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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

L-Glutamic acid, N-(1-oxooctadecyl)-, sodium salt (1:2) (INCI Name: Disodium Stearoyl Glutamate)

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

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

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Director
NICNAS

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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
LTD/1870	L'Oreal Australia Pty Ltd	L-Glutamic acid, N-(1-oxooctadecyl)-, sodium salt (1:2) (INCI Name: Disodium Stearoyl Glutamate)	Yes	≤ 1 tonne per annum	Cosmetic ingredient

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard classification	*Hazard statement*
Skin corrosion/irritation (Category 2)	H315 – Causes skin irritation
Eye irritation (Category 2A)	H319 – Causes serious eye irritation

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

R36: Irritating to eyes
R38: Irritating to the skin

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

Hazard classification	*Hazard statement*
Acute (Category 2)	H401 - Toxic to aquatic life
Chronic (Category 2)	H411 – Toxic to aquatic life with long lasting effects

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 ≤ 1% in leave-on cosmetic products and ≤ 3.5% in rinse-off cosmetics, the notified chemical is not considered to pose an unreasonable risk to public health.

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

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Skin corrosion/irritation (Category 2): H315 – Causes skin irritation
  - Eye irritation (Category 2A): H319 – Causes serious eye irritation

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

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

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical as introduced:
  - Exhaust ventilation
  - Enclosed and automated systems

- 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:
  - Coveralls
  - Eye protection
  - Impervious gloves
  - Respiratory protection

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

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

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

Public Health

- Formulators should consider that cosmetic products containing the notified chemical should be formulated in a manner to be non-irritating.

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, 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 importation volume exceeds one tonne per annum notified chemical;
- the concentration of the notified chemical exceeds or is intended to exceed 1% in leave-on cosmetic products and 3.5% in rinse-off cosmetic products.

or

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

ASSESSMENT DETAILS

This notification has been conducted under the cooperative arrangement with the Australian Therapeutic Goods Administration (TGA). The health hazard assessment component of the TGA report were provided to NICNAS and, where appropriate, used in this assessment report. The other elements of the risk assessment and recommendations on safe use of the notified chemical were carried out by NICNAS.

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
L'Oreal Australia Pty Ltd (ABN: 40 004 191 673)
564 St Kilda Road
MELBOURNE VIC 3004

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less per year) – Assessed by comparable agency.

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: analytical data, degree of purity, impurities, use details, 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 and dissociation constant.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
TGA (2013).

NOTIFICATION IN OTHER COUNTRIES
None.

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Disodium Stearoyl Glutamate (INCI Name)

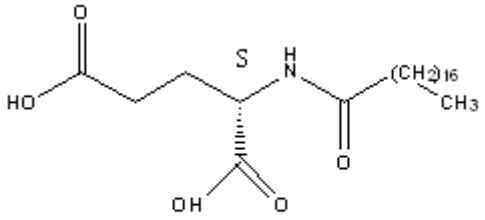
CAS NUMBER
38079-62-8

CHEMICAL NAME
L-Glutamic acid, *N*-(1-oxooctadecyl)-, sodium salt (1:2)

OTHER NAME(S)
Disodium Stearoyl Glutamate
Disodium Stearoyl-L-glutamate

MOLECULAR FORMULA
$C_{23}H_{43}NO_5.2Na$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
457.56 Da

ANALYTICAL DATA
A reference IR spectrum was provided.

3. COMPOSITION

DEGREE OF PURITY
> 85%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Pale yellow powder

Property	Value	Data Source/Justification
Melting Point/Freezing Point	> 316 °C	Measured
Boiling Point	Not determined	Notified chemical decomposed prior to boiling.
Density	1,150 kg/m^3 at 21.3 °C	Measured
Vapour Pressure	< 2.3 x 10^{-8} kPa at 25 °C	Measured
Water Solubility	260-270 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Does not contain hydrolysable functionalities.
Partition Coefficient (n-octanol/water)	log Kow = 1.23	Calculated. The notified chemical is a surfactant and is expected to concentrate at phase boundaries.
Surface Tension	53.0 mN/m at 25 °C	Measured
Adsorption/Desorption	Not determined	The notified chemical is expected to adsorb to organic carbon, soil and sediment because it is a surfactant
Dissociation Constant	Not determined	As a sodium salt of a carboxylic acid, the notified chemical is expected to be ionised over the environmental pH range (4–9)
Particle Size	Inhalable fraction (< 100 μm): 76.4% Respirable fraction (< 10 μm): 3.41%	Measured. Insufficient particles available to measure MMAD*
Flash Point	Not determined	Not expected to flash prior to decomposition.
Flammability	Not highly flammable	Measured
Autoignition Temperature	> 316 °C	Measured
Explosive Properties	Predicted negative	Estimated
Oxidising Properties	Predicted negative	Estimated

* MMAD = Mass Median Aerodynamic Diameter / MAD = Mean Aerodynamic diameter

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. It will be imported as the raw material at > 85% concentration for formulation of cosmetic products. The notified chemical will also be imported as a component of finished cosmetic products (at ≤ 3.5% concentration).

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

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

PORT OF ENTRY
Melbourne and Sydney

TRANSPORTATION AND PACKAGING
The notified chemical will be transported at > 85% concentration in 15 kg plastic bags within cardboard boxes and transported by sea. The notified chemical may also be imported as a component of finished cosmetic products at ≤ 3.5% concentration. Finished cosmetic products containing the notified chemical will be packaged in ≤ 500 mL plastic bottles or tubes for retail sale. These containers will be packaged in cartons and pallets for transport by sea.

USE
The notified chemical will be used as an ingredient in leave on cosmetic products (at concentrations ≤ 1%) and rinse-off products (at concentrations ≤ 3.5%).

OPERATION DESCRIPTION
The notified chemical will be imported in its raw form (at > 85% concentration) for formulation of cosmetic products, or as a component of finished cosmetic products (at ≤ 1% concentration for leave-on products and ≤ 3.5% concentration in rinse-off products) which will be sold to the public in the same form in which they are imported.

Reformulation
The procedures for incorporating the notified chemical (at > 85% concentration) into end-use products will vary depending on the nature of the cosmetic product being formulated and both manual and automated steps will likely be involved. However, in general, it is expected that for the reformulation process, the notified chemical will be weighed and added to the mixing tank where it will be blended with additional additives to form the finished cosmetic products. This will be followed by automated filling of the reformulated products into containers of various sizes. The blending operations are expected to be highly automated and use closed systems and/or adequate ventilation. During the formulation process, samples of the notified chemical and the finished cosmetic products will be taken for quality control testing.

