File No: STD/1098

March 2005

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Arlatone Dioic DCA

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Director
Chemicals Notification and Assessment

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Uniqema Australia Pty Ltd (ABN 00018084), Level 37, 101 Collins St MELBOURNE VIC 3000

Symex Holdings Pty Ltd (ABN 29 091 035 353), 14 Woodruff St PORT MELBOURNE VIC 3207

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: Chemical name, CAS No., molecular and structural formulae, molecular weight, spectral data, purity, additives and adjuvants.

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
Europe: Notification No. 96-03-0365-00.

2. IDENTITY OF CHEMICAL

OTHER NAME(S)
Dioic acid
Dioic DCA

MARKETING NAME(S)
Arlatone Dioic DCA

SPECTRAL DATA

ANALYTICAL METHOD	Ultraviolet/visible (UV/Vis), Infrared (IR) and Nuclear Magnetic Resonance (NMR) spectroscopy.
Remarks	Reference spectra were provided.
TEST FACILITY	Uniqema.

METHODS OF DETECTION AND DETERMINATION

ANALYTICAL METHOD	UV/Vis, IR and NMR spectroscopy.

3. COMPOSITION

DEGREE OF PURITY
High.

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
The notified chemical contains a range of impurities expected to have a similar toxicological profile to the main components.

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

ADDITIVES/ADJUVANTS
A stabiliser at < 2%.

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical may be imported as a component of a range of cosmetic products including: foundations creams and powders, concealers, day and night creams, body washes and creams, skin treatments and moisturisers in consumer sized products. The notified chemical may also be imported for formulation into products in 200 L steel drums and 20 L pails.

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

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

USE
Cosmetic skin treatment.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, transport and storage

PORT OF ENTRY
Not known.

IDENTITY OF MANUFACTURER/RECIPIENTS
Not known.

TRANSPORTATION AND PACKAGING
Transport will typically occur by road or rail. The consumer sized products will be typical of personal care products and packaged accordingly and the notified chemical itself will be imported in 200 L steel drums or 20 L pails.

5.2. Operation description
For reformulation the solid flakes will be manually transferred from drums or pails either to open or to closed mixing vessels to which other ingredients such as water, emulsifiers and oils are added. Following mixing automated packing into consumer sized containers will occur.

5.3. Occupational exposure
Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Delivery to wharf	10	4 hours/day	40 days/year
Distribution (transport and storage)	100	6 hours/day	240 days/year
Formulation	200	6 hours/day	240 days/year
Point of sale	1000	6 hours/day	240 days/year

Exposure Details
The notified chemical is said to be a non-dusting soft waxy solid. Therefore, inhalation exposure is unlikely. Dermal exposure is possible for transport and storage workers in the event of a breach of the import containers.

Formulation of personal care products can result in dermal exposure during weighing and addition of the notified chemical to mixers with secondary transfer from hands to eyes a possibility. Once the notified chemical has been added to the mixer the systems are typically automated and exposure is correspondingly reduced. In addition the maximum concentration of the notified chemical in the mixtures is typically 1% (maximum 5%). Once packed into consumer sized containers exposure of workers is unlikely. Some exposure may occur to workers conducting quality control sampling and cleaning of equipment but at this stage the quantity to which the workers are exposed is small and the concentration of chemical is less than 5%.

5.4. Release

RELEASE OF CHEMICAL AT SITE
The notified chemical will not be manufactured in Australia but it will be reformulated into personal skin care products. Waste notified chemical will be generated during reformulation via:

– Spills	up to 1%	maximum 100 kg,
– Import container residues	up to 1%	maximum 100 kg,
– Process Equipment cleaning	up to 1.5%	maximum 150 kg.

RELEASE OF CHEMICAL FROM USE
Approximately 1% of the contents of the end-product container will remain when it is disposed of to landfill, generally in domestic rubbish. This equates to approximately 100 kg of notified chemical annually. Since the notified chemical is a component in skin care products ultimately the majority of the notified chemical will be washed off the skin and into the sewer.

5.5. Disposal
Reformulation solid wastes, including spills and import containers and any residues present, will be disposed of to landfill. This represents up to 200 kg per year of the notified chemical. A further 100 kg will be disposed of to landfill in end-user containers.

