method EpiSkin™ Reconstituted Human Epidermis Model
Vehicle	None
Remarks - Method	The test substance (16 µL) was applied to the tissues in triplicate. Following 42 minute exposure periods, the tissues were rinsed and then incubated at 37 °C for approximately 42 hours. Following treatment with MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; 0.3 mg/mL], the tissues were incubated at 37 °C for 3 hours.

Positive (sodium dodecyl sulfate; 5%) and negative (phosphate buffered saline) controls were run in parallel with the test substance. It was verified that the test substance does not interact directly with the MTT.

The optical densities were determined at 540 nm.

Results

Test Material	*Mean OD_{540} of triplicate tissues*	*Relative mean viability (%)*	*± SD of relative mean viability (%)*
Negative Control	2.256	100*	3.6
Positive Control	0.054	2.4	6.2
Test Substance	2.272	100.7	2.7

OD = optical density; SD = standard deviation
*The mean viability of the negative control tissues is set as 100%.

Remarks - Results: The relative mean viability of the test substance treated tissues was 100.7 ± 2.7% after a 42 minute exposure period.
The positive and negative controls gave satisfactory results, confirming the validity of the test system.
A mean tissue viability of > 50% is considered as non-irritating.

CONCLUSION: The test substance was considered to be non-irritating to the skin.

TEST FACILITY: Albhades Provence (2010)

B.4. Irritation – skin

TEST SUBSTANCE: Analogue 2 (≤ 1% concentration)

METHOD: Similar to OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain: Rabbit/New Zealand White
Number of Animals: 3 males
Vehicle: None, administered as supplied.
Observation Period: 48 hours
Type of Dressing: Occlusive
Remarks - Method: Statement of GLP.
Significant protocol deviations:
1. No clinical observations made at 24 and 72 hours
2. Occlusive dressing used
3. Exposure period 24 h
4. Tested with and without scarification of the skin

The experimental conditions used in this study were such that they were more likely to produce an adverse effect than the standard OECD protocol.

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	0	1	< 48 h	0
Oedema	0	0	0	0	-	0

*Calculated on the basis of the scores at 48, for EACH animal.

Remarks - Results: Slight erythema was noted in only one animal after one hour after patch removal. By 48 hours this reaction was not observed in either animal.

CONCLUSION: The test substance is slightly irritating to the skin.

TEST FACILITY: COSMEPAR (1996b)

B.5. Irritation – eye (in vitro)

TEST SUBSTANCE	Simulgreen 18-2 (20% notified chemical) – substance diluted to 10% solution in distilled water.
METHOD	OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants
Test period	4 hours exposure followed by an incubation period of 180 minutes.
Vehicle	Minimal essential media (MEM)
Remarks - Method	No significant protocol deviations. Sodium chloride 0.9% in distilled water was used as a negative control and sodium hydroxide (10%) was used as a positive control in the study. According to OECD TG 437, a substance that induces an *in vitro* Irritancy Score ≥ 55.1 is defined as a corrosive or severe irritant. Such substances will be labelled within the European Union with the risk phase R41–'Risk of serious damage to eyes'. However, there are limitations for this test method based on false and positive rates for certain chemical and physical classes (e.g. alcohols, ketones and solids). In some circumstances, the assay may be useful for identification of categories of ocular irritants other than corrosive or severe, but the accuracy and reliability of the assay have not yet been formally evaluated for this purpose.

RESULTS

Test material	*Mean opacities of triplicate tissues (SD)*	*Mean permeabilities of triplicate tissues (SD)*	*IVIS (SD)*
Negative control	0.3 (0.6)	0.002 (0.000)	0.3 (0.6)
Test substance	0.3 (0.6)	0.129 (0.023)	2.3 (0.6)
Positive control	174.3 (7.1)	7.194 (0.011)	282.2 (7.1)

SD = Standard deviation; IVIS = in vitro irritancy score

Remarks - Results	The controls gave satisfactory results confirming the validity of the test system.
CONCLUSION	The notified polymer was not corrosive or a severe eye irritant under the conditions of the test.
TEST FACILITY	IEC (2010)

