File No: STD/1056

October 2003

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

2-O-α-D-glucopyranosyl-L-ascorbic acid

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Street Address: 334 - 336 Illawarra Road MARRICKVILLE NSW 2204, AUSTRALIA.
Postal Address: GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL: + 61 2 8577 8800
FAX + 61 2 8577 8888.
Website: www.nicnas.gov.au

Director
Chemicals Notification and Assessment

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2-O-α-D-glucopyranosyl-L-ascorbic acid

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Trimex Pty Ltd (ABN 40 001 198 787)
5 Crewe Pl
ROSEBERRY NSW 2018

Shiseido (Australia) Pty Limited (ABN 46 001 787 695)
6 – 10 Walker St
RHODES NSW 2138

Johnson & Johnson Pacific Pty Limited (ABN 73 001 121 446)
Level 1 Bay St
BROADWAY NSW 2007

Edward Keller Australia Pty Ltd (ABN 70 005 059 307)
14 – 17 Dansu Court
HALLAM VIC 3803

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are claimed exempt from publication.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: adsorption/desorption, dissociation constant, flash point.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None.

NOTIFICATION IN OTHER COUNTRIES
EC (No. 97-01-0459-00).

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
2-O-α-D-glucopyranosyl-L-ascorbic acid

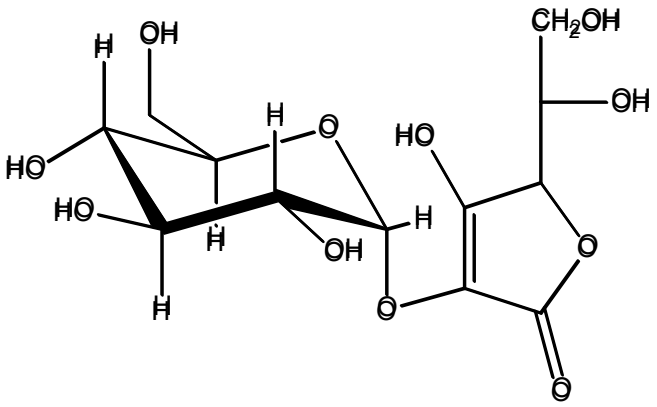
OTHER NAME(S)
Ascorbyl glucoside
Ascorbic acid, 2-glucoside
AA2G™

MARKETING NAME(S)
Ascorbyl glucoside
Ascorbic acid, 2-glucoside
AA2G™

CAS NUMBER
129499-78-1

MOLECULAR FORMULA
$C_{12}H_{18}O_{11}$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
338.26

SPECTRAL DATA

ANALYTICAL METHOD	Ultraviolet/visible (UV/Vis) spectroscopy.
Remarks	Maximum absorption 1.0 x 10^4 at 238 nm, pH 2.0 and 1.5 x 10^4 at 260 nm, pH 5.0, 7.0 and 9.0.
TEST FACILITY	Hayashibara Biochemical Laboratory (1996).
ANALYTICAL METHOD	Infrared (IR) spectroscopy.
Remarks	Characteristic spectrum provided.
TEST FACILITY	Hayashibara Biochemical Laboratory (1996).
ANALYTICAL METHOD	Nuclear Magnetic Resonance (NMR) spectroscopy.
Remarks	Characteristic ^1H and ^{13}C spectra provided. Peaks, ^1H (ppm): 5.55425, 5.54509, 4.96868, 4.96410, 4.80831, 4.78265, 4.11002, 4.10544, 4.09261, 4.08803, 4.07611, 4.07245, 4.02296, 4.01563, 4.00738, 3.99822, 3.98997, 3.98172, 3.88917, 3.86534, 3.84152, 3.78837, 3.78470, 3.77828, 3.75721, 3.74163, 3.73790, 3.68756, 3.67840, 3.66282, 3.65366, 3.52903, 3.50612, 3.50428, 3.48046; ^{13}C: 176.311, 169.568, 119.769, 101.875, 79.953, 75.852, 75.545, 74.115, 71.940, 65.080, 63.066.
TEST FACILITY	Hayashibara Biochemical Laboratory (1988).
ANALYTICAL METHOD	Mass spectroscopy (MS).
Remarks	Characteristic spectrum provided.
TEST FACILITY	Hayashibara Biochemical Laboratory (1988).

METHODS OF DETECTION AND DETERMINATION

ANALYTICAL METHOD UV/Vis, IR, NMR and Mass spectroscopy.

3. COMPOSITION

DEGREE OF PURITY
99.8 - 100%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None.

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight)
None.

ADDITIVES/ADJUVANTS
None.

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported as a component of face creams and toners in small (100-200 mL) plastic containers and as a pure chemical in polyethylene lined steel drums of 10 kg capacity.

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

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

USE
Ingredient in cosmetic preparations.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, Transport and Storage

PORT OF ENTRY
Not known.

IDENTITY OF MANUFACTURER/RECIPIENTS
Notifiers.

TRANSPORTATION AND PACKAGING
The notified chemical will be imported in polyethylene lined steel drums and imported products in small plastic consumer sized containers.

5.2. Operation Description

Consumer products will be imported and shipped to retail customers. Some product demonstration at retailers is expected.

The pure chemical will be formulated into consumer products by standard compounding techniques. The chemical will be weighed out and added to the mixing tank where the preparation will be mixed and dispensed in a largely automatic closed system. During mixing small samples will be removed for QC testing. The formulation will be dispensed automatically into containers and packed when mixing is completed.

