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January 2014

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Fatty acids, coco, 2-sulfoethyl esters, ammonium salts (INCI name: Ammonium Cocoyl Isethionate)

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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Director
NICNAS

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SUMMARY

The following details will be published in the NICNAS *Chemical Gazette:*

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1498	BASF Australia Ltd.	Fatty acids, coco, 2-sulfoethyl esters, ammonium salts (INCI name: Ammonium Cocoyl Isethionate)	Yes	≤ 10 tonne/s per annum	A rinse-off cosmetic component at concentrations up to 10%

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 for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the table below.

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

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

R41: Risk of serious damage to eyes

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

Hazard classification	*Hazard statement*
Acute (Category 2)	H401 - Toxic to aquatic life

Human health risk assessment
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

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Eye irritation (Category 1): H318 – Causes serious eye damage

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

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

CONTROL MEASURES

Occupational Health and Safety

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

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical :
  – Avoid contact with 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:
  – Goggles/ safety glasses with side shields

  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.

Product manufacturers

- Formulators should take into account the potential for the notified chemical to cause eye irritation and to increase the dermal absorption of other chemicals, when manufacturing rinse-off cosmetics containing the notified chemical.

Disposal

- The notified chemical should be disposed of to landfill.

Storage

- The handling and storage of the notified chemical should be in accordance with the Safe Work Australia Code of Practice for *Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012) or relevant State or Territory Code of Practice.

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 in leave-on cosmetic products;
- the notified chemical is proposed to be used in rinse-off cosmetic products at a concentration exceeding 10%.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a rinse-off cosmetic component, or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

The Director will then decide whether a reassessment (i.e. a secondary notification and assessment) is required.

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
BASF Australia Ltd (ABN: 62 008 437 867)
Level 12
28 Freshwater Place
Southbank VIC 3006

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: molecular and structural formulae, molecular weight, degree of purity, impurities, additives, use details and import volume.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Japan and the United States of America

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Ammonium Cocoyl Isethionate (INCI name)
Jordapon ACI 30 G (product containing approximately 30% notified chemical)

CAS NUMBER
223705-57-5

CHEMICAL NAME
Fatty acids, coco, 2-sulfoethyl esters, ammonium salts

MOLECULAR WEIGHT
< 500 Da

ANALYTICAL DATA
Reference HPLC spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 95%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
Below cut-off concentrations for classification.

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Straw coloured liquid- Clear, slightly yellow to milky, cloudy liquid with mild odour.*

Property	Value	Data Source/Justification
Melting Point/Freezing Point/Boiling Point	> 251.5 °C**	Measured, decomposes from 251.5 ± 0.5 °C at an atmospheric pressure of

		100.22 kPa
Relative Density	1,110 kg/m^3 at 20.5 ± 0.5 °C**	Measured
Vapour Pressure	9.8×10^{-11} kPa at 25 °C**	Measured
Water Solubility	> 5.65×10^2 g/L at 20 °C	Measured.
Hydrolysis as a Function of pH	$t_{½}$ > 1 year at 25 °C (pH 4 –7) $t_{½}$ = 9.75 days at 25 °C (pH 9)	Measured
Partition Coefficient (n-octanol/water)	Log Pow < -3.6 at 20 °C	Estimated. Expected to partition to the interface between octanol and water, based on its surfactant properties
Surface Tension	29.0 mN/m at 20.5 ± 0.5 °C**	Measured
Adsorption/Desorption	Not determined	Expected to partition to phase boundaries based on its surfactant properties
Dissociation Constant	Not determined	The notified chemical is a salt and is ionised in the environment
Flash Point	> 93.3°C	(M)SDS ASTM D93
Flammability	Not determined	Not expected to be flammable based on flash point
Autoignition Temperature	Not determined	Not expected to autoignite under normal conditions
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties.
Oxidising Properties	Not determined	Not expected to possess oxidising properties based on lack of structural alerts

* For a product containing approximately 30% of the notified chemical.
** For a product containing approximately 70% of the 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 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 not be manufactured in Australia. The notified chemical will be imported into Australia as a component of Jordapon ACI 30 G (containing approximately 30% of the notified chemical) for reformulation or in finished cosmetic products (≤ 10% notified chemical).

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	1 – 10	1 – 10	1 – 10	1 – 10	1 – 10

PORT OF ENTRY
Melbourne or Sydney

IDENTITY OF RECIPIENTS
BASF Australia Ltd.

TRANSPORTATION AND PACKAGING
The notified chemical will be imported into Australia as a component of Jordapon ACI 30 G (approximately 30% concentration) in plastic closed head drums of typically 195 kg size (216 L). The products containing the notified chemical will be transported from the port of entry by road.

USE
The notified chemical will be used as an anionic surfactant in rinse off cosmetic products at concentrations up to 10%. Such products include soap bars, liquid soaps and shampoos.

OPERATION DESCRIPTION
The notified chemical will not be manufactured within Australia. The notified chemical may be imported at approximately 30% concentration for reformulation or in finished cosmetic products containing the notified chemical at a concentration of ≤ 10%.

After the notified chemical has been imported it will be sold to personal-care product manufacturers where it will be reformulated to produce a variety of rinse off cosmetic products. Details on how the notified chemical is to be used may vary depending on the company doing the reformulation and the type of product being produced.

Reformulation
The imported product Jordapon ACI 30 G (approximately 30% notified chemical) will be weighed and added to the blending tank where it will be mixed with additional additives to form the finished cosmetic products. The reformulation facilities are expected to be mostly automated, well ventilated and use closed systems. After being reformulated, the finished products containing the notified chemical (≤ 10% concentration) will be transferred into retail packaging up to 500mL.

End use
The finished cosmetic products containing the notified chemical will be used by the public and may also be used in occupational settings by hairdressers and beauticians. Depending on the nature of the cosmetic product these could be applied a number of ways such as by hand, using an applicator or sprayed.

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 distribution personnel	4	240
Batch operators	8	240
Quality Control chemists	2	240
Packing operators	8	240
Store personnel	4	240
Point of sale	6	240
Hairdressers and beauticians	Unspecified	Unspecified

EXPOSURE DETAILS
Transport and distribution workers are not expected to be exposed to the notified chemical (up to 30% concentration) except in the event of an accidental rupturing of the packaging.