B.6. Irritation – eye

TEST SUBSTANCE	Analogue 2 (≤ 1% concentration)
METHOD	Similar to OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Observation Period	7 days
Remarks - Method	

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.7	0	0	1	> 48 h < 72 h	0
Conjunctiva: chemosis	0	0	0	0	0	0
Conjunctiva: discharge	0	0	0	2	< 24 h	0
Corneal opacity	0	0	0	0	0	0

Iridial inflammation	0	0	0	0	0	0

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

Remarks - Results: After one hour discharge of the conjunctiva was noted in all three animals but was not present after 24 hours. Slight redness of the conjunctiva was observed in all three animals after one hour and in one animal up to 48 hours.

CONCLUSION: The test substance is slightly irritating to the eye.

TEST FACILITY: EViC-CEBA (1998)

B.7. Skin sensitisation

TEST SUBSTANCE: Simulgreen 18-2 (20% notified chemical) – product in solid form

METHOD: OECD TG 406 Skin Sensitisation – Magnusson and Kligman method
EC Directive (EC) No 440/2008 B.6 Skin Sensitisation – Magnusson and Kligman method.

Species/Strain: Guinea pig/Dunkin Hartley - male

PRELIMINARY STUDY: Maximum non-irritating concentration:
intradermal: 1% (minimum dose tested)
topical induction: 50% (maximum dose tested)
topical challenge: 15% (minimum dose tested)

MAIN STUDY

Number of Animals: Test Group: 10 Control Group: 5

INDUCTION PHASE: Induction Concentration:
intradermal: 1%
topical: 50% – conducted one week after intradermal induction

Signs of Irritation: Discrete/patchy erythema during the induction was observed in 7/10 animals after 24 h and 2/10 animals after 48 h.

CHALLENGE PHASE

1st challenge: topical: 15%

2nd challenge: topical: Not performed

Remarks - Method: Polyethylene glycol 300 (PEG 300) solution was chosen as the vehicle. Adjuvant method used where both test and control animals were intradermally induced by both PEG300 and Freund's Complete Adjuvant (FCA)/physiological saline solution.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*			
		1st challenge		*2nd challenge*	
		24 h	*48 h*	*24 h*	*48 h*
Test Group	15% test substance in PEG300	2/10	0/10	-	-
	PEG300 only	0/10	0/10	-	-
Control Group	15% test substance in PEG300	0/5	0/5	-	-
	PEG300 only	0/5	0/5	-	-

Remarks - Results: The challenge indicated that 20% of guinea pigs had been sensitised under the conditions of the test. However, the study authors note that a response of at least 30% of the animals showing sensitisation to be considered positive when using the adjuvant test method. As the reaction faded at the 48 hr observation period, the study authors note the results indicate irritation rather than sensitisation.

CONCLUSION: There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY: Harlan (2010)

B.8. Skin sensitisation – human volunteers

TEST SUBSTANCE	Analogue 1
METHOD	Repeated insult patch test. Marzulli and Maibach's method
Study Design	The study consisted of an induction procedure and a challenge procedure.
Study Group	36 (or 35) females and 14 males aged from 19 to 59 years old
Vehicle	5% Montanov 68 in distilled water
Induction Procedure:	The test substance was applied to 9 volunteers in 9 consecutive applications of about 48 hours or for the first two weekends at 72 hours apart. In each application about 0.02 mL was applied to the same area by the occlusive epicutaneous route to the skin of the arm.
Rest Period:	15 weeks
Challenge Procedure:	The test substance was applied to 50 volunteers in a single application for about 48 hours. In each application. In each application about 0.02 mL was applied to the back by the occlusive epicutaneous route.
Remarks - Method	In the preliminary study only a slightly visible erythema was detected in 2 out of the 9 volunteers examined without any clear dose level/effect relation. In the main study neither pathological irritation, nor sensitisation reaction significant of a cutaneous intolerance was noted.
RESULTS	
Remarks - Results	The Mean Irritation Index (MII) obtained during induction was equal to 0.03, thus allowing arbitrary classification of the test article as 'non irritant'.
CONCLUSION	Montanov 68 diluted with distilled water to 5% was non-irritating and non-sensitising under the conditions of the test.
TEST FACILITY	IEC (1994)