5.3. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Compounder	1	4	3
Chemist	1	2	3
Packers	2	4	3

Exposure Details

The weighing and mixing areas in cosmetic formulation plants typically use local exhaust ventilation. Inhalation exposure of compounders is calculated at 2 - 5 mg/m^3. Dermal, and to a lesser extent, ocular exposure may occur during transfer operations and cleaning of tanks and lines; however, the total yearly exposure duration and frequency are likely to be low. Low exposure to the notified chemical in chemical formulations may occur during QC testing.

Exposure to the notified chemical in imported products will be limited to contact with consumer products containing a maximum of 2% notified chemical in the event of a transport or storage accident or during demonstration of product at a retail premises.

5.4. Release

RELEASE OF CHEMICAL AT SITE

Environmental release is unlikely during importation, storage and transportation, and spillage during a transport accident the most likely reason for environmental release. Individual container capacity (100-200 mL capacity plastic containers or 10 kg polyethylene-lined steel drums), container specifications and low concentration of the notified chemical in imported cosmetic would limit the extent of release.

Customers (up to 5 sites in Australia) of the notifier will blend the notified chemical into various cosmetic products using a batch-based process (~ 3 batches per site per annum). Release from the reformulation facilities is anticipated to be limited given the low concentration of the substance in the formulation, isolated and closed mixing systems, engineering controls on emissions, and automated repackaging systems. The waste containing the notified chemical from the blending process is expected to be limited to traces from the clean-up of spills that may potentially occur, residues in emptied imported containers and equipment cleaning wastes. Washwaters from equipment cleaning (2-3% of total annual import volume (TAIV) of the notified chemical will be discharged to sewer. Any spills would be contained within existing bunding and removed by a waste disposal company to landfill. Residues in emptied imported drums (~ 2% of TAIV) would also be removed by a waste company for disposal to landfill.

RELEASE OF CHEMICAL FROM USE

Since the notified chemical will be used in consumer cosmetic products, the majority will eventually be discharged to sewer (> 90% of TAIV). A small proportion (~ 2% of TAIV) will remain in emptied containers, which will be disposed of to landfill or recycled at commercial recycling facilities with washwaters sent to on-site wastewater treatment plant and/or sewer. A smaller fraction of the notified chemical may be spilled and washed to sewer or ground surfaces, absorbed into the body once applied skin surfaces and metabolised, or wiped off from applied skin surfaces and wastes disposed of to landfill.

5.5. Disposal

Lifecycle analysis indicates that the notified chemical will primarily be disposed of in either the sewer (~95%) or landfill (~5%).

5.6. Public exposure

The public should only come into contact with the notified chemical in imported products where the concentration is at most 2%. The products are designed to be applied to the face and remain on the skin for extended periods.

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa White or yellowish white powder or crystalline powder.

Melting Point 152 - 162ºC

METHOD OECD TG 102 Melting Point/Melting Range.
EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks Measured by differential scanning calorimetry.
TEST FACILITY RCC (1996)

Density 1586 kg/m^3 at 20.9ºC

METHOD OECD TG 109 Density of Liquids and Solids.
EC Directive 92/69/EEC A.3 Relative Density.
Remarks Determined with gas comparison pycnometer.
TEST FACILITY RCC (1998)

Vapour Pressure 1.1 x 10^{-13} kPa at 25ºC (estimated).

METHOD OECD TG 104 Vapour Pressure.
EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks Calculated from the estimated boiling point using the Modified Watson Correlation.
TEST FACILITY RCC (1996a)

Water Solubility 714 g/L at 19 ± 1ºC

METHOD OECD TG 105 Water Solubility and EEC Directive 92/69 Part A, A.6 Water Solubility (Flask Method).
Remarks About 40 g of test substance was added to 20 mL double distilled water in each of 6 Erlenmeyer flasks and the mixtures were agitated (30 mins) in an ultrasonic water bath. The flasks were then shaken for 24, 48 or 72 h in a water bath at 30°C. After shaking, two flasks were removed and incubated for another 24 h at 19±1°C. The test solutions were centrifuged at 3000 rpm for 1 min, and an aliquot of each supernatant was filtered (0.2 µm). An aliquot of 1 mL was diluted in deionised water to the various test dilutions. Standard solutions were also prepared. The concentration was measured using photometric UV/VIS spectroscopy.
CONCLUSION The test substance is readily soluble in water (Mensink et al., 1995).
TEST FACILITY RCC (1996b)

Hydrolysis as a Function of pH Half-life at 50ºC was greater than 1 year at pH 4, 7 and 9.

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

pH	*T (°C)*	*Hydrolysis after 5 Days (%)*
4.0	50	<10
7.0	50	<10
9.0	50	<10

Remarks About 11 mg of the test substance was added to 100 mL of prepared buffer solutions of pH 4.0, 7.0 and 9.0 (duplicated 50 mL each). Following incubation, 100 µL aliquots of the test substance were analysed (UV/VIS) after GPC separation. The pH 7.0 solution was analysed without dilution. The pH 4.0 and 9.0 solutions were diluted 1:1 ratio with eluent (20 mL 70% nitric acid added to 2000 mL water) the corresponding buffer solution. Seven standard solutions were also prepared in the range 2.915-116.6 µg/mL.