During reformulation exposure to the notified chemical (up to 30% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. The principal route of exposure would be dermal, while ocular and inhalation exposure is also possible. The notifier claims this exposure is expected to be minimised due to the likely use of automated processes and PPE by workers. The notifier suggests operators will wear safety glasses with shields, gloves, apron or coverall, with respiratory protection available if required.

Hairdressers, beauticians and sales workers may be exposed to the notified chemical at ≤ 10% concentration when applying products containing it to clients. The principal route of exposure will be dermal, while ocular exposure is also possible. Inhalation is not anticipated, given the rinse off nature of cosmetic products containing the notified chemical.
PPE is not expected to be worn, however good hygiene practices are expected to be in place.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical (at ≤ 10% concentration) through the use of body and hair cleansing products. The principal route of exposure will be dermal, while oral and ocular exposure is also possible.

Data on typical use patterns of cosmetic product categories in which the notified chemical may be used are shown in the following table (SCCS, 2012; Cadby *et al*., 2002). For the purposes of the exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. An adult bodyweight of 60 kg was used for calculation purposes. Based on the (limited) dermal absorption data available on the notified chemical, a dermal absorption of 100% was assumed for the notified chemical.

Product type	**Amount** (mg/day)	**C** (%)	**RF** (unitless)	**Daily systemic exposure** (mg/kg bw/day)
Shampoo	10460	10.0	0.01	0.31
Conditioner	3920	10.0	0.01	0.33
Shower gel	18670	10.0	0.01	0.17
Hand soap	20000	10.0	0.01	0.07
Facial Cleanser	800	10.0	0.01	0.01
Total				0.90

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 0.9 mg/kg bw/day.

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 6390 mg/kg bw (equivalent to > 2000 mg solids/kg bw) low toxicity*
Rat, acute oral toxicity	LD50 > 5,000 mg/kg bw: low toxicity*
Rat, acute dermal toxicity	LD50 > 6,390 mg/kg bw (equivalent to > 2,000 mg solids/kg bw) low toxicity*
Rabbit, skin irritation – 4 hour application	slightly irritating#
Rabbit, skin irritation – 24 hour application	irritating*
Rabbit, skin irritation – 24 hour application	slightly irritating*
Rabbit, skin irritation – 24 hour application	irritating*
Rabbit, skin irritation – 4 hour application	slightly irritating*
Rabbit, eye irritation	irritating*
Rabbit, eye irritation	irritating†
Rabbit, eye irritation	severely irritating*
Guinea pig, skin sensitisation – Maximisation test adjuvant test	Non-sensitizing#
Rat, repeat dose toxicity – 28 days.	NOAEL 150 mg/kg bw/day*
Mutagenicity – bacterial reverse mutation	non mutagenic*
Genotoxicity – in vitro	non genotoxic*

* Test studies conducted on Jordapon ACI 30 G with the notified chemical at approximately 30% concentration.
# Test studies conducted on Jordapon ACI 93 G with the notified chemical at approximately 93% concentration.
† Test studies conducted where the concentration of the notified chemical in the test substance was not specified.

Toxicokinetics, metabolism and distribution.
Based on the low molecular weight (< 500 Da), the fact that it is an ionisable surfactant, and slightly irritating to the skin, the notified chemical may be absorbed across biological membranes. This is supported by systemic effects seen in a repeated dose study with the notified chemical following oral administration.

Acute toxicity.
The notified chemical is considered to be of low acute toxicity via the oral and dermal routes based on tests conducted in rats.

Irritation and sensitisation.
The notified chemical was applied to rabbits to evaluate the skin irritation potential in five separate tests. Three tests were conducted using a 24 hour exposure period, which is longer than the 4 hours recommended under current OECD guidelines (OECD TG 404). The concentration of the notified chemical in the three 24 hour tests was approximately 30% and in two of the tests the reactions were sufficient to classify the chemical as a skin irritant; however, in the third study the effects were not sufficient for classification. There were also two skin irritation studies conducted where the exposure period to the test substance was 4 hours, and the concentration of the notified chemical was either approximately 30% or 93%. In both of these studies, there were irritant effects noted; however, these were not sufficient for classification. Four (three 24 hour and one 4 hour exposure, all approximately 30% concentration) of the five skin irritation studies did not measure skin irritation in the test subjects for longer than 72 hours and irritant effects were still present in these studies at this time. Therefore, these studies could not be used to determine the reversibility of the irritant effects seen. The remaining study with a 4 hour exposure period was conducted at the higher concentration of 93%, with observations conducted until irritant effects had subsided. As this skin irritation study was the only one conducted to current OECD guidelines and it was also the one which tested the highest concentration of the notified chemical, it is the most relevant for classification purposes. Based on this study, the notified chemical is not classified as a skin irritant.

Three eye irritations tests have been conducted on rabbits with the notified chemical at approximately 30% concentration. In two of the studies effects seen were sufficient to classify the chemical as a category 2A - serious eye irritant, under GHS; however, both of these studies failed to make observations after 72 hours, when effects were still present, and hence were not sufficient to determine if the effects were reversible. In a third eye irritation study the notified chemical observations were conducted for 28 days at the end of which corneal and conjunctive effects were still present in 2/6 rabbits. Based on the signs of irritation in the eyes of 2/6 rabbits not reversing after 28 days, the notified chemical (approximately 30% concentration) should be classified as causing serious eye damage (category 1) under GHS.

The notified chemical was not a skin sensitiser in a guinea pig maximisation test.

Repeated dose toxicity.
A 28 day repeat dose study by oral gavage was conducted in rats with the notified chemical at dose levels of 15, 150 and 1000 mg/kg/day. Animals treated with a dose of 1,000 mg/kg bw/day had a range of clinical signs, a significantly elevated monocyte count, and a number of treatment related effects in the stomach including gastritis, acanthosis of the forestomach and hyperkeratosis of the forestomach. These effects were considered to be adverse and hence the lower concentration of 150 mg/kg bw/day was established as the No Observed Adverse Effect Level (NOAEL) for systemic toxicity, based on the absence of effects at this dose.

Mutagenicity/Genotoxicity.
The notified chemical was not mutagenic in a bacterial reverse mutation study (in the presence or absence of metabolic activation) and was not clastogenic in an in vitro mammalian chromosome aberration test.