B.9. Skin sensitisation – human volunteers

TEST SUBSTANCE	Analogue 2
METHOD	Marzulli and Maibach's method Repeated epicutaneous 48-hour applications under occlusive patch.
Preliminary Study	Four successive occlusive epicutaneous applications to the arm of 10 volunteers (9 women and 1 man), for 48 or 72 hours. Three concentrations were tested on each subject: 1%, 2.5% and 5% (w/w).
Main Study Design	Induction Procedure: Nine consecutive applications of 5% (w/w) Montanov 202, to the arm, for 24–72 hours. Rest Period: 15 days Challenge Procedure: Single application of 5% (w/w) Montanov 202, to the back, for 48 hours.
Main Study Group	50 adult Caucasian volunteers (45 women and 5 men) started the study 49 were evaluated for irritation (44 women and 5 men) and 48 were evaluated for sensitisation (43 women and 5 men)
Vehicle	Distilled water
Remarks - Method	Macroscopic examinations of test sites for signs of irritation and/or sensitisation were performed 24 and 48 hours after the 8th induction application, and after the challenge application, by comparison with a negative vehicle-only control patch. Both irritation and sensitisation were scored on a scale of 0 (no reaction) to 4 (severe erythema and/or oedema). A mean irritation index was calculated for the entire cohort. Classification of irritancy potential was according to the following:

Mean Irritation Index	Classification

<0.25	Non-irritant
0.25 ≤ MII < 1	Slightly irritant
1 ≤ MII < 2	Irritan
2 ≤ MII < 3	Very irritant
3–4	Severely irritant

An individual sensitisation score of 3 or more was considered positive evidence for sensitising potential of the test substance.

RESULTS

Preliminary Study: No irritation was observed at any of the concentrations tested.

Main Study-Induction: A single instance of slight irritation (irritation score of 1) was observed in 10/49 of subjects. Several instances of slight irritation were observed in 4/49 of subjects. The mean irritation index for all subjects during the induction phase was 0.06.

Main Study-Challenge: A single instance of slight reaction (sensitisation score of 1) was observed in 2/48 subjects. Slight to mild reaction (sensitisation scores of 1–2) was observed at both 24 and 48 hour time points in 1 subject. No subject showed a response that was considered positive for sensitisation.

CONCLUSION: Montanov 202 was non-irritating and showed limited evidence of sensitisation under the conditions of the test.

TEST FACILITY: IEC (1997)

B.10. Repeat dose toxicity

TEST SUBSTANCE: Analogue 1

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

Species/Strain: Rat/Sprague-Dawley

Route of Administration: Oral – gavage

Exposure Information: Total exposure days: 28 days
Dose regimen: 7 days per week
Post-exposure observation period: 0

Vehicle: Olive oil

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	100	0/10
mid dose	5M/5F	300	0/10
high dose	5M/5F	1000	0/10

Mortality and Time to Death

There were no unscheduled deaths throughout the study.

Clinical Observations

No adverse clinical signs were observed throughout the study.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Males and females treated with 300 and 1000 mg/kg/day had higher triglyceride levels with the highest dose group also exhibiting higher urea and cholesterol levels. Epididymal sperm count and the percentage of morphologically normal sperm was decreased for all groups treated with the test article.

Effects in Organs

No effects on organs or organ weights were observed.

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) was established as < 100 mg/kg bw/day in this study, based on effects on seminology at all doses tested.