CONCLUSION The test substance is hydrolytically stable at pH 4, 7 and 9. The estimated half-time in water is >1 year under representative environmental conditions (25 °C).
TEST FACILITY RCC (1998a).

Partition Coefficient (n-octanol/water) log Pow at 20ºC = < -2

METHOD OECD TG 107 Partition Coefficient (n-octanol/water) and EEC Directive 92/69/EEC A.8 Partition Coefficient (Shake Flask Method).
Remarks The stock solution was prepared by dissolving 2700 mg of the notified chemical in 10 mL of n-octanol by treating the mixture for 30 mins in an ultrasonic water bath. The mixture was filtered (0.2 µm) to prepare a saturated solution of notified chemical in octanol, which was analysed without further dilution by UV/VIS spectrometer. Standard solutions were prepared in the range 11.7-117 µg/mL. The saturation concentration of the test substance in octanol was 16.3 mg/L. An estimated log Pow of < -4.6 was derived based on the method used; however, this is outside the range accessible by the flask shaking method.
TEST FACILITY RCC (1996c)

Adsorption/Desorption Not determined
REMARKS Test not undertaken as the notified chemical is highly soluble in water and is expected to be mobile in soils and sediments.

Dissociation Constant Not determined
REMARKS Test not undertaken as the notified chemical is a covalent organic material with no dissociable hydrogens.

Surface Tension 71 mN/m at 20.3 ± 0.5ºC

METHOD OECD TG 115 Surface Tension of Aqueous Soutions and EEC Directive 92/69/EEC A.5 Surface Tension.
Remarks Solutions of the test substance were prepared by weighing 99 mg of the test substance into a 100 mL flask and filled up to the mark with purified milli-Q water. Milli-Q water was used instead of distilled water, which should not affect the test results. This was treated ultrasonically for 5 minutes to dissolve all of the test substance. Two tests were conducted using a Krüss GmbH Tensiometer fitted with a platinum-irridium ring, with the ring lowered into the test substance and raised and the force measured. The tests were done at 20±0.5ºC .
CONCLUSION Not a surface-active substance (>60 mN/m).
TEST FACILITY RCC (1998c)

Particle Size

METHOD Based on OECD TG 110 Particle Size Distribution/Fibre Length and Diameter Distributions.

Range (µm)	*Mass (%)*
< 8	0.22
8 – 15	2.00
15 – 32	91.70
32 – 200	6.04
> 200	0.14

Remarks MMAD (Mass Median Aerodynamic Diameter) = 24 µm. Approximately 1.5% of particles were below 10 µm diameter.
TEST FACILITY S.A.F.E. (1998).

Flash Point Not determined.

Remarks Not applicable for a solid.

Flammability Limits Not highly flammable.

METHOD EC Directive 92/69/EEC A.10 Flammability (Solids).
Remarks The notified chemical could not be ignited with a flame. In contact with the ignition source, the notified chemical melted and coloured black but could not sustain and burning reaction.
TEST FACILITY RCC (1996).

Autoignition Temperature Not autoflammable.

METHOD 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
TEST FACILITY RCC (1998d).

Explosive Properties Not explosive.

METHOD EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks Not explosive by thermal or mechanical means.
TEST FACILITY Institute of Safety and Security (1998).

Oxidising Properties Non-oxidising.

Remarks The notified chemical has no functional groups associated with oxidising activity and the oxygen balance is negative.
TEST FACILITY RCC (1998e).

Reactivity

Remarks Stable under normal environmental conditions.

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral LD50 > 2000 mg/kg bw	low toxicity
Rat, acute dermal LD50 > 2000 mg/kg bw	low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation - adjuvant test.	no evidence of sensitisation.
Rat, oral repeat dose toxicity - 28 days.	NOAEL = 1000 mg/kg bw/day
Genotoxicity - bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosomal aberrations	non genotoxic
Genotoxicity – in vivo mouse micronucleus	non genotoxic

7.1. Acute toxicity – oral

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 401 Acute Oral Toxicity – Limit Test.
Species/Strain Rat/Crj:CD.
Vehicle Deionised water.
Remarks - Method No deviations from standard method.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5/sex	0	None
2	"	1000	"
3	"	2000	"

LD50 > 2000 mg/kg bw
Signs of Toxicity Soft stool or muddy stool were sporadically observed in every group on the day after administration.
Effects in Organs No signs.

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

TEST FACILITY Fuji Biomedix (1996).

7.2. Acute toxicity - dermal

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 402 Acute Dermal Toxicity – Limit Test.
EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal) – Limit Test.
Species/Strain Rat/Wistar.
Vehicle Distilled water.
Type of dressing Semi-occlusive.
Remarks - Method No deviations from standard method.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5/sex	2000	None

LD50 > 2000 mg/kg bw
Signs of Toxicity - Local Yellow discolouration produced by the test substance was observed on the application site of all animals, starting on day 2 (removal of bandage)

and partly lasting until termination.

Signs of Toxicity - Systemic	None.
Effects in Organs	None.

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

TEST FACILITY RCC (1998f).

7.3. Irritation – skin

TEST SUBSTANCE Notified chemical.

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

Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Vehicle	Distilled water.
Observation Period	72 hours.
Type of Dressing	Semi-occlusive.
Remarks - Method	Protocol deviations are stated as: test article stored in the refrigerator at ca. 4°C and the purity of the test article was 100%.