End-use
Finished products containing the notified chemical at ≤ 1% concentration for leave-on products and ≤ 3.5% concentration in rinse-off products will be used by the public and may also be used by professionals such as hairdressers and workers in beauty salons. Depending on the nature of the product, these could be applied by hand, sprayed or by 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
Professional users – (e.g. hair and beauty salon workers)	Not specified	Not specified

EXPOSURE DETAILS

Transport, storage and retail workers may come into contact with the notified chemical at > 85% concentration, or at ≤ 3.5% concentration in cosmetic products only in the event of accidental rupture of packages.

Reformulation

During reformulation into cosmetic products, dermal, ocular and inhalation exposure of workers to the notified chemical at > 85% concentration may occur. Exposure is expected to be minimised through the use of exhaust ventilation and/or automated/enclosed systems as well as through the use of personal protective equipment (PPE) such as coveralls, eye protection, impervious gloves and respiratory protection (as appropriate).

End-use

Exposure to the notified chemical in end-use products at ≤ 3.5% concentration may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. 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, but this is not expected to occur in all workplaces. However, 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 at ≤ 1% concentration for leave-on products and ≤ 3.5% concentration in rinse-off products. The principal route of exposure will be dermal. Accidental ocular and oral exposure is also possible. Inhalation exposure is not expected based on the use pattern and low vapour pressure of the notified chemical.

6.2. Human Health Effects Assessment

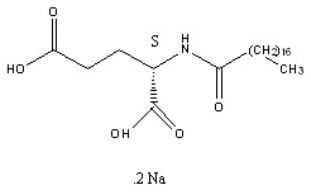
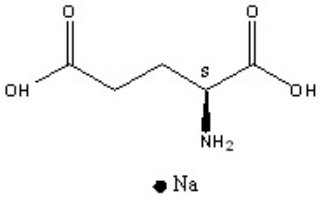
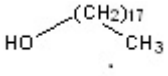
The results from toxicological investigations conducted on the notified chemical are summarised in the following table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*	*Test Substance*
Rat, acute oral toxicity	LD50 = 4,920 mg/kg bw; low toxicity	Notified Chemical
Rat, acute oral toxicity (Harlan 2009)	LD50 > 2,000 mg/kg bw; low toxicity	Notified Chemical
Skin irritation (in vitro) – EpiSkin (Episkin 2008)	test not valid	Notified Chemical
Skin irritation (in vitro) – EpiSkin (Safepharm 2008c)	non-irritating	Notified Chemical
Rabbit, skin irritation	irritating	Notified Chemical (5%)
Eye irritation (in vitro) – BCOP (IEC 2006a)	not a severe eye irritant	Notified Chemical (1% and 5%)
Eye irritation (in vitro) – BCOP (IEC 2006b)	not a severe eye irritant	Notified Chemical (0.2%)
Eye irritation (in vitro) – HET-CAM (EVIC 2006)	irritating	Notified Chemical (1% and 5%)

Eye irritation (in vitro) – Human Corneal Epidermis Cytotoxicity (Episkin 2009)	inconclusive	Notified Chemical
Eye irritation (in vitro) – Reconstituted Human Corneal Epithelium (Safepharm 2009d)	non-irritating	Notified Chemical
Rabbit, eye irritation	irritating	Notified Chemical (5%)
Guinea pig, skin sensitisation – non-adjuvant test.	inadequate evidence	Notified Chemical (2.5%)
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation	Notified Chemical (10%)
Human, skin sensitisation – RIPT	no evidence of sensitisation	Notified Chemical (1%)
Human, skin sensitisation – RIPT	no evidence of sensitisation	Notified Chemical (0.85%)
Human, skin sensitisation – RIPT	no evidence of sensitisation	Notified Chemical (0.8%)
Mutagenicity – bacterial reverse mutation	non mutagenic	Notified Chemical
Mutagenicity – bacterial reverse mutation	non mutagenic	Notified Chemical

No repeated dose toxicity data were submitted for the notified chemical. L-Glutamic acid, sodium salt (1:1) [sodium hydrogen glutamate] has been used as an analogue (analogue 1) to the glutamic acid component of the notified chemical. Repeated dose toxicity studies based on 1-Octadecanol (analogue 2) are available (UNEP).

Comparison of structural and physicochemical properties of analogue chemicals with the notified chemical:

	Notified Chemical	*Analogue 1*	*Analogue 2*
Chemical Name	L-Glutamic acid, N-(1-oxooctadecyl)-, sodium salt (1:2)	L-Glutamic acid, sodium salt (1:1)	1-Octadecanol
INCI Name	Disodium Stearoyl Glutamate		
CAS Number	38079-62-8	142-47-2	112-92-5
Structural Formula			
Molecular Weight	457.57 Da	187.13	270.49
Water Solubility	260 – 270 g/L at 20 ^{0}C	8.64 g/L	< 0.001 g/l
Partition Coefficient (Log Pow)	1.23 (calc.)	< -4	7.4

Toxicokinetics, metabolism and distribution
No toxicokinetic data on the notified chemical were submitted. Low levels of the notified chemical are expected to be absorbed through the skin based on a percutaneous study on acetyl tyrosine (an amino acid alkyl amide like the notified chemical) (CIR 2014). Where dermal penetration occurs, the notified chemical, may be catalysed by amidases into glutamic acid and octadecanoic acid (CIR 2014).

Acute toxicity
The notified chemical is expected to have a low acute oral toxicity based on studies conducted on rats.

Irritation
The notified chemical is irritating to the skin at a concentration of 5% based on a study conducted on rabbits. An *in vitro* study conducted using a reconstructed Human Epidermis model (EpiSkin™) showed no skin irritation. Overall as the irritant effects seen at a concentration of 5% on rabbits were significant the notified chemical is considered to be irritating to the skin, despite the *in vitro* study being negative for irritation. In human repeat

insult patch tests (HRIPT) under occlusive and prolonged exposure conditions mild erythema was observed in a small number of the test subjects when the notified chemical was present at a concentration of 0.8% or 0.85%, although no signs of irritation were seen at a concentration of 1%. The HRIPT studies suggest that the notified chemical is unlikely to be irritating to the skin when used in products at concentrations ≤ 1%.