The process equipment cleaning effluent containing up to 150 kg of notified chemical will be disposed of to sewer. Approximately 95.5% of the notified chemical will end up in the sewer due to use of the end-product. A total of 97% of the imported volume of notified chemical will therefore go to sewer, ie up to 9700 kg per annum.

5.6. Public exposure
Exposure to the pure notified chemical is unlikely except in the event of a transport accident.

Exposure of the public to the formulated personal care products is intended to be deliberate and widespread and mainly will be dermal with incidental ocular exposure.

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa Cream coloured pellets.

Melting Point/Freezing Point 27 - 57°C

METHOD EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks Differential scanning calorimeter. Reaction or decomposition observed above 92°C.
TEST FACILITY Notox (1996a).

Boiling Point > 150°C at 101.3 kPa

METHOD EC Directive 92/69/EEC A.2 Boiling Temperature.

Remarks	Differential scanning calorimeter. Reaction or decomposition observed above 150°C.
TEST FACILITY	Notox (2000a).

Density 1100 kg/m^3 at 20°C

METHOD	EC Directive 92/69/EEC A.3 Relative Density.
Remarks	Gas comparison pycnometer.
TEST FACILITY	Notox (2000b).

Vapour Pressure 3.6 x 10^{-4} kPa at 20°C

METHOD	OECD TG 104 Vapour Pressure. EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks	Static technique using capacitance manometer fitted with a 133 Pa capacitive sensor. The sample temperature was measured with a platinum resistance thermometer. The sample vessel was filled with 1 g of test material. The vessel evacuated prior to measurements starting at 36.35°C, then 29.42 °C, and finally 24°C. For each temperature a number of measurements were taken. The vapour pressure curve was derived according to Clarke and Glew (1966).
TEST FACILITY	Notox (1996b).

Water Solubility < 0.7 mg/L at ambient temperature.

METHOD	OECD TG 105 Water Solubility (column elution method – flask method). EC Directive 92/69/EEC A.6 Water Solubility.
Remarks	The test material is a mixture of several components, thus only preliminary tests were done. First preliminary test: Excess test material was stirred with double distilled water overnight at ambient temperature. Undissolved material was observed in the solutions. Samples of the water phases were centrifuged and then the clear supernatant separated and again centrifuged. The resultant supernatant was diluted and analysed by HPLC. The resultant chromatogram was compared to the chromatogram of a 308 mg/L solution of the test solution. The comparison indicated that the test material was a mixture with components having a range of water solubilities – some very low. Second preliminary test: Test material (3.51 mg) stirred with double distilled water (5 L) for 8 days at ambient temperature. Undissolved material was observed on the surface of the solution after mixing and therefore solubility was concluded to be < 0.7 mg/L.
TEST FACILITY	Notox (1996c).

Surface Tension 47.2 mN/m at 20°C for 90% saturated solution.

METHOD	OECD TG 115 Surface Tension of Aqueous Solutions. EC Directive 92/69/EEC A.5 Surface Tension.
Remarks	Apparatus: tensiometer with a platinum-iridium ring with a wire radius of 0.185 mm and a ring radius of 9.545 mm. Test solution was prepared by stirring excess test substance with water for 23 hours then centrifuging at 3500 g at 20°C. The resultant clear supernatant was diluted with water to obtain a 90% saturated solution, which was used for the measurements. As the result was below 60 mN/m, the test substance was surface active.

TEST FACILITY Notox (2000c)

Hydrolysis as a Function of pH Not determined.

Remarks Not possible to determine due to the low water solubility. No hydrolysable groups are present.

Partition Coefficient (n-octanol/water) log P_{ow} = 2.4 to 5.0 at 20°C

METHOD OECD TG 117 Partition Coefficient (n-octanol/water).
EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks HPLC Method
Eight reference substances were used for comparison with log P_{ow}s ranging from 0.3 to 4.7. The chromatogram indicated that the material was a mixture of 16 substances with the first eluted component having a log P_{ow} of 2.4 and the last having a log P_{ow} of 5.0.
TEST FACILITY Notox (1996d)

Adsorption/Desorption
Remarks Not attempted. The notified chemical is likely to display moderate to high adsorption to soil, sediment or sludge due to its partition coefficient range and low water solubility.

Dissociation Constant Not determined.

Remarks The notified chemical is expected to ionise below pH 5.