RESULTS

Remarks - Results	Neither erythema nor oedema was observed in any animal at any time point.

CONCLUSION The notified chemical is non-irritating to skin.

TEST FACILITY RCC (1996).

7.4. Irritation - eye

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Observation Period	7 days.
Remarks - Method	Protocol deviations are stated as: test article stored in the refrigerator at ca. 4°C and the purity of the test article was 100%.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.67	1	2	2	72 hours	0
Conjunctiva: chemosis	0.33	0.67	2	2	72 hours	0
Conjunctiva: discharge						
Corneal opacity	0	0	1	1	72 hours	0
Iridial inflammation	0	0	0	0		0

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

Remarks - Results Discharge and slight iris effects occurred in 1 animal.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY RCC (1996).

7.5. Skin sensitisation

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 406 Skin Sensitisation – Maximisation Test.
EC Directive 96/54/EC B.6 Skin Sensitization - Maximisation Test.

Species/Strain Guinea pig/

PRELIMINARY STUDY Maximum Non-irritating Concentration:
intradermal: < 1%
topical: 75%

MAIN STUDY

Number of Animals Test Group: 20 Control Group: 10

INDUCTION PHASE Induction Concentration:
intradermal injection, 1%
topical application, 75%

Signs of Irritation Not stated for intradermal induction; one test group animal exhibited slight erythema at 24 hours after epidermal induction.

CHALLENGE PHASE

1st challenge topical application: 15, 25, 50 and 75%

2nd challenge Not conducted.

Remarks - Method All animals of the test and control groups were pretreated with 10% SLS in paraffin liquid 1 day prior to topical induction.

RESULTS

Remarks - Results No control or test group animal exhibited erythema or oedema at the challenge site.

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

TEST FACILITY RCC (1996).

7.6. Repeat dose toxicity

TEST SUBSTANCE Notified chemical.

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

Species/Strain Rat/Wistar.

Route of Administration Oral – gavage.

Exposure Information Total exposure days: 28 days;
Dose regimen: 7 days per week.

Vehicle Distilled water.

Remarks - Method No deviations from standard method.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	10/sex	0	None
II (low dose)	"	50	"
III (mid dose)	"	200	"
IV (high dose)	"	1000	"

Clinical Observations

No clinical signs or effects on food consumption or body weight gain were noted. An increased incidence of persistent pupillary membranes in high dose males was present at pretest. In the modified Irwin screen all treated female groups exhibited increased forelimb grip strength.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

No treatment related changes.

Effects in Organs

No changes in organ weights, macroscopic or microscopic findings.

Remarks - Results	The increased incidence of persistent pupillary membranes in high dose males was not considered to be treatment related and the increased forelimb grip strength in females was considered to be in the normal range.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day in this study.

TEST FACILITY RCC (1996).

7.7. Genotoxicity - bacteria

TEST SUBSTANCE	Notified chemical.
METHOD	Commentary on the Guidelines for Toxicity Studies of Drugs, edited by the Evaluation and Registration Divisions, Pharmaceutical Affairs Bureau, Japanese Ministry of Health and Welfare. New Guidebook for Mutagenicity Tests with Microorganisms, edited by the Chemicals Survey Division, Industrial Safety and Health Department, Japanese Ministry of Labor. Plate incorporation procedure.
Species/Strain	*S. typhimurium*: TA1537, TA1535, TA98, TA100. *E. coli*: WP2 uvrA.
Metabolic Activation System	Rat liver S9 fraction (preparation method not described).
Concentration Range in Main Test	a) With metabolic activation: 0-5000 µg/plate. b) Without metabolic activation: 0-5000 µg/plate.
Vehicle	Distilled water.
Remarks - Method	A dose finding test and single main test were performed. Original data tables were not provided.

RESULTS

Remarks - Results	No dose-dependent increases in mutation frequency were detected with the notified chemical in any strain. Negative and positive controls gave appropriate responses.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Toxicological Research Laboratory (1991a).

7.8. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical.
METHOD	Commentary on the Guidelines for Toxicity Studies of Drugs, edited by the Evaluation and Registration Divisions, Pharmaceutical Affairs Bureau, Japanese Ministry of Health and Welfare.

Cell Type/Cell Line	Chinese Hamster Don cells.
Metabolic Activation System	Rat liver S9 fraction (preparation method not described).
Vehicle	Growth medium.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 500*, 1000*, 2000*	16 hours	16 hours
Test 2	0*, 500*, 1000*, 2000*	32 hours	32 hours
Test 3	0*, 500*, 1000*, 2000*	4 hours	20 hours
Present			
Test 1	0*, 500*, 1000*, 2000*	4 hours	20 hours

*Cultures selected for metaphase analysis.

RESULTS

Remarks - Results	The 50% growth inhibition dose with or without S9 fraction was approximately 2000 μg/mL. No increase in the frequency of cells containing chromosomal aberrations was observed over control levels either with or without S9 present. Positive controls gave the expected responses.
CONCLUSION	The notified chemical was not clastogenic to Chinese Hamster Don cells treated in vitro under the conditions of the test.
TEST FACILITY	Toxicological Research Laboratory (1991b).