TEST FACILITY CIT (2008)

B.11. Repeat dose toxicity

TEST SUBSTANCE Analogue 1

METHOD OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents.
Species/Strain Rat/Wistar
Route of Administration Oral – gavage
Exposure Information Total exposure days: 90 days
Dose regimen: 5/7 days per week
Post-exposure observation period: 28 days
Vehicle Olive oil
Remarks - Method The study included clinical pathology and histopathological evaluations of male reproductive organs of the control and high dose groups using the testing methods from OECD TG 416 Two-generation Reproduction Toxicity Study. No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	10M/10F	0	0/20
low dose	10M/10F	100	0/20
mid dose	10M/10F	300	0/20
high dose	10M/10F	1000	0/20
control recovery	5M/5F	0	0/10
high dose recovery	5M/5F	1000	0/10

Mortality and Time to Death
There were no unscheduled deaths throughout the study.

Clinical Observations
Salivation was observed in all animals in all test groups between 10–45 minutes following treatment. It was observed intermittently and not in the same animals. A slightly higher incidence of salivation was observed in the high dose group. No other clinical signs were observed.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No test-item related changes were observed in clinical chemistry, haematology and urinalysis at any dose level.

Effects in Organs
There were no effects observed on organs at any dose level.

Sperm Evaluation
Sperm motility was decreased and abnormal sperm morphology was slightly increased in the high dose group. Cauda epididymal sperm count and weight was not significantly different to controls.

Remarks – Results
The salivation observed in all rats was determined to be a transient non-adverse effect and likely due to taste effects or mild gastro-eosophageal reflux following gavage dosing. The changes in sperm parameters were not dose related and were not considered to be biologically significant.

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) was established as 1000 mg/kg bw/day in this study, based on no test item related effects at this dose level.

TEST FACILITY DSA (2013)

B.12. Repeat dose toxicity

TEST SUBSTANCE Analogue 3

METHOD Not specified (study summary only)
Species/Strain Rat (strain unspecified)
Route of Administration Oral – gavage
Exposure Information Total exposure days: 90 days
Dose regimen: 5/7 days per week
Post-exposure observation period: 27
Vehicle Unknown
Remarks - Method Full study report not cited.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	males and females (no. unknown)	0	0
II (low dose)	males and females (no. unknown)	250	0
III (mid dose)	males and females (no. unknown)	500	0
IV (high dose)	males and females (no. unknown)	1000	0
VI (high dose recovery)	males and females (no. unknown)	1000	0

Mortality and Time to Death
No deaths were reported.

Clinical Observations
No adverse treatment-related effects reported.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No adverse treatment-related effects reported.

Effects in Organs
Adverse treatment-related effects were limited to the forestomach in both males and females in the mid and high dose group although these effects were reversible after 27 days. No other adverse treatment-related effects were reported.

Remarks – Results
A LOAEL of 500 mg/kg bw/day was established based on acanthosis, subepithelial inflammatory oedema, and hyperkeratosis (females only) of the forestomach at this dose level.

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) was established as 250 mg/kg bw/day in this study, based on treatment-related effects at higher dose levels.

TEST FACILITY USEPA (2005)

B.13. Developmental toxicity

TEST SUBSTANCE Analogue 1

METHOD OECD TG 414 Prenatal Developmental Toxicity Study.
Species/Strain Rat/Sprague-Dawley
Route of Administration Oral – gavage
Exposure Information Total exposure days: up to 21 days post-coitum
Post-exposure observation period: 0
Vehicle Olive oil

Remarks - Method	Chemical analysis of the dosage forms was not performed. No other significant protocol deviations. Only the first 20 pregnant females were taken into consideration for foetal examinations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	24F	0	0/10
low dose	24F	100	0/10
mid dose	24F	300	0/10
high dose	24F	1000	0/10

Mortality and Time to Death

One female treated with 100 mg/kg/day was sacrificed on day 7 post-partum following signs of dypsnea, chromorhinorrhea and loud breathing due to a suspected gavage error. There were no other unscheduled deaths throughout the study.

Effects on Dams

Salivation were noted in 5, 9 and 20 females treated in the low, mid and hgh dose groups respectively during the second half of the treatment period, lasting between 1 and 11 days. One female from each treatment group showed soiled urogenital are on day 20/21 post-coitum. No effects on maternal body weight gain or food consumption were recorded.