The notified chemical was irritating to the eyes of rabbits at a concentration of 5%. Slight corneal opacity, congestion in the iris, conjunctival redness, swelling and an adhering discharge were recorded 24 hr after exposure. Signs of recovery 3 days after exposure were indicated. An *in vitro* study using reconstituted human corneal epithelium (SkinEthic) indicated that the notified chemical was non-irritating to the eye when tested undiluted. Additionally, two *in vitro* studies using the bovine corneal model (BCOP) indicated that the notified chemical is not a severe eye irritant at concentrations up to 5%. A embryonic hens egg chorioallantoic method (HET-CAM) model indicated that the notified chemical is irritating to the eye at concentrations up to 5%. Overall, the notified chemical at concentrations up to 5% is irritating to the eye but is not expected to be a severe eye irritant.

Sensitisation
In three human repeat insult patch tests (HRIPT), the notified chemical showed no evidence of sensitisation when tested in end-use products containing the notified chemical at up to 1% concentration. The test conditions used in a non-adjuvant sensitisation study on guinea pigs were inadequate to show if the notified chemical was a sensitiser. A local lymph node assay on mice showed no evidence of the notified chemical being a skin sensitiser when tested up to 10% concentration.

The notified chemical does not contain any structural alerts for sensitisation.

Repeated dose toxicity
Analogue 1 and its parent acid (L-glutamic acid; CAS No. 56-86-0) are of low systemic toxicity (Walker and Lupien, 2000; OECD, 2013).
A NOAEL of > 1,000 mg/kg bw/day was determined for analogue 2 based on a sub-chronic study on rats (performed in accordance with OECD test guideline 407) (UNEP).

Mutagenicity/Genotoxicity
The notified chemical has been found to be negative in two independent bacterial reverse mutation assays.

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

Hazard classification	***Hazard statement***
Skin corrosion/irritation (Category 2)	H315 – Causes skin irritation
Serious eye damage/eye irritation (Category 2A)	H319 – Causes serious eye irritation

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrase(s):
R38: Irritating to skin
R36: Irritating to eyes

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the available information, the notified chemical is expected to be of low systemic toxicity, presenting as a skin and eye irritant. The main route of exposure is expected to be dermal with some potential for accidental ocular or oral exposure.

Reformulation
During reformulation workers may be at risk of skin and eye irritation effects when handling the notified chemical at > 85% concentration. This risk should be reduced through the expected use of engineering controls and personal protective equipment (PPE) including eye protection.

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.

End-use
Workers involved in professions where the services provided involve the application of cosmetic products containing the notified chemical to clients (*e.g.*, hairdressers and beauty salon workers) may be exposed to the notified chemical at concentrations up to 3.5%. If PPE is used, the risk to these workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical (for details of the public health risk assessment, see Section 6.3.2).

6.3.2. Public Health
Cosmetic products containing the notified chemical at ≤ 1% concentration for leave-on products and ≤ 3.5% concentration in rinse-off products will be available to the public. The main route of exposure is expected to be dermal with some potential for accidental ocular or oral exposure.

Amino acid alkyl amides such as the notified chemical mainly act as skin and hair conditioning agents and as surfactants-cleansing agents (CIR, 2014). The CIR Panel (2014) noted that most surfactants exhibit some irritancy, and that products containing these ingredients should be formulated to be non-irritating.

Local effects
The notified chemical is not expected to be a skin sensitiser based on animal studies. The notified chemical is irritating to the skin and eyes. However, skin irritation effects were not observed in skin sensitisation studies where the notified chemical was regularly applied at a concentration of ≤ 1%. The notified chemical is expected to have skin and eye irritating effects at the proposed use concentration in rinse-off products (≤ 3.5%). However, based on the nature of these products, exposure to the notified chemical is expected to be low.

Systemic effects
Based on the acute toxicity of the notified chemical and the repeated-dose toxicity of analogues 1 and 2, the notified chemical is expected to have low systemic toxicity.

Overall, based on the information available, the risk to the public associated with the use of the notified chemical at up to 1% in leave-on cosmetics and up to 3.5% in rinse off 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 or as a raw material for local reformulation. The reformulation process will involve blending operations that will be highly automated and are expected to occur in a fully enclosed environment. The process will be followed by automated filling of the formulated products into containers of various sizes. Typical wastes generated during reformulation that may contain the notified chemical include reformulation equipment washings, empty import containers and spilt materials. The waste is expected to be collected and released landfill or to sewers for the worst case scenario.

RELEASE OF CHEMICAL FROM USE
The notified chemical is used as a component in cosmetics and applied to the skin or hair. Therefore, it is expected that the majority of the annual import volume will be released to the sewer during washing by consumers.

RELEASE OF CHEMICAL FROM DISPOSAL
As the notified chemical is used in cosmetics it is expected that the majority of the annual import volume will be released to the sewer through consumer use. It has been estimated that ≤ 3% of notified chemical may remain as residues within end use containers, while ≤ 1% may remain in raw material containers. It is expected that end use containers containing residues of the notified chemical will either be recycled or disposed of as domestic garbage and end up in landfill sites.

7.1.2. Environmental Fate

Following its use in Australia, the majority of the notified chemical is expected to enter the sewer system through its use as a component of cosmetic products, before potential release to surface waters nationwide. The notified chemical is not readily biodegradable (52% in 28 days). For details of the environmental fate studies, please refer to Appendix C. Based on its surface active property and the modelled bioconcentration factor (BCF = 43.27), the notified chemical is not expected to bioaccumulate. In surface waters the notified chemical is expected to disperse and degrade through abiotic and biotic processes to form water and oxides of carbon and nitrogen.

The notified chemical is expected to partition to phase boundaries as it is surface active. 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, or disposed to landfill as collected spills and empty containers. The notified chemical residues in landfill, soil and sludge are expected to have low mobility based on surface activity, and is expected to eventually degrade to form water and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated assuming a worst case scenario of 100% release of the notified chemical into sewer systems nationwide and no removal from STPs.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.61	µg/L
PEC - Ocean:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.61 µg/L may potentially result in a soil concentration of approximately 4.04 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 20.2 µg/kg and 40.4 µg/kg, respectively.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemical are summarised in the table below. The provided studies include acute toxicity of the notified chemical to aquatic invertebrates and algae. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Daphnia Toxicity (48 hours)	EC_{50} > 100% v/v*	Not toxic to aquatic invertebrates
Algal Toxicity (72 hours)	ErC_{50} = 4.3 mg/L	Toxic to algae

*The concentration of the test material could not be determined in the test media. The 48-hour EC50 was 100% v/v and so the no observed effect concentration (NOEC) was established at the value of 100% saturation solution.