7.9. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 473 In vitro Mammalian Chromosomal Aberration Test. EC Directive 92/69/EEC B.10.
Cell Type/Cell Line	Chinese Hamster V79 cells.
Metabolic Activation System	Phenobarbital and β-naphthoflavone induced rat liver S9 fraction.
Vehicle	Growth medium.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 106.25, 212.5, 425, 850*, 1700*, 3400*	4 hours	18 hours
Test 2	0*, 850*, 1700*, 3400*	18 hours	18 hours
Test 3	0*, 425, 850, 1700, 3400*	28 hours	28 hours
Present			
Test 1	0*, 106.25, 212.5, 425*, 850, 1700*, 3400*	4 hours	20 hours
Test 2	0*, 106.25, 212.5, 425, 850*, 1700*, 3400*	4 hours	20 hours

*Cultures selected for metaphase analysis.

RESULTS

Remarks - Results	No cytotoxicity was observed at doses up to 3400 μg/mL in either the presence of absence of S9 fraction. No increase in the frequency of cells containing chromosomal aberrations was observed over control levels either with or without S9 present. Positive controls gave the expected responses.
CONCLUSION	The notified chemical was not clastogenic to Chinese Hamster V79 cells

treated in vitro under the conditions of the test.

TEST FACILITY RCC (1998g).

7.10. Genotoxicity – in vivo

TEST SUBSTANCE Notified chemical.

METHOD Commentary on the Guidelines for Toxicity Studies of Drugs, edited by the Evaluation and Registration Divisions, Pharmaceutical Affairs Bureau, Japanese Ministry of Health and Welfare.

Species/Strain Mouse/ S1c: ICR.

Route of Administration Intraperitoneal.

Vehicle Physiological saline.

Remarks - Method Mitomycin C was used as the positive control.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
1	5 males	0	24
2	"	500	"
3	"	1000	"
4	"	2000	"

RESULTS

Doses Producing Toxicity One animal out of 5 died in the preliminary test at 2000 mg/kg bw but no animals out of 10 died in the main group.

Genotoxic Effects None.

Remarks - Results No increases in the frequency of micronucleated polychromatic erythrocytes were observed above control levels. The positive control, mitocmycin C, gave the expected results.

CONCLUSION The notified chemical was not clastogenic in this in vivo mouse bone marrow micronucleus test under the conditions of the test.

TEST FACILITY Toxicological Research Laboratory (1991c).

8. ENVIRONMENT

8.1. Environmental fate

8.1.1 Ready biodegradability

TEST SUBSTANCE: Notified chemical.

METHOD: OECD TG 301E Ready Biodegradability: Modified OECD Screening Test

Inoculum	Activated sludge from a domestic wastewater treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Dissolved Organic Carbon (DOC)
Remarks - Method	Test concentration was 40 mg/L (35.1 mg DOC/L). Test containers (50 mL Erlenmeyer flasks) maintained in dark during tests. The reference material was aniline at 25 mg/L (19.1 mg DOC/L). Abiotic control containing sterile filtered test medium (0.45 μm) was at 80 mg/L (32.9 mg DOC/L). Test temperature range was 20.5 - 22°C.

RESULTS

	% Degradation (DOC Removal)		
Incubation time	*Notified Chemical*	*Aniline*	*Abiotic Control*
Days	*Mean*	*Mean*	*Mean*
7	81	113	4
14	92	100	47
21	100	104	68
27	100	104	79
28	100	99	72

Remarks - Results: As after 7 days, 81% of the test substance was degraded, and 100% within 21 days (greater than 20%), the notified chemical can be regarded as readily biodegradable. Degradation of the reference substance (more than 70% after 14 days) indicates the viability of the culture and test conditions.

CONCLUSION: The test substance is readily biodegradable as ~ 100% was eliminated after 28 days and the 10-day window was met. At the tested concentrations and conditions, the notified chemical had no inhibitory effect on sewage sludge micro-organisms.

TEST FACILITY: RCC (1996)

8.1.2. Bioaccumulation

No bioaccumulation test data or comments were provided in the notification dossier. The very high water solubility and the very low log P_{ow} suggest that the notified chemical has a poor affinity to lipids and hence there is a low potential for the notified chemical to diffuse across biological membranes and bioaccumulate (Connell, 1990). The notified chemical is readily metabolised following oral administration to rats and guinea pigs (Yamamoto et al., 1990).

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE: Notified chemical.

METHOD: OECD TG 203 Fish, Acute Toxicity Test and EEC Directive 92/69/EEC C.1 Acute Toxicity for Fish, Static Conditions

Species	Rainbow Trout (*Oncorhynchus mykiss*)
Exposure Period	96 hours

Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC Chromatography and UV/VIS detection
Remarks – Method	Since no mortality was observed in a range-finding test at 100 mg/L, only test concentrations of 0 and 100 mg/L were used in the main test. Trout were obtained from trout breeding station, Zeiningen, Switzerland. Acclimation period was 7 days prior to testing. No fish died within 4 weeks prior to test. Mean body length 5.2 ± 0.4 cm (mean ± SD) and mean body weight 1.7 ± 0.4 g (mean ± SD). Test conditions (satisfactory): temperature 12 - 13°C, photoperiod 16 light: 8 dark at 50 - 200 lux, pH range 7.6 - 8.0, dissolved oxygen 9.0 - 9.5 mg/L. Fish were observed at 2, 24, 24, 72 and 96 hours. NOEC (LC0) determined directly from the test data due to absence of toxic effect up to the test concentration. The concentration of test substance was measured analytically at 0 and 96 hours, with acceptable stability during the test. Test solution preparation: 1.5 g of notified chemical was dissolved in 3 L water (stirred 10 mins). The solution was transferred to test aquaria (15 L) and intensively mixed. A control was also tested.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual (mean)*		*2 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	0	7	0	0	0	0	0
100	97.7 (t = 0 h) 79.9 (t = 96 h)	7	0	0	0	0	0