Health hazard classification
Based on the available information, the notified chemical is 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. The recommended hazard classification is presented in the following table.

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

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

Xi: R41 Risk of serious damage to eyes

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Hairdressers, beauticians and sales workers may be exposed to the notified chemical at ≤ 10% concentration when applying products containing it to clients. The risk for beauty care professionals who regularly use products containing the notified chemical is expected to be similar to 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.

Workers involved in the reformulation of the imported products into cosmetic products may be exposed to the notified chemical at concentrations up to approximately 30%. Exposure is expected to be limited during product reformulation by the engineering controls and the PPE used.

Under the proposed occupational settings the notified chemical is not considered to pose an unreasonable risk to workers.

6.3.2. Public Health

The general public will be repeatedly exposed to the notified chemical during the use of rinse off cosmetic products containing the notified chemical at up to 10% concentration.

Local effects

The notified chemical was found to cause serious eye damage when administered to rabbits at a concentration of approximately 30% and is slightly irritating to the skin. However, as the notified chemical will be present in cosmetic products at concentrations ≤ 10%, skin and eye irritation effects are expected to be reduced. The notified chemical is also proposed to be used only in rinse off cosmetic products, further reducing the potential for exposure.

Systemic effects

The potential systemic exposure to the public from the use of the notified chemical in cosmetic products was estimated to be 0.90 mg/kg bw/day. Using a NO(A)EL of 150 mg/kg bw/day, which was derived from a 28 day repeated dose toxicity study on the notified chemical, the margin of exposure (MOE) was estimated to be 167. A MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences; therefore, the MOE is considered to be acceptable.

As the notified chemical may also increase the dermal absorption of other components of cosmetic products, due to its surfactant nature, care should be taken when reformulating the notified chemical into the end-use products.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 10% in rinse off cosmetic 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 to Australia, and will be reformulated into end-use cosmetic and personal cleaning products. Reformulation will take place in closed automated systems. Residues of the notified chemical remaining in blending equipment are expected to be released in washings from the cleaning of blending equipment. It is estimated by the notifier that 2-3% of the total import volume of the notified chemical will be released from the reformulation process to the wastewater collection system. The wastewater will be treated at a biological treatment plant and subsequently released to sewer. Accidental spills during transport or reformulation are expected to involve minimal amounts of the notified chemical and are expected to be collected with inert material and disposed of to landfill.

RELEASE OF CHEMICAL FROM USE
The majority of the notified chemical is expected to be washed to sewer as a result of their use pattern (cosmetic products and rinse off personal cleaning products such as soap bars, liquid soaps and shampoos).

RELEASE OF CHEMICAL FROM DISPOSAL
Residue of the notified chemical in empty containers (1%) will share the fate of the container and will either be disposed of to landfill, or washed to sewer when containers are rinsed before recycling. Waste and expired material is expected to be disposed of to landfill.

7.1.2. Environmental Fate

For the details of the environmental fate study please refer to Appendix C. The notified chemical is readily biodegradable based on a biodegradation study of the notified chemical. The notified chemical is hydrolytically stable at pH 4 and 7, however, its half-life at pH 9 is 9.75 days based on the study provided.

The majority of the notified chemical is expected to be released to Sewage Treatment Plants (STPs) via domestic wastewater. Based on its ready biodegradability, the notified chemical is expected to be largely degraded by sewage treatment processes. The notified chemical is expected to partition to phase boundaries as it is surface active. Therefore, the notified chemical in sewage released to STPs is expected to partition to sludge. Notified chemical remaining in treated sewage effluents is likely to be released to surface waters or applied to land when used for irrigation. Notified chemical in sewage sludge is anticipated be disposed of to landfill or applied to land when sludge is used for soil remediation. Based on its surface active property, the notified chemical is not expected to bioaccumulate due to its surfactant property. The notified chemical is expected to degrade in STPs, surface waters, soils and landfill due to its ready biodegradability to form water, oxides of carbon, sulphur and nitrogen, and inorganic salts.

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 cosmetics and personal cleaning products, it is assumed that 100% of the total import volume of the chemical is released to sewer on a nationwide basis over 365 days per year.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	10,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	10,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	27.4	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:	6.06	µg/L
PEC - Ocean:	0.61	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 6.1 µg/L may potentially result in a soil concentration of approximately 40.4 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 201.9 µg/kg and 403.9 µg/kg, respectively.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemical are summarised in the table below. Details of the studies of the analogue can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	LC50 (96 h) = 8.8 mg/L	Toxic to fish
Daphnia Toxicity	EC50 (48 h) = 23.0 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	E_rC50 (72 h) > 100 mg/L	Not harmful to algae
Inhibition of bacteria respiration	EC50 (3 h) = 680 mg/L	Not inhibitory to microbial activity

On the basis of the acute toxicity data, the notified chemical is toxic to fish, harmful to aquatic invertebrates and not harmful to algae. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009), the notified chemical is formally classified as Acute Category 2; Toxic to aquatic life. Based on the acute toxicity and ready biodegradability, the notified chemical has not been formally classified for long term hazard under the GHS.

7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) was calculated based on the endpoint for the most sensitive species (fish, LC50) and an assessment factor of 100. The conservative assessment factor of 100 was used since measured ecotoxicological data for three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Invertebrates).	8.8	mg/L
Assessment Factor	100	
PNEC:	88.0	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	***PEC µg/L***	***PNEC µg/L***	***Q***
Q - River:	6.06	88	0.069
Q - Ocean:	0.61	88	0.007

The Risk Quotients (Q = PEC/PNEC) for the notified chemical has been calculated to be < 1 for the river and ocean compartments. Therefore, the notified chemical is unlikely to result in ecotoxicologically significant concentrations in the aquatic environment from the assessed use pattern. The notified chemical is readily biodegradable, thus it is unlikely to persist in surface waters or soils. The notified chemical is considered to have low potential for bioaccumulation. Therefore, the notified chemical is not expected to pose an unreasonable risk to the aquatic environment from the assessed use pattern.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point/Boiling Point > 251.5 ± 0.5 °C at an atmospheric pressure of 100.22 kPa