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is toxic to algae, and is formally classified as 'Acute Category 2: Toxic to aquatic life'. Based on the acute toxicity, lack of ready biodegradability and low bioaccumulation potential of the notified chemical, it is classified 'Chronic Category 2: Toxic to aquatic life with long lasting effects.

7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) was calculated using the most sensitive toxicity endpoint of the notified chemical among the two test species (ErC_{50} = 4.3 mg/L for algae). A conservative assessment factor of 1000 was used since only two trophic levels of ecotoxicological data (invertebrates and algae) have been provided.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Alga).	4.30	mg/L
Assessment Factor	1,000	
PNEC:	4.30	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) has been calculated for a worst case discharge scenario based on the predicted PEC and PNEC.

Risk Assessment	***PEC µg/L***	***PNEC µg/L***	***Q***
Q - River:	0.61	4.3	0.141
Q - Ocean:	0.06	4.3	0.014

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment (Q < 1) 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 not expected to be readily biodegradable or bioaccumulate in the environment. Therefore, the notified chemical is unlikely to result in ecotoxicologically significant concentrations in the aquatic Therefore, on the basis of the PEC/PNEC ratio and the assessed use pattern the notified chemical is not expected to pose an unreasonable risk to the environment

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point > 316 °C

Method	ASTM E537-86 Method A1 of Commission Directive 92/69/EEC
Remarks	Differential scanning calorimetry.
Test Facility	SafePharm (2008a)

Density 1,150 kg/m^3 at 21.3 °C

Method	Method A3 of Commission Directive 92/69/EEC
Remarks	Gas comparison pycnometer
Test Facility	SafePharm (2008a)

Vapour Pressure < 2.3 x 10^{-8} kPa at 25 °C

Method	Method A4 of Commission Directive 92/69/EEC
Remarks	Vapour pressure balance
Test Facility	SafePharm (2008b)

Water Solubility 260-270 g/L at 20 °C

Method	EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks	Flask Method. The standard A6 Method was not applicable to this test material due to high indeterminable saturation levels.
Test Facility	SafePharm (2008a)

Surface Tension 53.0 mN/m at 25 °C

Method	Method A.5 of Commission Directive 92/69/EEC
Remarks	Concentration: 1.008 mg/mL; ISO 304 ring method
Test Facility	SafePharm (2008a)

Particle Size

Method OECD TG 110 Particle Size Distribution/Fibre Length and Diameter Distributions.

Range (μm)	*Mass (%)*
< 100.0	76.4
< 10.0	3.41
< 5.5	1.42
< 2.4	0.88
< 1.61	0.64
< 0.307	0.51

Remarks	Cascade Impactor
Test Facility	SafePharm (2008a)

Flammability Not highly flammable

Method	Method A10 of Commission Directive 92/69/EEC
Remarks	Notified chemical failed to ignite within required time frame
Test Facility	SafePharm (2008b)

Autoignition Temperature > 316 °C

Method	Method A16 of Commission Directive 92/69/EEC
Remarks	Notified chemical failed to ignite below its melting temperature.
Test Facility	SafePharm (2008b)

Explosive Properties Predicted negative

Method	EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks	The notified chemical was assessed for chemical groups that would imply explosive properties.
Test Facility	SafePharm (2008b)

Oxidizing Properties Predicted negative

Method	EC Council Regulation No 440/2008 A.17 Oxidizing Properties (Solids). EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids).
Remarks	The notified chemical was assessed for chemical groups that would imply oxidising properties.
Test Facility	SafePharm (2008b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure.
- Species/Strain: Mouse/ddy
- Vehicle: Distilled water
- Remarks - Method: Ten groups of ten male mice were tested. One group served as a negative control. Test substance (or negative control) was administered by oral gavage. Animals were observed for 14 days.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	10 M	0	0/10
2	10 M	3,500	0/10
3	10 M	4,000	1/10
4	10 M	4,600	4/10
5	10 M	5,300	6/10
6	10 M	6,100	10/10
7	10 M	7,000	10/10
8	10 M	8,100	10/10
9	10 M	9,300	10/10
10	10 M	10,600	10/10

- LD50: 4,920 mg/kg bw
- Signs of Toxicity: No details provided in report.
- Effects in Organs: No details provided in report.
- Remarks - Results: The majority of the deaths occurred within 2 hours of the administration of the test substance.

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

TEST FACILITY: Confidential (1971)

B.2. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 420 Acute Oral Toxicity - Fixed Dose Method.
EC Directive92/69/EEC B.1bis Acute Toxicity (Oral) Fixed Dose Method.
- Species/Strain: Rat/HsdRccHan®™:WIST®™
- Vehicle: Arachis oil BP
- Remarks - Method: GLP Compliant.

RESULTS

Sighting Study

Dose mg/kg bw	*Administered*	*Evident Toxicity*	*Mortality*
2,000	2000	-	0/1

- Signs of Toxicity: None.
- Effects in Organs: No abnormalities were detected.

Main Study

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	4 F	2,000	0/4

Discriminating Dose: > 2,000 mg/kg bw

Signs of Toxicity: Hunched posture, lethargy and decreased respiratory rate were observed in 1 animal at 30 min, 1, 2 and 4 hrs. These effects were not observed in the animal 24 hr after dosing. No adverse effects were observed in the remaining 3 animals.

Effects in Organs: No abnormalities were detected.

Remarks - Results: The animal exhibiting adverse effects following exposure gained significantly less bodyweight during the first week of observation (compared to other animals in the group and sighting study). However, weight gain in this animal was as expected in the second week of the observation period. All other animals made the expected gains in bodyweight.

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

TEST FACILITY: Harlan (2009a)

B.3. Irritation – skin (in vitro)

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 439 In vitro Skin Irritation: Reconstructed Human *Epidermis* Test Method EpiSkin^{SM}

Vehicle: None

Remarks - Method: The study authors recorded that the test substance does not interact with MTT.

The test substance (10 mg) was applied to the tissues in duplicate. Following 15 minute exposure periods, the tissues were rinsed and then incubated for approximately 42 hours. A third test was performed 12 month later (under new acceptability criteria). Residues of the test substance remained after rinsing.

Positive (sodium dodecyl sulphate; 5%) and negative (phosphate buffered saline) controls were run.