LC50	> 80 mg/L at 96 hours based on actual measured concentrations.
NOEC	80 mg/L at 96 hours
Remarks – Results	No sublethal effects were observed in the control or any of the treatments. The actual concentrations of test media varied from 98 - 80% of the nominal values between the beginning and end of exposure. No changes were observed in the test substance when in the test media during the tests.

CONCLUSION The test substance is practically non-toxic to fish.

TEST FACILITY RCC (1998h)

8.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test, and EEC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia – Static

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC Chromatography and UV/VIS detection
Remarks - Method	Young *Daphnia magna* Strauss (6-24 h old) were RCC-laboratory bred, were not fed, and aquaria were not aerated during the tests. Test conditions (satisfactory): temperature 20.0 - 20.6°C, photoperiod 16 light: 8 dark at 540 - 760 lux with a 30 min transition period, pH range 6.8 - 8.0, dissolved oxygen > 8.3 mg/L. *Daphnia* were observed at 24 and 48 hours. NOEC (LC0) determined directly from the test data due to absence of toxic effect up to the test concentration. The concentration of test substance was measured analytically at 0 and 48 hours, with acceptable stability during the test. Test solution preparation: The highest

test concentration (200 mg/L) was prepared by dissolving 280 mg of the test substance in 1400 mL test water. Samples were diluted to the other required test concentrations. The test solutions, prepared just before introduction of *Daphnia*, were transferred to test aquaria (100 mL). A control was also tested.

RESULTS

Concentration mg/L		*Number of D. magna*	*% Immobilised*	
Nominal	*Actual (mean)*		*24 h*	*48 h*
Control	0	10	0	0
9.2	Not analysed	10	0	0
20	Not analysed	10	0	0
42	Not analysed	10	0	0
92	Not analysed	10	0	0
200	192.5 (t = 0 h) 189.5 (t = 48 h)	10	0	0

EC50	> 190 mg/L at 48 hours based on actual measured concentrations
NOEC	190 mg/L at 48 hours
Remarks – Results	No immobilisation of *Daphnia* was observed in the control and at any test concentration after 24 and 48 hours.

CONCLUSION The test substance is practically non-toxic to *Daphnia magna*.

TEST FACILITY RCC (1996c).

8.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 201 Alga, Growth Inhibition Test and EC Directive 92/69/EEC C.3 Algal Inhibition Test.

Species	Green alga *Scenedesmus subspicatus* CHODAT
Exposure Period	72 hours
Concentration Range Nominal	Test concentrations of 0 mg/L and 100 mg/L
Concentration Range Actual	0 and 98.2 mg/L
Auxiliary Solvent	None
Analytical Monitoring	HPLC Chromatography and UV/VIS detection
Remarks – Method	Initial algal biomass ~ 10000 cells/mL test medium. Aquaria with 15 mL of algal suspension per replicate were continuously stirred during the tests. Test conditions (satisfactory): temperature 24°C, photoperiod continuous light at ~ 8300 lux, pH range 8.1 - 9.2, water hardness 24 mg/L. The concentration of test substance was measured analytically at 0 and 72 hours, with acceptable stability during the test. Test solution preparation: The test medium of the single test concentration of nominal 100 mg test substance/L was prepared by dissolving 50 mg of test substance in 500 mL test water. A control was also tested. Algal cell densities were counted in control and test media using a Coulter Counter Model ZM; 2 reps per sample).

RESULTS

Biomass	*Growth*	*NOEC*
E_bC50 mg/L at 72 h	*E_rC50 mg/L at 72 h*	*mg/L at 72 h*
> 98.2	> 98.2	98.2 (highest actual test conc.)

Remarks – Results The measured test concentrations marginally varied from 98% to 97% of

	the nominal concentrations at the beginning and end of the exposure. Test results are based on actual concentrations.
CONCLUSION	The test substance is practically non-toxic to algae.
TEST FACILITY	RCC (1998i)

8.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test and EC Directive 87/302/EEC L.133/118-122
Inoculum	Activated sludge obtained from a domestic wastewater treatment plant
Exposure Period	3 hours
Concentration Range Nominal	Five test concentrations: 10, 32, 100, 320 and 1000 mg/L
Remarks – Method	Test concentrations of the reference substance (3,5-dichlorophenol) were 10, 32 and 100 mg/L, with the 3 h EC50 of 13 mg/L within acceptable criteria.
RESULTS	
NOEC	1000 mg/L (highest concentration tested)
Remarks – Results	Up to and including the highest test concentration (nominal 1000 mg/L), the test substance had no significant inhibitory effect (< 15%) on the respiration rate of activated sludge after an incubation period of 3 hours.
CONCLUSION	Limited microbial respiration inhibition was observed at the highest test concentration.
TEST FACILITY	RCC (1998j)

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The notified chemical is non-volatile and atmospheric losses following environmental releases are expected to be low. Furthermore, it is not readily hydrolysed in water at environmentally relevant pH values. However, it is readily biodegradable, with 100% elimination after 21 days in sewage treatment plant sludge inocula under test conditions, is readily soluble in water and potentially has a low affinity to adsorb to particulate organic material or to bioaccumulate due to its low log P_{ow} value.