Method Commission Directive 92/69/EEC A.1 Melting/Freezing Temperature, A.2 Boiling Temperature
ASTM E537-86.
Remarks No exact value could be determined due to the decomposition of the test material. The test was conducted using differential scanning calorimetry (DSC) and no value for either melting or boiling temperature could be determined prior to decomposition.
Test Facility Safepharm (1998b)

Relative Density 1,110 kg/m^3 at 20.5 ± 0.5 °C

Method Commission Directive 92/69/EEC A.3 Relative Density.
Remarks Determined by Quantachrome MVP-2 Gas Comparison Pyncometer
Test Facility Safepharm (1998b)

Vapour Pressure 9.8×10^{-11} kPa at 25 °C (7.4×10^{-10} mmHg)

Method Commission Directive 92/69/EEC A.4 Vapour Pressure.
Remarks Determined using vapour pressure balance system and linear regression analysis.
Test Facility Safepharm (1997a)

Water Solubility > 5.65×10^2 g/L (> 56.5% w/w) at 20 °C

Method OECD TG 105 Water Solubility.
Commission Directive 92/69/EEC A.6 Water Solubility.
Remarks Adaptation of the Flask Method. Test substance was added to double-distilled water in four flasks and shaken at approximately 30 °C for 18 hours and 45 minutes. Following shaking the flasks were left to stand at 20.5 °C for 3 hours and 15 minutes to allow the mixture to equilibrate. The water solubility of the notified chemical was visually observed and determined.
Test Facility Safepharm (1998b)

Hydrolysis as a Function of pH

Method OECD TG 111 Hydrolysis as a Function of pH.
Commission Directive 92/69/EEC C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH.

pH	*T (°C)*	*$t_{½}$*
4	25 °C	$t_{½}$ > 1 year
7	25 °C	$t_{½}$ > 1 year
9	25 °C	$t_{½}$ = 9.75 days

Remarks Aliquots were analysed spectrophotometrically.
Test Facility Safepharm (1998b)

Partition Coefficient (n-octanol/water) Log Pow < -3.6 at 20 °C

Method Adaptation of the Commission Directive 92/69/EEC A.8 Partition Coefficient.
Remarks Testing could not be undertaken using the definitive procedures due to the surface-active nature of the test material.
Estimation based on the ratio of the solubilities in n-octanol (1.4×10^{-2} g/L) and in water (> 5.65×10^2 g/L).
Test Facility Safepharm (1998b)

Surface Tension 29 mN/m at 21.5 ± 0.5 °C

Method	ISO 304 Ring Method Commission Directive 92/69/EEC A.5 Surface Tension.
Remarks	Determined by a White Electrical Institute Interfacial Tension Balance Concentration: 1.02 g/L solution Considered to be a surface active material. (< 60 mN/m)
Test Facility	Safepharm (1998b)

Adsorption/Desorption Not determined
– screening or main test

Method	OECD TG 106 Adsorption - Desorption Using a Batch Equilibrium Method.
Remarks	
Test Facility	Safepharm (1998b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical (approximately 30% concentration)
METHOD	US Federal Guidelines 16 CFR 1500.3 PSL Protocol 001/P203
Species/Strain	Rat/ Sprague-Dawley
Vehicle	Test substance administered as supplied
Remarks - Method	No significant protocol deviations. The rats were observed at 1, 2 and 5 hours post-dosing and at least once daily thereafter for the 14 day period.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	5,000	0/10

Single-Dose $LD_{oral}50$	> 5,000 mg/kg bw
Signs of Toxicity	Hunched posture and lethargy were observed in multiple animals from 1 hour post-dosing through to day 2. One male was seen to exhibit mouth discharge and gasping from 5 hours post dosing through to day 1. Another male exhibited abnormal gait from the 5 hour until the day 1 observation. There were no other signs of gross toxicity, adverse pharmacologic effects or abnormal behaviour.
Effects in Organs	There were no macroscopic pathological findings in the animals sacrificed at the end of observation period.
Remarks - Results	All animals survived and gained weight. By day 3 all animals has recovered and appeared active and healthy.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Product Safety Labs, New Jersey (1991a)

B.2. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical (approximately 30% concentration)
METHOD	OECD TG 401 Acute Oral Toxicity – Limit Test. Commission Directive 92/69/EEC B.1 Acute Toxicity (Oral) – Limit Test.
Species/Strain	Rat/ Sprague-Dawley
Vehicle	Test substance administered as supplied
Remarks - Method	No significant protocol deviations. A single oral dose of 6,390 mg/kg bw. equivalent to 2,000 mg solids/kg bw. was administered to test animals. The rats were observed for deaths or overt signs of toxicity at ½, 1, 2 and 4 hours post-dosing and once daily thereafter for the 14 day period.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	2,000	0/10

Single-Dose $LD_{oral}50$	> 6,390 mg/kg bw. (equates to > 2,000 mg solids/kg bw)
Signs of Toxicity	Hunched posture was noted in 2 males. Decreased respiratory rate and noisy respiration were also noted in 1 male. These animals fully recovered from 1 to 2 days after dosing. All other animals appeared normal throughout the study period.
Effects in Organs	No abnormalities were noted at necropsy.

Remarks - Results	All animals survived and showed the expected weight gain during the study.

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

TEST FACILITY Safepharm (1997b)

B.3. Acute toxicity – dermal

TEST SUBSTANCE Notified chemical (approximately 30% concentration)

METHOD OECD TG 402 Acute Dermal Toxicity – Limit Test.
Commission Directive 92/69/EEC B.3 Acute Toxicity (Dermal) – Limit Test.

Species/Strain	Rat/ Sprague-Dawley
Vehicle	Test substance administered as supplied
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose Mg solid/kg bw*	*Mortality*
1	5 per sex	2,000	0/10

$LD_{dermal}50$	> 6,390 mg/kg bw. (equates to > 2,000 mg solids/kg bw)
Signs of Toxicity - Local	Slight straw-coloured staining was noted at the treatment sites of 8 animals. The staining did not affect evaluation of skin responses. Skin effects at the application site comprised erythema (up to grade 2), superficial epidermal cracking and desquamation were observed from day 1 up to day 8. All treated skin sites appeared normal on day 9.
Signs of Toxicity - Systemic	No signs of systemic toxicity were noted during the study.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	All animals survived and showed the expected weight gain during the study.