RESULTS

Test material	*Mean OD_{570} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	≥ 0.600	-	-
Test substance	-	74	42.5
Positive control	-	≤ 35	< 18

OD = optical density; SD = standard deviation

Remarks - Results: The viability of the test substance treated tissues for each tissue run was 97.1%, 100% and 25%. The relative mean viability of the test substance treated tissues was 74 ± 42.5% after a 15-minute exposure period.

The study authors indicated that the positive and negative controls validated the test results.

A mean tissue viability of > 50% is considered as non-irritating. The notified chemical was described as potentially irritating by the study authors.

Only one of the three test substance runs met the criteria to be considered irritating, however, the large variability in the results for the test substance suggests that this particular study had some technical problems and should not be considered valid.

CONCLUSION The test was not valid and cannot be used to predict the irritant properties of the test substance.

TEST FACILITY EPISKIN (2008)

B.4. Irritation – skin (in vitro)

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 439 In vitro Skin Irritation: Reconstructed Human *Epidermis* Test Method EpiSkin™

Vehicle None

Remarks - Method The test substance (10 ± 2 mg) was applied to the tissues in triplicate. Following an exposure period of 15 minutes at room temperature, the tissues were rinsed with PBS and then incubated for approximately 42 hours at 37 °C. The tissues were then treated with MTT and incubated at 37 °C for 3 hours. Following extraction, the optical densities were determined (540 nm).

A preliminary test was performed which indicated that the test substance does not directly reduce MTT.

Positive and negative controls were run in parallel with the test substance:
- Negative control: PBS (irritation test)
- Positive control: sodium dodecyl sulphate (5%)

RESULTS

Test material	*Mean OD_{540} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	0.783 ± 0.014	100	1.81
Test substance	0.808 ± 0.030	103.2	3.35
Positive control	0.093 ± 0.026	11.9	3.87

OD = optical density; SD = standard deviation

Remarks - Results The relative mean tissue viability was 103.2% (> 50%).

The positive and negative controls gave satisfactory results, confirming the validity of the test system.

CONCLUSION The notified chemical was non-irritating to the skin under the conditions of the test.

TEST FACILITY Safepharm (2008c)

B.5. Irritation – skin

TEST SUBSTANCE Notified chemical at 5% concentration

METHOD Similar to OECD TG 404 Acute Dermal Irritation/Corrosion.

Species/Strain Rabbit

Number of Animals 4

Vehicle Water

Observation Period 7 days

Type of Dressing Not provided.

Remarks - Method

A 5% solution of sodium lauryl sulfate (SLS) was used as a positive control. The positive control group (4 rabbits) was run concurrently with animals exposed to the test substance.
The sex or strain of the rabbits was not provided.
Individual erythema and oedema results were not provided.
There is no evidence the study was conducted to GLP standards.

RESULTS

Lesion	*Mean Score*[1]			*Maximum Value*[2]	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	24 hr	48 hr	72 hr			
Erythema/Eschar	2.0	3.5	3.5	4	≥ 7 d	≥ 2
Oedema	1.0	2.0	0.75	4	< 7 d	0

[1] for all animals at 24, 48, and 72 hours.
[2] based on description of results

Remarks - Results

After 24 hr exposure to the test substance, all animals exhibited well-defined erythema, with well-defined oedema in 1/4 animals and very slight oedema in 2/4 animals. At the 48 hr and 72 hr observations, crusting was observed in 2/4 animals and moderate to severe erythema observed in 2/4 animals. After 48 hr, very slight to severe oedema was observed in 3/4 animals with the effect lessening at the 72 hr observation where very slight to well defined oedema was observed in 2 animals. At the end of the observation period (7 d), crusting was observed in 2 animals and scaling was observed in 2 animals.

Animals exposed to the positive control exhibited the expected irritation effects.

CONCLUSION

The notified chemical at a concentration of 5% is irritating to the skin.

TEST FACILITY

Confidential (1997a)

B.6. Irritation – eye (in vitro)

TEST SUBSTANCE

Notified chemical at 1% and 5% concentration

METHOD

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

Vehicle

Distilled water

Remarks - Method

Each dilution of test substance was tested in triplicate for each exposure period (10 and 30 minutes) at 32 °C in a water-bath. At the end of the exposure period, corneas were rinsed and opacity measured just after rinsing.

Corneas were then incubated for 2 h in a water bath at 32 °C. After the 2 hr incubation, the corneas were incubated with a fluorescein solution for 90 minutes at 32 °C. Optical density was measured at 490 nm. The optical density measurements taken after the 2 h incubation period were used to determine the in vitro irritancy score (IVIS).

Negative (distilled water) and positive (0.5% cetyl trimethylammonium bromide) controls were tested in triplicate and run concurrently with the test substance.

RESULTS

Test material	*Mean opacities of triplicate tissues (SD) after:*		*Mean permeabilities of triplicate tissues (SD) after:*		*IVIS (SD) after:*	
	10 min	*30 min*	*10 min*	*30 min*	*10 min*	*30 min*
Vehicle control	-1.8 (1.3)	-3.2 (0.6)	0.008 (0.005)	0.024 (0.007)	0	0
*Test substance (1% concentration)**	1.1 (0.2)	-0.5 (0.9)	0.149 (0.048)	2.436 (0.110)	3.3 (0.9)	36.0 (1.6)
*Test substance (5% concentration)**	-1.2 (2.1)	-1.5 (0.3)	0.813 (0.172)	2.938 (0.225)	11.0 (0.7)	42.6 (3.5)

SD = Standard deviation; IVIS = in vitro irritancy score
*Corrected for background values

Remarks - Results

Positive control measurements were not provided in the report. However, the positive control was reported to have performed as expected.

The negative control performed as expected.

Under the conditions of the test, at 1% concentration the test substance was classified as moderately irritating to irritant; and at 5% concentration was classified as irritant to severely irritant by the study authors.

CONCLUSION

The notified chemical was not corrosive or a severe eye irritant under the conditions of the test.

TEST FACILITY

IEC (2006a)

B.7. Irritation – eye (in vitro)

TEST SUBSTANCE

Notified chemical at 0.2% concentration

METHOD

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

Vehicle

Distilled water

Remarks - Method

Test substance was tested in triplicate for each exposure period (10 and 30 minutes) at 32 °C in a water-bath. At the end of the exposure period, corneas were rinsed and opacity measured just after rinsing.