Landfilled wastes containing the notified chemical (50 - 500 kg per annum) are expected to biodegrade within the landfill environment over time and are not likely to pose an unacceptable risk to the environment.

The waste from the manufacturing process is expected to be limited to traces remaining from the clean-up of spills, residues in emptied containers and equipment washwaters/wastes.

The majority (~ 95%) of the notified chemical in cosmetic products will eventually be released into the sewerage systems the predicted environmental concentration (PEC) in the treated effluent, and downstream waterways, has been estimated with a sewage treatment plant (STP) model developed by the Department of the Environment and Heritage (DEH, 2003). The model assumes that the total quantity of the notified chemical imported (1 - 10 tonnes per annum) is used and discharged into sewerage systems throughout Australia and none is attenuated or biodegraded within these systems. Australia has a population of ~ 19.5 million people, and an average value for water consumption of 200 L/person/day has been adopted for this national-level assessment (3900 ML/day for total population). Therefore, the concentration of notified chemical in the Australian sewerage network may approximate 0.7 - 7 µg/L (ie. 1 x 10^9 mg ÷ 365 days/year ÷ 3900 x 10^6 L ÷ 1000). Based on dilution factors of 1 and 10 for inland and ocean discharges of STP-treated effluents, outfalls PECs of the notified chemical in freshwater and marine surface waters may, under these assumptions, approximate 0.7 - 7 µg/L ($PEC_{freshwater}$) and 0.07 - 0.7 µg/L (PEC_{marine}), respectively.

The SIMPLETREAT model (European Commission, 1996) for modelling partitioning and losses in sewage treatment plants was used to estimate the proportions of the chemical that partition into the different environmental compartments. The model assumed ready biodegradability of the notified chemical in the STP system as ready biodegradability test results showed that 100% of the notified chemical was eliminated after 21 days. The model results indicate that when the notified chemical is released into the aqueous phase of a standard STP, about 50% may be biodegraded and 50% remain in the effluent, while there is very limited release to air through volatilisation or partitioning to biosolids. The standard STP operation parameters include a hydraulic retention time of 10.4 h.

These results are consistent with the non-volatility, high solubility, low log P_{ow} and expected low K_{oc} values of the notified chemical. Assuming 50% of the notified chemical (up to 4900 kg) may potentially remain in solution, $PEC_{freshwater}$ and PEC_{marine} values of 0.3 - 3 µg/L and 0.03 - 0.3 µg/L, respectively, have been derived. Further biodegradation of the notified chemical is expected should it be discharged in STP effluent into the aquatic compartment.

Bioaccumulation in aquatic organisms is not expected due to the high water solubility of the notified chemical and its low log P_{ow} that indicates a poor affinity to lipids. The ready biodegradability of the notified chemical and amenability to metabolic processes would also limit its bioaccumulation potential

9.1.2. Environment – effects assessment

The results of the aquatic toxicity tests available indicate that the lowest available NOEC is for *Daphnia magna*, with a NOEC of 190 mg/L. In each of the three tests available, no adverse effects were noted at the highest concentrations tested. A predicted no effect concentration for aquatic organisms ($PNEC_{aquatic}$) of 19 mg/L (19000 µg/L) has been derived by dividing the

lowest acute NOEC value by a safety factor of 10, used to account for interspecies sensitivity, acute to chronic effects ratio and other adverse factors that may potentially arise in the environment if organisms are exposed to the notified chemical.

9.1.3. Environment – risk characterisation

The risk quotient values (PNEC/PEC) estimated based on the scenario of discharging 95% of the notified chemical into sewage systems, assuming no attenuation/biodegradation in Australia are 0.0004 or lower. Likely biodegradation in STPs and the aquatic compartment further reduces the risk. Therefore, the proposed use of the notified chemical is unlikely to pose an unacceptable risk to the aquatic life.

The notifier provided a risk assessment for European conditions on the notified chemical according to EU Directive 93/67/EEC (RCC, 1997). Import tonnage was < 1 tpa. It was estimated that ~ 91% of the notified chemical discharged to sewer would be treated/retained within the STP system. This was based on calculation assumptions of ready biodegradation rate of 100%, log Kow of < -2, vapour pressure (1×10^{-10} Pa at 25°C) and water solubility of 714 g/L. A $PNEC_{aquatic}$ of > 2 mg/L was derived by dividing the lowest acute toxicity data (48 h EC50 for *Daphnia* of > 200 mg/L nominal) by a safety factor of 100. PEC values for processing and use of the notified chemical were 0.036 mg/L and 0.0128 mg/L, assuming inherent biodegradation. With PNEC/PEC ratios of < 0.00002, it was concluded that the notified chemical posed no immediate concern for aquatic organisms. With the proposed greater import volume into Australia than used in the RCC (1997) risk assessment model, the resulting low PNEC/PEC ratios would continue to support the view that the notified chemical is unlikely to pose an adverse risk to the aquatic environment with the expected use and disposal pattern.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

Inhalation exposure of workers is likely to be at a maximum for compounders of cosmetic products and is estimated to be no more than 5 mg/m^3 for 4 hours on 3 days/year. Typically, cosmetic product compounders wear hand and eye personal protective equipment so that contact with the notified chemical is unlikely during transfer to the mixing tank. Once the chemical is in the finished product it is at a low concentration of 2%. Other workers (QC chemists and packers) are less likely to be exposed to the notified chemical than are compounders.