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

TEST FACILITY Safepharm (1997c)

B.4. Irritation – skin

TEST SUBSTANCE Notified chemical (approximately 93% concentration)

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
Commission Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 Male
Vehicle	Test substance administered as supplied
Observation Period	14 days
Type of Dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations. Single 4-hour semi-occlusive application to intact skin. The rabbits were observed for deaths or overt signs of toxicity at 1, 24, 48 and 72 hours post-dosing. Additional observations were made on Days 7 and 14 to assess the reversibility of skin reactions.

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	1	2	2	2	≤ 7 days	0
Oedema	0.3	1.7	1	2	≤ 7 days	0

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

Remarks - Results

Well defined erythema was noted on two treated skin sites at up to and including the 72 hour observation, with very slight erythema seen at the remaining treated skin site in that time period. Very slight or slight oedema was observed at all treated skin sites and persisted till 72 hours in two animals.
Desquamation was noted in all treatment sites at the Day 7 observation and persisted at 1 treated skin site on Day 14.
All other treated skin sites appeared normal at the Day 14 observation.
No corrosive effects were noted.

CONCLUSION

The notified chemical is classified as a slight irritant to rabbit skin based on the test conditions.

TEST FACILITY

Safepharm (1997d)

B.5. Irritation – skin

TEST SUBSTANCE

Notified chemical (approximately 30% concentration)

METHOD

Primary Dermal Irritation Test
US Federal Guidelines 16 CFR 1500.41 PSL Protocol 002/P201

Species/Strain	Rabbit/New Zealand White
Number of Animals	6
Vehicle	Test substance administered as supplied
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks - Method	Single 24-hour semi-occlusive application to intact and abraded skin. Observations were only made at 24 and 72 hours. The FHSA Primary Skin Irritation Scoring system was used to grade the skin reaction observations.

RESULTS

Lesion	*Mean Score**		*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	Abraded	Intact			
Erythema/Eschar	2.5	2.6	4	> 72 hours	3
Oedema	2.4	2.6	3	> 72 hours	3

*Calculated on the basis of the scores at 24 and 72 hours for ALL animals.

Remarks – Results

One animal was found dead prior to scoring on Day 3. In this animal gross necropsy revealed dark red mottled edematous lungs and pink fluid in the abdominal cavity. In the remaining animals, there were no signs of systemic toxicity, adverse pharmacologic effects or abnormal behaviour.

Well-defined to severe erythema and slight to moderate oedema were noted at all dose sites at the 24-hour observation. Incidence and severity remained similar at the 72-hour observation.

CONCLUSION	The notified chemical is irritating to the skin.
TEST FACILITY	Product Safety Labs (1991b)

B.6. Irritation – skin

TEST SUBSTANCE	Notified chemical (approximately 30% concentration)
METHOD	Primary Dermal Irritation Test US Federal Guidelines 16 CFR 1500.41 PSL Protocol 002/P201
Species/Strain	Rabbit/New Zealand White
Number of Animals	6
Vehicle	Test substance administered as supplied
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks - Method	Single 24-hour semi-occlusive application to intact and abraded skin. Observations were only made at 24 and 72 hours. The FHSA Primary Skin Irritation Scoring system was used to grade the skin reaction observations.

RESULTS

Lesion	*Mean Score**		*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	Abraded	Intact			
Erythema/Eschar	2.2	2.1	3	> 72 hours	3
Oedema	1.4	1.6	3	> 72 hours	2

*Calculated on the basis of the scores at 24 and 72 hours for ALL animals.

Remarks – Results	At the 24-hour observations, well-defined to moderate erythema and slight to moderate oedema were seen at all dose sites. By the 72-hour observations, the severity of irritation had decreased at all sites, clearing entirely from 1 animal. Slight brown discolouration was noted at 1 abraded site. There were no signs of gross toxicity seen in necropsy observations.
CONCLUSION	The notified chemical is slightly irritating to the skin.
TEST FACILITY	Product Safety Labs (1991c)

B.7. Irritation – skin

TEST SUBSTANCE	Notified chemical (approximately 30% concentration)
METHOD	Primary Dermal Irritation Test US Federal Guidelines 16 CFR 1500.41 PSL Protocol 002/P201
Species/Strain	Rabbit/New Zealand White
Number of Animals	6
Vehicle	Test substance administered as supplied
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks - Method	Single 24-hour semi-occlusive application to intact and abraded skin. Observations were only made at 24 and 72 hours. The FHSA Primary Skin Irritation Scoring system was used to grade the skin reaction observations.

RESULTS

Lesion	*Mean Score**		*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	Abraded	Intact			
Erythema/Eschar	3.5	3.4	4	> 72 hours	4
Oedema	3.5	3.2	4	> 72 hours	4

*Calculated on the basis of the scores at 24 and 72 hours for ALL animals.

Remarks – Results

At the 24-hour observations, well-defined to moderate erythema and slight to moderate oedema were seen at all dose sites. Slight brown discolouration was noted at the dose sites of 2 animals. By the 72-hour observations, irritation at all sites had increased to severe. Discolouration was noted at all sites, with skin hardening noted at all sites except on 1 animal.
There were no signs of gross toxicity seen in necropsy observations.

CONCLUSION

The notified chemical is irritating to the skin.

TEST FACILITY

Product Safety Labs (1991d)

B.8. Irritation – skin

TEST SUBSTANCE

Notified chemical (approximately 30% concentration)

METHOD

Primary Dermal Irritation Test
US Federal Guidelines 16 CFR 1500.41 PSL Protocol 002/P201

Species/Strain	Rabbit/New Zealand White
Number of Animals	6
Vehicle	undiluted
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks - Method	Single 4-hour semi-occlusive application to intact and abraded skin. Observations were taken at 4, 24, 48 and 72 hours post-dosing. The FHSA Primary Skin Irritation Scoring system was used to grade the skin reaction observations.

RESULTS

Lesion	*Mean Score**		*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	Abraded	Intact			
Erythema/Eschar	0.95	0.95	2	> 72 hours	1
Oedema	0.56	0.39	2	> 72 hours	1

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

Remarks – Results

At 4 hours post-dosing, very slight to well defined erythema and very slight oedema were noted at all abraded sites. From 24 to 48 hours, the severity of irritation decreased at most dose sites. By the 72-hour observations, the severity of irritation had decreased. Only slight erythema and oedema remained evident in 3 animals and the other 3 animals were free from irritation.