Corneas were then incubated for 2 h in a water bath at 32 °C. After the 2 hr incubation, the corneas were incubated with a fluorescein solution for 90 minutes at 32 °C. Optical density was measured at 490 nm. The optical density measurements taken after the 2 h incubation period were used to determine the in vitro irritancy score (IVIS).

Negative (distilled water) and positive (0.5% cetyl trimethylammonium bromide) controls were tested in triplicate and run concurrently with the test substance.

RESULTS

Test material	*Mean opacities of triplicate tissues (SD) after:*		*Mean permeabilities of triplicate tissues (SD) after:*		*IVIS (SD)*	
	10 min	*30 min*	*10 min*	*30 min*	*10 min*	*30 min*
Vehicle control	-0.5 (1.8)	-1.7 (1.4)	0.017 (0.005)	0.007 (0.010)	0	0
*Test substance**	-1.2 (0.3)	1.1 (1.1)	0.216 (0.069)	0.690 (0.23)	2.1 (0.7)	11.5 (1.1)

SD = Standard deviation; IVIS = in vitro irritancy score
*Corrected for background values

Remarks - Results

Positive control measurements were not provided in the report. However,

the positive control was reported to have performed as expected.

The negative control performed as expected.

Under the conditions of the test, the test substance was classified as moderately irritating by the study authors.

CONCLUSION The notified chemical was not corrosive or a severe eye irritant under the conditions of the test.

TEST FACILITY IEC (2006b)

B.8. Irritation – eye (in vitro)

TEST SUBSTANCE Notified chemical at 1% and 5% concentration

METHOD Based on method described by Luepke N.P. and Kemper F.H. (1986). The method used is similar to that described by National Toxicology Program. (NTP, 2010)

Eggs were incubated for 10 days at 37.8 °C and reversed at least twice per day. Eggs were placed in an upright position of the eighth day of incubation. On the tenth day, the chorioallantoic membrane (CAM) was exposed by removing the outer shell and shell membrane.

Each dilution of test substance was tested on 4 eggs. Each CAM was exposed to 300 µL of test substance for 20 seconds before being rinsed with 0.9% sodium chloride isotonic solution and then observed for 5 min..

Vehicle Distilled water

Remarks - Method Observations were performed visually under lamp. Hyperhemia, haemorrhage and coagulation were recorded as being present or absent and the time of occurrence was recorded.

The arithmetical mean of the scores for each egg was used to classify the potential eye irritation effect. Scores were assigned based on time of onset. Early onset of an adverse effect was assigned the highest score

Historical positive (lauryl sulfobetaine) and negative (0.9% sodium chloride) control data indicated that the test conformed to expected results (controls tested in November and December 2005 respectively).

RESULTS

Test material	*Effect recorded*			*Score/egg*
	Hyperhemia	*Haemorrhage*	*Coagulation*	
Test substance (1% concentration)	5	6.5	0	11.5
Test substance (5% concentration)	5	7	0	12

Remarks - Results Hyperhemia was observed in 4/4 eggs within 30 sec following exposure to the notified chemical at 1% concentration, followed by haemorrhage in 3/4 eggs within 30 sec and 1/4 eggs at 31 sec after exposure.
Observations of hyperhemia followed by haemorrhage were observed in 4/4 eggs within 30 sec following exposure to the notified chemical at 5% concentration.
Coagulation was not observed in any of the eggs exposed to either 1% or 5% concentration of the test substance.

CONCLUSION	The notified chemical was considered irritating to the eye at 1% and 5% concentrations under the conditions of the test. However, the test conditions employed are insufficient for regulatory classification. Therefore, no conclusion is made.
TEST FACILITY	EVIC (2006)

B.9. Irritation – eye (in vitro)

TEST SUBSTANCE	Notified chemical
METHOD	Cytotoxicity Study on Human Corneal Epidermis
Vehicle	None
Remarks - Method	The test substance (30 mg) was applied to the tissues in duplicate. Application time and post-incubation times were 1 h and 16 h respectively. Positive (absolute ethanol) and negative controls were run in parallel with the test substance. No pre-test performed to determine if the test substance directly reduced MTT. Individual optical density results not provided.

RESULTS

Test material	*Viability (%)*	*Relative mean viability (%)*
Test substance – Run 1	7.7	14.1 ± 9
Test substance – Run 2	20.4	

OD = optical density

Remarks - Results	The relative mean viability of the test substance treated tissues after a 1 h exposure period was 14.1%.
CONCLUSION	The notified chemical was considered to be irritating to the eye under the conditions of the test. However, the test conditions are not sufficiently documented. Therefore, on the basis of inadequate evidence, no conclusion is made.
TEST FACILITY	Episkin (2009)

B.10. Irritation – eye (in vitro)

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 492 Reconstructed human Cornea-like Epithelium (RhCE) test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage
Vehicle	None.
Remarks - Method	The test substance (30 mg) was applied to the tissues in triplicate. Following 10 minute exposure periods, the tissues (2/group, with the others being retained for histopathology if necessary) were rinsed and then treated with MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; 0.5 mg/mL; incubation period of 3 hours at 37 °C]. Following extraction, the optical densities were determined (540 nm). Positive (sodium dodecyl sulphate; 1%) and negative controls were run in parallel with the test substance. The test substance was considered by the study authors to be an irritant if

the relative mean tissue viability was < 60%.

Under the conditions of a per-test that was conducted, the test substance was shown not to directly reduce MTT.

RESULTS

Test material	*Mean OD_{540} of duplicate tissues*	*Relative mean viability (%)*
Negative control	1.008	100
Test substance	0.672	66.7
Positive control	0.488	48.4

OD = optical density

Remarks - Results: The relative mean viability of the test substance treated tissues after a 10-minute exposure period was 85%.

CONCLUSION: The notified chemical was considered to be non-irritating to the eye under the conditions of the test.

TEST FACILITY: Safepharm (2008d)

B.11. Irritation – eye

TEST SUBSTANCE: Notified chemical at 5% concentration

METHOD: Similar to OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain: Rabbit/New Zealand White
Number of Animals: 4
Observation Period: 72 hrs
Remarks - Method: 0.1 mL of test substance was applied to both eyes of each animal. Ocular irritation was recorded at 24, 48 and 72 hrs.

A positive control (sodium lauryl sulfate) group of 4 animals was also tested in parallel with the notified chemical.