Effects on Foetus

No animals showed any treatment related foetal malformations. At soft tissue and skeletal examinations several foetal variations were observed but the incidences were low with no clear dose-relationship. The number of corpora lutea, implantation and live pups born were similar to control group levels.

Remarks – Results

Salivation was attributed to the test item but was considered non-adverse. Variations at foetal examination were not considered adverse.

CONCLUSION

The No Observed (Adverse) Effect Level (NO(A)EL) for maternal and developmental toxicity was established as 1000 mg/kg bw/day in this study, based on no observed adverse effects at this dose level.

TEST FACILITY CIT (2008)

B.14. Repeat dose/Developmental toxicity

TEST SUBSTANCE Analogue 2

METHOD OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test.

Species/Strain	Rat/Sprague-Dawley
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: up to 61 Post-exposure observation period: 0
Vehicle	Olive oil
Remarks - Method	Chemical analysis of the dosage forms was not performed. No other significant protocol deviations. A functional observation battery was included in the protocol.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	10M/10F	0	0/10
low dose	10M/10F	100	0/10

mid dose	10M/10F	300	0/10
high dose	10M/10F	1000	0/10

Mortality and Time to Death
There were no unscheduled deaths.

Clinical Observations
Hypersalivation and reflux were noted in all groups including controls following dosing. Markedly reduced movement in females treated at 1000 mg/kg/day was noted. No other clinical signs were noted.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No treatment related effects were noted for clinical chemistry, haematology and urinalysis.

Effects in Organs
There were no treatment related effects on organs observed.

Remarks – Results
Hypersalivation was attributed to the test item but was considered non-adverse. No animals showed any treatment related effects on mating or fertility. The number of corpora lutea, implantation and live pups born were similar to control group levels.

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) for parental toxicity was established as 1000 mg/kg bw/day in this study, based on no observed adverse effects at this dose level. The NOEL for reproductive performance was 1000 mg/kg bw/day and the NOEL for progeny was 1000 mg/kg bw/day.

TEST FACILITY CIT (2010)

B.15. Genotoxicity – bacteria

TEST SUBSTANCE Simulgreen 18-2 (20% notified chemical)

METHOD
OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria.
Plate incorporation (test 1) and pre-incubation (test 2) procedures

Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100 *Escherichia coli*: WP2uvrA (pKM101)
Metabolic Activation System	Aroclor 1254-induced rat liver S9 mix
Concentration Range in Main Test	a) With metabolic activation: 50, 150, 500, 1500 and 5000 µg/plate b) Without metabolic activation: 50, 150, 500, 1500 and 5000 µg/plate
Vehicle	Dimethyl sulfoxide (DMSO)
Remarks - Method	There were no significant protocol deviations.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 5000	≥ 5000	5000	Negative
Test 2		≥ 1500	5000	Negative
Present				
Test 1	≥ 5000	≥ 5000	5000	Negative
Test 2		≥ 5000	5000	Negative

Remarks - Results
There was no significant increase in the number of aberrant cells in any cell line, either with or without metabolic activation.

The positive controls caused statistically significant increases in the

	proportion of aberrant cells, demonstrating the validity of the test system.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	LEMI (2010)

B.16. Genotoxicity – in vitro

TEST SUBSTANCE	Analogue 3
METHOD	In vitro Mammalian Cytogenetics Assay.
Remarks	No study details were provided in the summary.
CONCLUSION	The test substance was negative with and without activation, in vitro, under the conditions of the test.
TEST FACILITY	USEPA (2005)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Product containing ≤ 20% notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Not reported
Remarks - Method	The method was conducted according to test guidelines using good laboratory practice (GLP) with no significant deviations. The test was conducted on a product containing ≤ 20% notified chemical and ≥ 80% unreacted, non-aqueous starting material.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	36.9	7	78.3
14	53.2	14	90.9
28	67.3	28	92.7