There were no signs of gross toxicity seen in necropsy observations.

CONCLUSION

The notified chemical is slightly irritating to the skin.

TEST FACILITY

Product Safety Labs (1991e)

B.9. Irritation – eye

TEST SUBSTANCE	Notified chemical (approximately 30% concentration)
METHOD	Primary Eye Irritation US Federal Guidelines 16 CFR 1500.42 PSL Protocol 003/P202
Species/Strain	Rabbit/New Zealand White
Number of Animals	6
Observation Period	72 hours
Remarks - Method	Single ocular instillation into the right eye of the test animals with 0.1mL of the test material. Observations were taken at 24, 48 and 72 hours post-dosing. The Draize Scoring system was used to grade the eye reaction observations.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	2.7	3	> 72	2
Conjunctiva: chemosis	2.5	3	> 72	2
Conjunctiva: discharge	2.1	3	> 72	2
Corneal opacity	1.4	2	> 72	2
Iridial inflammation	0.9	1	> 72	1

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

Remarks - Results	Corneal opacity and conjunctival irritation were noted in all treated eyes at the 24, 48 and 72 hour observations. The severity of both conditions decreased from 48 to 72 hours. Iritis was observed in all animals at 24 hours and remained evident in all but 1 treated eye for the entire study.
CONCLUSION	The notified chemical is irritating to the eye.
TEST FACILITY	Product Safety Labs(1991f)

B.10. Irritation – eye

TEST SUBSTANCE	Notified chemical (concentration not specified)
METHOD	Primary Eye Irritation US Federal Guidelines 16 CFR 1500.42 PSL Protocol 003/P202
Species/Strain	Rabbit/New Zealand White
Number of Animals	6
Observation Period	72 hours
Remarks - Method	Single ocular instillation into the left eye of the test animals with 0.1 mL of the test material. Observations were taken at 24, 48 and 72 hours post-dosing. The Draize Scoring system was used to grade the eye reaction observations.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	2.6	3	> 72 hours	2
Conjunctiva: chemosis	2.2	3	> 72 hours	3
Conjunctiva: discharge	1.4	3	> 72 hours	1
Corneal opacity	1	1	> 72 hours	1
Iridial inflammation	0.8	1	> 72 hours	1

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

Remarks - Results	Corneal opacity and conjunctival irritation was noted in all treated eyes at the 24 hour observation and continued for the entire study period. Iritis was observed in all animals at 24 hours and remained evident in 3/6 eyes at the 72 hour observation.
CONCLUSION	The notified chemical/polymer is irritating to the eye.
TEST FACILITY	Product Safety Labs(1991g)

B.11. Irritation – eye

TEST SUBSTANCE	Notified chemical (approximately 30% concentration)
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion. Commission Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	6 Female
Observation Period	72 hours
Remarks - Method	No significant protocol deviations Single ocular instillation into the right eye of the test animals with 0.1 mL of the test material. Observations were taken at 1, 24, 48 and 72 hours post-dosing and on Days 4, 7, 14, 21 and 28 if irritation persisted. The Draize Scoring system was used to grade the eye reaction observations.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	2.9	3	> 28 days	1
Conjunctiva: chemosis	2.9	4	> 28 days	1
Conjunctiva: discharge	1.7	3	< 28 days	0
Corneal opacity	1.3	2	> 28 days	2
Iridial inflammation	0.8	1	< 28 days	0

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

Remarks - Results	There were no deaths or remarkable body weight changes during the study. The test material induced positive conjunctival, iridial and corneal effects in all animals. All irritation was reversible and completely subsided by the day 21 observation for 4 rabbits. The remaining 2 rabbits had corneal and minor conjunctival effects on the day 28 observation.
CONCLUSION	The notified chemical is severely irritating to the eye.
TEST FACILITY	WIL Research Laboratories Inc. (1998)

B.12. Skin sensitisation

TEST SUBSTANCE	Notified chemical (approximately 93% concentration)
METHOD	OECD TG 406 Skin Sensitisation – maximisation test. EC Directive 96/54/EC B.6 Skin Sensitisation – Guinea Pig Maximisation Test.
Species/Strain	Guinea pig/Dunkin Hartley
PRELIMINARY STUDY	Maximum Non-irritating Concentration: intradermal: < 1% topical: 2% (24 hour exposure): < 1% (48 hour exposure)

MAIN STUDY

Number of Animals	Test Group: 20 Control Group: 10
INDUCTION PHASE	Induction Concentration: intradermal: 1% w/v in water 1% w/v in a mixture of FCA plus water (1:1) topical: 5%
Signs of Irritation	Well defined to severe erythema was seen in all animals following the intradermal injections. After Topical Induction, very slight to well-defined erythema and incidents of very slight oedema were noted in 11/20 test animals.
CHALLENGE PHASE	
1st challenge	topical: 5% and 2 %
2nd challenge	topical: 2% and 1%
Remarks - Method	No significant protocol deviations. Observations were also made at 72 hours in the first challenge. A rechallenge was conducted based on low levels of irritation seen in the original challenge.

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	1	-	-	0/20	0/20
	2	2/20	2/20	0/20	0/20
	5	5/20	3/20	-	-
Control Group	1	-	-	0/10	0/10
	2	0/10	0/10	0/10	0/10
	5	3/10	3/10	-	-

Remarks - Results

There were no deaths or substance-related signs of toxicity during the study. After challenge with a 5% concentration of the test substance 5/20 (25%) animals showed signs of irritation at the 24 hour observation, with irritation persisting in 3/20 (15%) animals at the 48 hour observation and 2/20 (10%) animals at the 72 hour observation. After challenge with a 2% concentration 2/20 (10%) of animals showed signs of irritation which was still present at the 72 hour observation. This was below the 30% cut-off for evidence of positive responses to meet the classification criteria. In addition 3/10 (30%) of animals in the control group challenged with a 5% concentration of the test substance showed signs of irritation. In a second challenge at 1% and 2% concentrations of the test substance no skin reactions were noted at the challenge sites of the test and control group animals.

The positive control confirmed the sensitivity of the test system.

No significant effects were noted on bodyweight in test group animals or the additional control group animals during the rechallenge procedure.