RESULTS

Remarks - Results: Individual results for each animal were not provided. The following adverse reactions were recorded 24 hrs after exposure to the notified chemical: slight opacity in the cornea, congestion in the iris, redness in the conjunctiva, swelling and an adhering discharge. While no individual results were recorded, mean irritation scores at 24, 48 and 72 h (21.0, 9.5 and 3.3 respectively) indicate that the effects of exposure to the notified chemical had largely reversed within the observation period. The scores provided for SLS at 24, 48 and 72 h were 22.5, 16.3 and 2.0 respectively.

CONCLUSION: The notified chemical is irritating to the eye.

TEST FACILITY: Confidential (1987)

B.12. Skin sensitisation

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 406 Skin Sensitisation – Maximisation Test.
Species/Strain: Guinea pig
PRELIMINARY STUDY: None
MAIN STUDY
Number of Animals: Test Group: 10 Control Group: 5
Vehicle: Not described

Positive control	Not conducted
INDUCTION PHASE	Induction Concentration: topical: 5%
Signs of Irritation	There was no mention of whether irritant effects were seen in the induction.
CHALLENGE PHASE	
1st challenge	topical: 2.5%
Remarks - Method	Summary of results only was provided for review. Skin reactions were recorded 24 and 48 hours after removal of the challenge dose.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*	
		24 h	*48 h*
Test Group	2.5%	0/10	0/10
Control Group	2.5%	0/5	0/5

Remarks - Results	No visible changes were observed in any of the animals following exposure to the notified chemical.
CONCLUSION	The notified chemical may not have skin sensitising ability but the test conditions employed are inadequate or not sufficiently documented. Therefore, on the basis of inadequate evidence, no conclusion is made.
TEST FACILITY	Confidential (1997b)

B.13. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain	Mouse/CBA/CaOlaHsd
Vehicle	1% pluronic L92 in distilled water
Preliminary study	Yes
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using 10% w/w 2,4-dinitrobenzenesulfonic acid, sodium salt.
Remarks - Method	No adverse effects were observed in animals exposed to a 10% concentration of the notified chemical in the preliminary screening test.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	4 F	302.96	-
2.5	4 F	272.71	0.9
5	4 F	307.12	1.01
10	4 F	479.14	1.58

Remarks - Results	No mortalities or signs of systemic toxicity. No significant changes in bodyweight were observed. A positive linear relationship was observed between increasing concentration of notified chemical and stimulation index. However, all SI values were < 3.
CONCLUSION	There was no evidence of induction of a lymphocyte proliferative response

	indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Harlan (2009b)

B.14. Skin sensitisation – human volunteers

TEST SUBSTANCE	Product containing notified chemical at 0.8% concentration
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.02 mL test substance were applied 3 times per week (Tuesday, Thursday and Saturday) for a total of 9 applications. Patches were removed by the test facility after 48 h (or 72 h for patches applied on Saturday) and graded 15 - 30 min after patch removal. Rest Period: 11 - 13 days Challenge Procedure: A patch was applied to the original site and a naïve site (opposite side to the induction site). Patches were removed after 48 h. Sites were graded 30 min and 48 h post-patch removal.
Study Group	84 F, 24 M; age range 18 - 66 years
Vehicle	None
Remarks - Method	Occluded (Finn Chambers on Scanpor). The test substance was spread on a 50 mm^2 patch. A patch containing no test substance was also applied to test subjects to act as a negative control. A moderate to well defined erythema which develops and lasts in time during the challenge phase was considered to be generally indicative of an allergic reaction rather than an irritative type.
RESULTS	
Remarks - Results	101/108 subjects completed the study. Seven subjects withdrew from the study (One after one induction, two after two inductions, one after three inductions, one after four inductions, and two after nine inductions). During the induction phase, mild erythema was observed in twelve test subjects; eight subjects showed a reaction at sites exposed to the test substance, while four subjects showed a reaction at areas exposed to the control patch. In the challenge phase, mild erythema was observed 30 min after patch removal in nine test subjects; three subjects showed a reaction at sites exposed to the test substance (one at the naïve site, one at the induction site, and one at both sites) and five subjects showed a reaction at sites exposed to the control patch (one at the naïve site, one at the induction site and three at both sites), while the reaction on one subject was determined by the authors to be a reaction to the tape used. No reactions were observed 48 hr after the challenge. However, two subjects exhibited dryness at test-substance exposed induction (both subjects) and naïve sites (one subject) 48 hr after challenge patch removal.
CONCLUSION	The test substance (containing the notified chemical at 0.8% concentration) was non-sensitising under the conditions of the test.
TEST FACILITY	IEC (2007)

B.15. Skin sensitisation – human volunteers

TEST SUBSTANCE	Product containing notified chemical at 1%

METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 15 µL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed by the test facility after 48 h (or 72 h for patches applied on Friday) and graded 30 min after patch removal. Rest Period: 14 days Challenge Procedure: A patch was applied to the original site and a naïve site (opposite side to the induction site). Patches were removed after 48 h. Sites were graded 30 min and 48 h post-patch removal.
Study Group	29 F, 26 M; age range 18-70 years
Vehicle	None
Remarks - Method	Occluded. The test substance was spread over the surface of a filter paper disc situated in the L1 chamber of an eight-chambered Finn patching device. The device was then applied to the upper left of the test subject's back. A freshly prepared patching device was used for each application.
RESULTS	
Remarks - Results	50/55 subjects completed the study. Five subjects voluntarily withdrew (one after the first induction reading, one after the second induction reading, two after the third induction reading and one after the seventh induction reading). No adverse responses were noted during the induction phase or at challenge.
CONCLUSION	The test substance (containing the notified chemical at 1% concentration) was non-sensitising under the conditions of the test.
TEST FACILITY	Product Investigations (2007)

B.16. Skin sensitisation – human volunteers

TEST SUBSTANCE	Product containing notified chemical at 0.85%
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 20 mg test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed by the test facility after 48 h (or 72 h for patches applied on Friday) and graded 15 to 30 min after patch removal. Rest Period: 7 - 14 days Challenge Procedure: A patch was applied to the original site and a naïve site (opposite side to the induction site). Patches were removed after 48 h. Sites were graded 30 min and 48 h post-patch removal.
Study Group	82 F, 38 M; age range 18 - 64 years
Vehicle	None
Remarks - Method	Occluded. The test substance applied to the surface of a filter paper disc and then added to the Finn chamber device. The device was then applied to the test subject's back.
RESULTS	
Remarks - Results	104/120 subjects completed the study. Sixteen subjects were lost to follow up from the study (Two prior to the first induction reading, three after one induction, one after two inductions, two after three inductions, three after four inductions, two after five inductions and 3 after nine inductions). Adverse reactions were not recorded in the subjects who did not complete the challenge phase of the study. One subject exhibited mild erythema after induction applications 6, 7 and 8, with no erythema observed after the final induction application, or

during the challenge phase. No other test subjects exhibited and adverse response during the induction or challenge phases.