9.2.2. Public health – exposure assessment

The public will` be exposed to the notified chemical at a maximum concentration of 2% in consumer products normally applied up to 2 times per day.

9.2.3. Human health - effects assessment

The notified chemical was of low acute toxicity in rats via the oral and dermal routes (LD_{50} > 2000 mg/kg bw in each study), was not a skin irritant in rabbits or a skin sensitiser in guinea pigs and was a slight eye irritant in rabbits. No target organ was identified in a 28-day oral repeated dose study in rats at concentrations up to 1000 mg/kg bw/day and the notified chemical was not mutagenic in bacteria, clastogenic in Chinese Hamster V79 cells in vitro or genotoxic to mouse bone marrow polychromatic erythrocytes in vivo.

9.2.4. Occupational health and safety – risk characterisation

The notifier submitted a risk assessment (RCC, 1997) which concluded the following: If inhalation exposure is a maximum of 5 mg/m^3 during product manufacture and the inhaled volume is 10 m^3/day (1.67 m^3/4 hours), the maximum exposure for a 70 kg worker is calculated at 8.35 mg/day or 0.12 mg/kg/day. Dermal exposure is expected to be accidental and calculated to be 0 – 0.1 mg/cm^2/day. Assuming that both hands can be exposed, the dermal area is 840 cm^2 and the predicted dermal exposure is 0 – 84 mg/day or 0 – 1.2 mg/kg/day for a 70 kg worker. Given these exposure levels, which are acceptable estimates, no risk of adverse health effects is likely given the NOAEL for the 28-day oral repeated dose study in rats was 1000 mg/kg/day.

9.2.5. Public health – risk characterisation

According to the risk assessment submitted by the notifier (RCC, 1997) 0.8 g of face cream would be applied per application and 100% would remain on the skin after use. If the

bodyweight of the user is assumed to be 55 kg, the consumer product is used up to 2 times per day and the concentration of notified chemical in the product is 2%, the assessed dermal exposure would be (800 x 2 x 100 x 2)/(100 x 100 x 55) = 0.58 mg/kg/day bw. Given the NOAEL for the 28-day oral repeated dose study in rats was 1000 mg/kg/day, the risk of adverse health effects is very low.

10. CONCLUSIONS – ASSESSMENT LEVEL OF CONCERN FOR THE ENVIRONMENT AND HUMANS

10.1. Hazard classification

Based on the available data the notified chemical is not classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999).

and

The classification of the notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (UN, 2003) was not possible as the notified chemical is readily biodegradable and practically non-toxic to aquatic organisms (ie. L(E)C50 > 100 mg/L).

10.2. Environmental risk assessment

On the basis of the reported use pattern, aquatic PEC/PNEC ratios, ecotoxicity data and expected low environmental persistence, the notified chemical is not considered to pose an unacceptable risk to the environment.

10.3. Human health risk assessment

10.3.1. Occupational health and safety

There is Low Concern to occupational health and safety under the conditions of the occupational settings described.

10.3.2. Public health

There is Negligible Concern to public health when used as described.

11. MATERIAL SAFETY DATA SHEET

11.1. Material Safety Data Sheet

The MSDS of the notified chemical and products containing the chemical provided by the notifiers were in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994a). They are published here as a matter of public record. The accuracy of the information on the MSDS remains the responsibility of the applicant.

11.2. Label

The label for the notified chemical and products containing the chemical provided by the notifiers were in accordance with the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994b). The accuracy of the information on the label remains the responsibility of the applicant.

12. RECOMMENDATIONS

CONTROL MEASURES
Occupational Health and Safety

- A copy of the MSDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances*, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Environment

Disposal

- The notified chemical should be disposed of to sewer and/or landfill in accordance with State/Local Government waste management regulations. Spill residues should be buried in authorised landfill.

Emergency procedures

- Spills containing the notified chemical in pure form should be swept up and placed in sealed containers for recycling or disposal. The manufacturer should be consulted for recycling options. The spill area should be washed with water and wash water disposed of to sewer in accordance with waste management authority regulations. The solution may be acidic and large spills may require neutralisation prior to disposal. Runoff into stormwater drains and waterways should be prevented.

- Small spills of formulations should be cleaned up with absorbent material or adsorbed to a substrate and wastes placed in containers for disposal to landfill. The spill area should be flushed with water. Larger spills of formulated products should be prevented from entering stormwater drains or waterways. Spills should be contained with adsorbent material (ie. sand, earth, vermiculite), swept up and placed in containers for landfill disposal or recycling. Spill area should be washed with water and washwater collected for disposal to sewer. Manufacturer should be contacted for recycling options. Spill residues should be buried in authorised landfill.

12.1. Secondary notification

The Director of Chemicals Notification and Assessment must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(2) of the Act:
- if any of the circumstances listed in the subsection arise.

The Director will then decide whether secondary notification is required.

No additional secondary notification conditions are stipulated.

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