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

TEST FACILITY Safepharm (1997e)

B.14. Repeat dose toxicity

TEST SUBSTANCE Notified chemical (approximately 30% concentration)

METHOD OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.

Species/Strain Rats/Wistar

Number of animals	30 (15 F & 15 M)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week
Vehicle	Distilled water
Remarks - Method	No significant protocol deviations. The test substance was dosed at higher values (3876, 581 and 58.1 mg/kg bw/day) so that the amount of solid material being administered to the rats was either 15, 150 or 1000 mg/kg bw/day depending on the test group.

RESULTS

Group	*Number and Sex of Animals (M/F)*	*Equivalent Dose mg/kg bw/day**	*Mortality (M/F)*
control	5/5	0	0/0
low dose	5/5	15	0/0
mid dose	5/5	150	0/0
high dose	5/5	1,000	0/0
control recovery	5/5	0	0/0
high dose recovery	5/5	1,000	0/0

* Equivalent to solids mg/kg bw/day

Mortality and Time to Death

No mortality was observed during the treatment or recovery phases.

Clinical Observations

Analysis of clinical appearance, functional observations, body weight, food and water consumption did not reveal any toxicologically significant abnormalities between the treated and the control groups. Clinical signs that some test animals exhibited in the high dose group (1,000 mg/kg bw/day) included increased salivation, staining to the outside body surface, noisy respiration, decreased respiratory rate and hunched posture. There were no clinically observable signs in the 15 and 150 mg/kg bw/day dose groups that were due to the test substance.

All clinical signs regressed completely in recovery high dose animals upon cessation of treatment.

Laboratory Findings – Clinical Chemistry, Haematology

High dose group animals of both sexes showed a statistically significant increase in monocyte count compared with that of controls. Monocyte count remained elevated for recovery 1,000 mg/kg bw/day animals after 14 days without treatment. The monocyte count was also significantly elevated in the female group being dosed with 150 mg/kg bw/day, the study authors have stated that this result was due to one individual in this group of 5 being an outlier and the result therefore being fortuitous and hence not toxicologically relevant.

There were no changes in the haematological parameters measured for 15 and 150 mg/kg bw/day animals that could be considered attributable to treatment with the test material.

No treatment-related effects on blood chemistry or urinalysis were detected.

Effects in Organs

Changes in the stomach were evident in the high dose group and considered to be treatment related. They included gastritis, acanthosis of the forestomach and hyperkeratosis of the forestomach. No differences in the frequencies or severities of these conditions were noted between animals of any sex treated with 15 or 150 mg/kg bw/day. There were also no similar gastric changes in the recovery 1000 mg/kg bw/day animals at the end of the 14 day treatment-free period.

No treatment-related effects on organ weights or macroscopic abnormalities were detected.

Remarks – Results

Animals treated with a dose of 1,000 mg/kg bw/day had a range of clinical signs, a significantly elevated monocyte count, and a number of treatment related effects in the stomach including gastritis, acanthosis of the

forestomach and hyperkeratosis of the forestomach. These effects were considered to be adverse and hence the lower concentration of 150 mg/kg bw/day was the dose where no adverse treatment related effects were observed.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) for systemic toxicity was established by the study authors as 150 mg/kg bw/day based on adverse effects seen in animals in the higher dose group.

TEST FACILITY Safepharm (1998c)

B.12. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical (approximately 30% concentration)

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria.
Ames test- Plate incorporation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98 and TA100 *E. coli*: WP2uvrA$^-$
Metabolic Activation System	S9 fraction from Aroclor 1254 induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 5 – 5000 µg/plate b) Without metabolic activation: 5 – 5000 µg/plate
Vehicle	Water
Remarks - Method	No significant protocol deviations. A dose finding test was conducted using TA100 and WP2uvrA without metabolic activation between 50 – 5000 µg/plate.

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	1,500	> 5,000	negative
Test 2		≥ 1,500	> 5,000	negative
Present				
Test 1		1,500	> 5,000	negative
Test 2		≥ 1,500	> 5,000	negative

Remarks - Results

The test material caused visible reduction in the growth of bacterial background lawn to all of the Salmonella tester strains without metabolic activation and all with metabolic activation except TA98. The first indication of a toxic response was observed at 1500 µg/plate. No toxicity was observed to E.coli tester strain W2PuvrA.

The test material was tested up to the maximum recommended dose level of 5000 µg/plate. No toxicologically significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test material, either with or without metabolic activation.

The positive controls produced satisfactory responses, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

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

TEST FACILITY Safepharm (1997f)

B.15. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical (approximately 30% concentration)
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test. EC No. 440/2008 B.10 Mutagenicity – In Vitro
Cell Type/Cell Line	Chinese Hamster Lung
Metabolic Activation System	S9 fraction from Aroclor 1254 induced rat liver
Vehicle	Eagle's Minimal Essential Medium
Remarks - Method	No significant protocol deviations A preliminary cytotoxicity assay was performed both with and without the metabolic activation. Vehicle and positive controls (mitomycin C without metabolic activation and cyclophosphamide with metabolic activation) were used in parallel with the test substance.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 10, 20*, 40*, 80*, 120, 160	12 hours	12 hours
Test 2a	0*, 5, 10, 20, 40*, 60*, 80*	24 hours	24 hours
Test 2b	0*, 5, 10, 20*, 40*, 60*, 80	48 hours	48 hours
Test 2c	0*, 10, 20, 40*, 80*, 120*, 160	6 hours	24 hours
Test 2d	0*, 10, 20*, 40*, 80*, 100, 120	12 hours	12 hours
Present			
Test 1	0*, 20, 40, 80*, 160*, 320*, 480	4 hours	12 hours
Test 2a	0*, 20, 40, 80*, 160*, 320*, 480	6 hours	24 hours
Test 2b	0*, 80, 160, 240*, 320*, 400*, 480*	4 hours	12 hours

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 156.25	≥ 120	> 160	negative
Test 2a	≥ 78.13	> 80	> 80	negative
Test 2b	≥ 78.13	≥ 80	> 80	negative
Test 2c	≥ 156.25	≥ 120	> 160	negative
Test 2d		≥ 100	> 120	negative
Present				
Test 1	≥ 625	≥ 320	> 480	negative
Test 2a	≥ 312.5	≥ 480	> 480	negative
Test 2b		≥ 400	> 480	negative