CONCLUSION The test substance (containing the notified chemical at 0.85% concentration) was non-sensitising under the conditions of the test.

TEST FACILITY TKL (2011)

B.17. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 471 Bacterial Reverse Mutation Test.
Pre incubation procedure

Species/Strain	*S. typhimurium*: TA98, TA100
Metabolic Activation System	S9
Concentration Range in Main Test	a) With metabolic activation: 5, 10, 20, 39, 78, 156, 313, 625, 1,250, 2,500, 5,000 µg/plate b) Without metabolic activation: 3, 5, 10, 20, 39, 78, 156, 313, 625, 1,250 µg/plate
Vehicle	Distilled water
Remarks - Method	A preliminary test was performed to determine the concentration of test substance in the main test. The test results were not provided. Negative controls were run in triplicate, and all other samples were tested in duplicate. Positive controls: with metabolic activation - 2-Aminoanthracene; without metabolic activation – Furylfuramide.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 156	≥ 1,250	-	negative
Present				
Test 1	> 5,000	≥ 5,000	-	negative

Remarks - Results In both tests, no biologically relevant increase in the frequency of revertant colonies was obtained in the presence or absence of metabolic activation. Growth inhibition was observed in the presence and absence of metabolic activation at the highest concentrations tested. A 50% reduction in the number of revertants was also observed in TA98 strain mutants (in the presence and absence of metabolic activation) at these concentrations.

Positive and negative controls performed as expected.

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

TEST FACILITY Confidential (1992)

B.18. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
Plate incorporation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA$^-$

Metabolic Activation System	S9 mix from phenobarbitone/β-naphthoflavone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 5 – 5,000 µg/plate b) Without metabolic activation: 5 – 5,000 µg/plate
Vehicle	Distilled water
Remarks - Method	A preliminary test and range-finding test (test 1) were performed to determine the concentration of test substance in the main test (Test 2). Positive controls: with metabolic activation - 2-Aminoanthracene [TA100, TA1535, TA1537, WP2uvrA$^-$], Benzo(a)pyrene [TA98]; without metabolic activation – N-ethyl-N'-nitro-N-nitrosoguanidine [WP2uvrA$^-$, TA100, TA1535], 9-Aminoacridine [TA1537], 4-Nitroquinoline-1-oxide [TA98].

RESULTS

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

Remarks - Results	No biologically relevant increase in the frequency of revertant colonies was obtained in the presence or absence of metabolic activation. Growth inhibition and a significant reduction in the number of revertants was observed in all *S. typhimurium* strains in the presence and absence of metabolic activation from 500 µg/plate. A decrease in the number of revertant colonies was also observed for *E. coli* in the presence and absence of metabolic activation. However, this decrease did not always relate to a corresponding increase in test substance. The precipitate observed at and above 1,500 µg/plate did not prevent scoring of revertant colonies. Positive and negative controls performed as expected.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Safepharm (2008e)

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: CO_2 Evolution Test.
Inoculum	Activated sludge
Exposure Period	28 days.
Auxiliary Solvent	None.
Analytical Monitoring	Theoretical Oxygen Demand (ThOD).
Remarks - Method	No significant deviation in protocol. Percentage biodegradation values of the test material and the toxicity control were determined.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
1	5	1	24
8	52	8	52
10	50	10	52
14	52	14	105
22	52	22	103
28	53	28	115
29	52	29	105

Remarks - Results	All validity criteria for the test were satisfied. The test item attained 52% biodegradation after 28 days and therefore cannot be considered to be readily biodegradable under the strict terms and conditions.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	SafePharm (2008f)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - static. EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia - static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None reported
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	High performance liquid chromatography with mass spectrometry (HPLC-MS)
Remarks - Method	The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed. Pre-study solubility work showed that the test material was readily soluble/dispersible in deionised reverse osmosis water. However, in the test media (reconstituted water), the test material formed a precipitate.

RESULTS

Concentration mg/L *Nominal*	*Number of D. magna*	*Number Immobilised* *24 h [acute]*	*48 h [acute]*
(> 100 % v/v saturation)	20	0	0

LC50	> 100 % v/v saturation
Remarks - Results	Analysis of the test preparations at 0 and 48 hours showed measured test concentrations to be less than the limit of quantitation (LOQ) of the analytical method. The concentration of the test material could not be determined in the test media (At the highest attainable test concentration of 1.7 mg/l, no irnmobilisation or adverse reactions to exposure were observed). Therefore the results are based on concentration as % v/v saturated solution. Based on this the 48-Hour EC50 of the test material was greater than 100 % v/v saturated solution. Correspondingly the no observed effect concentration (NOEC) was 100 % v/v saturated solution.
CONCLUSION	Not toxic to aquatic invertebrates at saturation under the experimental conditions employed.
Test Facility	Harlan (2009c)

C.2.2. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC Council Regulation No 440/2008 C.3 Algal Inhibition Test.
Species	*Desmodesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Geometric mean measured test concentrations: 0.34, 0.51, 0.92, 1.7 and 5.3 mg/L
Auxiliary Solvent	None reported
Water Hardness	None reported
Analytical Monitoring	High performance liquid chromatography with mass spectrometry (HPLC-MS)
Remarks - Method	The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed. Whilst the test material was observed to be readily soluble in water, upon addition to culture medium the test material was observed to form a precipitate.

RESULTS

Biomass		*Growth*	
E_yC50 *mg/L at 72h*	*NOE_yC* *mg/L at 72h*	*E_rC50* *mg/L at 72 h*	*NOE_rC* *mg/L at 72h*
1. 8	0.51	4.3	0.51
95% confidence limits (1.6-2.0 mg/L)		95% confidence limits (1.5-2.2 mg/L)	

Remarks - Results	All validity criteria for the test were satisfied. A decline in measured concentrations was observed. This decline was in line with the preliminary stability analyses conducted which indicated that the test material was unstable in culture medium over the test duration. Therefore, geometric mean measured concentrations were used for calculating EC50 values.
CONCLUSION	The notified chemical is toxic to algae
TEST FACILITY	Harlan (2009d)

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