Remarks - Results	All relevant test validity criteria were met. Toxicity controls experienced > 25% degradation in 24 days, indicating that the test substance does not inhibit microbial respiration. The 60% degradation in 10 day window requirement was not met, and therefore the test substance cannot be considered readily biodegradable.
CONCLUSION	The test substance is not readily biodegradable.
TEST FACILITY	FCBA (2010)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Product containing ≤ 20% notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi Static.
Species	*Danio rerio* (Zebra fish)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	GC/FID
Remarks – Method	The method was conducted according to test guidelines using good laboratory practice (GLP) with no significant deviations. The test was conducted on a product containing ≤ 20% notified chemical and ≥ 80% unreacted, non-aqueous starting material. Water accommodated fractions (WAF) were prepared by stirring the test concentration in dilution water over 24 hours and filtering through a membrane filter. Water accommodated fractions were thus used as test solutions. Test solutions were renewed every 24 hours during the test.

RESULTS

Concentration mg/L *Nominal*	*Number of Fish*	*Mortality* *24 h*	*48 h*	*72 h*	*96 h*
Control	7	0	0	0	0
1	7	0	0	0	0
10	7	0	0	0	0
100	7	0	0	0	0

LC50 > 100 mg/L at 96 hours (filtered WAF)
NOEC > 100 mg/L at 96 hours (filtered WAF)
Remarks – Results All relevant test validity criteria were met.

CONCLUSION The test substance is not expected to be harmful to fish.

TEST FACILITY FCBA (2011a)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Product containing ≤ 20% notified chemical

METHOD OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Semi Static.
Species *Daphnia magna*
Exposure Period 48 hours
Auxiliary Solvent None
Water Hardness 260 mg $CaCO_3$/L
Analytical Monitoring GC/FID
Remarks - Method The method was conducted according to test guidelines using good laboratory practice (GLP) with no significant deviations. The test was conducted on a product containing ≤ 20% notified chemical and ≥ 80% unreacted, non-aqueous starting material. Water accommodated fractions (WAF) were prepared by stirring the test concentration in dilution water over 24 hours and filtering through a membrane filter. Water accommodated fractions were thus used as test solutions. Test solutions were renewed at 24 hours during the test.

RESULTS

Concentration mg/L *Nominal*	*Number of D. magna*	*Number Immobilised* *24 h*	*48 h*
Control (filtered)	6 × 5	0	0
Control (unfiltered)	6 × 5	0	0
1	6 × 5	0	0
10	6 × 5	0	0
100	6 × 5	0	0

EC50 > 100 mg/L at 48 hours (filtered WAF)
NOEC (or LOEC) > 100 mg/L at 48 hours (filtered WAF)
Remarks - Results All relevant test validity criteria were met.

CONCLUSION The test substance is not expected to be harmful to aquatic invertebrates.

TEST FACILITY FCBA (2011b)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Product containing ≤ 20% notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test.
Species *Pseudokirchneriella subcapitata*
Exposure Period 72 hours
Concentration Range Nominal: 1, 10 and 100 mg/L

Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	GC/FID
Remarks - Method	The method was conducted according to test guidelines using good laboratory practice (GLP) with no significant deviations. The test was conducted on a product containing ≤ 20% notified chemical and ≥ 80% unreacted, non-aqueous starting material. Water accommodated fractions (WAF) were prepared by stirring the test concentration in dilution water over 24 hours and filtering through a membrane filter. Water accommodated fractions were thus used as test solutions.

RESULTS

Biomass	*Growth*		
	E_rC50	*NOEC*	*LOEC*
	mg/L at 72 h	*mg/L*	*mg/L*
Not reported	> 100	10	100

Remarks - Results	All relevant test validity criteria were met. Growth rates were reduced by approximately 20% at concentrations of 100 mg/L, as reflected by the NOEC and LOEC. However, the E_rC50 remained at > 100 mg/L at 72 hours.
CONCLUSION	The test substance is not expected to be harmful to algae.
TEST FACILITY	FCBA (2011c)

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