Remarks - Results	There were no statistically significant increases in the number of cells with aberrations or the number of polyploid cells or the number of cells with endoreduplicated chromosomes, with or without metabolic activation. The test material did not disturb mitotic processes and cell cycle progression. The positive controls produced the expected significant increases in the frequency of chromosomal aberrations, demonstrating the sensitivity of the experimental conditions employed.
CONCLUSION	The notified chemical was not clastogenic to Chinese Hamster Lung cells treated in vitro under the conditions of the test.
TEST FACILITY	Safepharm (1998d)

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 reported
- Analytical Monitoring: Shimadzu TOC-5050A analyser.
- Remarks - Method: The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
3	33	3	50
6	79	7	73
14	95	14	96
28	101	28	100

- Remarks - Results: All validity criteria for the test were satisfied. The reference compound, sodium benzoate, reached the 60% pass level by day 7 indicating the suitability of the inoculum. The toxicity control exceeded 25% biodegradation within 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the notified chemical after the cultivation period was 100.1% and it reached the pass level within the 10-day window. Therefore, the test substance is classified as readily biodegradable according to the OECD (301 B) guideline.

CONCLUSION: The notified chemical is readily biodegradable

TEST FACILITY: Safepharm (1998e)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 203 Fish, Acute Toxicity Test - Semi-Static Test
- Species: *Oncorhynchus mykiss*
- Exposure Period: 96 hours
- Auxiliary Solvent: None reported
- Water Hardness: 102 mg $CaCO_3$/L
- Analytical Monitoring: Spectrophotometer (Perkin-Elmer Lambda 20 or Perkin-Elmer Lambda 2)
- Remarks – Method: The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Nominal Concentration at 0 hour (mg/L)	*Time-weighted mean measured concentration (mg/L)*	*Number of Fish*	*Mortality (%)*					
			3 h	*6 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	0	20	0	0	0	0	0	0
3.2	1.9	20	0	0	0	0	0	0
5.6	3.2	20	0	0	0	0	0	0
10	6.5	20	0	0	0	0	10	25
18	16.0	20	0	5	55	100	100	100
32	32.0	20	0	85	100	100	100	100

LC50	8.8 (7.5 – 10.0) mg/L at 96 hours (time-weighted mean measured concentrations)
NOEC	3.2 mg/L at 96 hours (time-weighted mean measured concentrations)
Remarks – Results	All validity criteria for the test were satisfied. All the exposure solutions containing the test substance were observed to be homogeneous dispersions without a precipitate. Due to a significant decline in measured test concentrations at 72 and 96 hours, it was appropriate to use the time-weighted mean measured concentrations for the analyses. Analysis of the mortality (LC50) was done by the moving average method (Thompson, 1947) based on the time-weighted mean measured test concentrations.

CONCLUSION The notified chemical is toxic to fish

TEST FACILITY Safepharm (1998f)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

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

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Not reported
Water Hardness	Not reported
Analytical Monitoring	Spectrophotometer (Perkin-Elmer Lambda 20 or equivalent)
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Nominal Concentration	*Time-weighted mean measured concentration*	*Number of D. magna*	*Cumulative % Immobilised*	
(mg/L)	*(mg/L)*		*24 h*	*48 h*
Control	0	20	0	0
1.0	0.5	20	0	0
1.8	1.3	20	0	0
3.2	2.4	20	0	0
5.6	3.4	20	0	0
10.0	7.8	20	0	0
18.0	13.0	20	0	0
32.0	24.0	20	0	20
56.0	33.0	20	0	75
100.0	76.0	20	0	100

EC50 23.0 (20.0 – 27.0) mg/L at 48 hours (time-weighted mean measured

	concentrations of filtered media) 33.0 (28.0 – 38.0) mg/L at 48 hours (time-weighted mean measured concentrations of unfiltered media)
NOEC	9.5 mg/L at 48 hours (time-weighted mean measured concentrations of filtered media) 13.0 mg/L at 48 hours (time-weighted mean measured concentrations of unfiltered media)
Remarks - Results	All validity criteria for the test were satisfied. At 0 hour, 1.0 mg/L to 10 mg/L exposure solutions containing the test substance were observed to be clear and colourless, however, 18 mg/L to 100 mg/L exposure solutions were observed to be pale white dispersions with a fine white precipitate at the bottom of the vessels. Observations made on the test media showed that the amount of precipitate at the bottom of the test vessels increased with increasing test concentration. Due to a significant decline in measured test concentrations at 48 hours, it was appropriate to use the time-weighted mean measured concentrations for the analyses. Analysis of the immobilisation (EC50) was done by the moving average method (Thompson, 1947) based on the time-weighted mean measured test concentrations.
CONCLUSION	The notified chemical is harmful to aquatic invertebrates
TEST FACILITY	Safepharm (1998g)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 0, and 100 mg/L
Auxiliary Solvent	Not reported
Analytical Monitoring	Not reported
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Biomass (Nominal concentration)		*Growth* (Nominal concentration)	
E_yC50	NOE_yC	E_rC50	NOE_rC
mg/L at 96 h	*mg/L at 96 h*	*mg/L at 96 h*	*mg/L at 96 h*
Not reported	Not reported	> 100 mg/L	≥ 100 mg/L

Remarks - Results	All validity criteria for the test were satisfied. The concentration of the test substance in the test solutions at 96 hours was less than the limit of quantification of the analytical method. Therefore, it was not possible to calculate E_rC50 values in terms of the measured concentrations. Consequently, the results are estimated based on the nominal test concentrations.
CONCLUSION	The notified chemical is not harmful to algae
TEST FACILITY	Safepharm (1998h)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Activated sludge
Exposure Period	3 hours
Concentration Range	Nominal: 100,180, 320, 560, and 1000 mg/L
Remarks – Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.
RESULTS	
EC50	680 mg/L
NOEC	None reported
Remarks – Results	All validity criteria for the test were satisfied. Based on the test result, the test substance is not expected to inhibit the respiration and biodegradation activities of microorganisms within an STP
CONCLUSION	The notified chemical is not expected to inhibit respiration of microorganisms
TEST FACILITY	Safepharm (1997g)

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