Particle Size Not determined

Remarks The notified chemical is a low melting point waxy solid.

Flash Point Not determined.

Remarks Not determined for a solid.

Flammability Limits Not flammable.

METHOD EC Directive 92/69/EEC A.10 Flammability (Solids).
Remarks The notified chemical could not be ignited with a flame.
TEST FACILITY Notox (1996e).

Autoignition Temperature > 400°C

METHOD 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
TEST FACILITY Notox (2000d).

Explosive Properties Not expected to be explosive.

Remarks Not expected to be explosive based on structure.
TEST FACILITY Notox (2000e).

Oxidising Properties Not oxidising.

Remarks Not expected to be oxidising based on structure.
TEST FACILITY Notox (2000f).

Reactivity

Remarks Expected to be stable under normal conditions of use.

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	slightly irritating
Rabbit, eye irritation	severely irritating
Guinea pig, skin sensitisation – adjuvant test.	no evidence of sensitisation.
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 50 mg/kg/day
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosomal aberrations in human lymphocytes	genotoxic
Genotoxicity – in vivo mouse bone marrow micronucleus test	non genotoxic
In vitro dermal absorption – pig skin	4.9 – 6.9% absorption

7.1. Acute toxicity – oral

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 401 Acute Oral Toxicity – Limit Test.
EC Directive 92/69/EEC B.1 Acute Toxicity (Oral) – Limit Test.
Species/Strain Rat/Wistar.
Vehicle Propylene glycol.
Remarks - Method No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5/sex	2000	0

LD50 > 2000 mg/kg bw
Signs of Toxicity None.
Effects in Organs None.
Remarks - Results None.

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

TEST FACILITY Notox (1996f).

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 Propylene glycol.
Type of dressing Occlusive.
Remarks - Method Homogenised mixtures of the notified chemical and vehicle, prepared immediately prior to treatment, were applied at 40°C.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5/sex	2000	0

LD50 > 2000 mg/kg bw
Signs of Toxicity - Local All animals except one female exhibited focal erythema, scales, necrosis,

scabs.

Signs of Toxicity - Systemic	Chromodarcryorrhea. Lethargy was noted in one male and one female on day 1.
Effects in Organs	No abnormalities noted.
Remarks - Results	All animals appeared normal by day 13.

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

TEST FACILITY Notox (2000g).

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	The notified chemical formed a waxy mass on moistening with distilled water.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0.33	0.33	0.33	2	2 days	0
Oedema	0	0	0	1	1 day	0

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

Remarks - Results None.

CONCLUSION The notified chemical is slightly irritating to the skin.

TEST FACILITY Notox (1996g).

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	21 days.
Remarks - Method	The notified chemical was applied after breaking into small pieces; following instillation it formed a waxy mass.

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	3	3	2.7	3	14 days	0
Conjunctiva: chemosis	1.7	2.3	2.3	3	14 days	0

Conjunctiva: discharge						
Corneal opacity	1.7	1.3	1.3	2	21 days	1
Iridial inflammation	1	1	1	1	14 days	0

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

Remarks - Results: Reduced elasticity of the eyelid was observed at 72 hours and 7 days in 2 animals. The notified chemical is considered severely irritating because of corneal effects in one animal at the end of the observation period.

CONCLUSION: The notified chemical is severely irritating to the eye.

TEST FACILITY: Notox (1996h).

7.6. Skin sensitisation

TEST SUBSTANCE: Notified chemical.

METHOD: OECD TG 406 Skin Sensitisation – maximisation test
EC Directive 96/54/EC B.6 Skin Sensitisation – maximisation test.

Species/Strain: Guinea pig/ Himalayan strain.

PRELIMINARY STUDY: Maximum Non-irritating Concentration:
intradermal: 50%
topical: 5%

MAIN STUDY

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

INDUCTION PHASE: Induction Concentration:
intradermal: 50%
topical: 5%

Signs of Irritation: Necrosis and moderate erythema were observed for all treated and control animals after injection. Topical application resulted in mild erythema in 2 treated animals.

CHALLENGE PHASE

1st challenge: topical: 5%

Remarks - Method: The notified chemical was dissolved at 50% in propylene glycol. A 1:1 (w/w) mixture of Freund's Complete Adjuvant (FCA) and test substance divided in separate layers, therefore, the FCA and test substance were injected separately close together.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	5%	0	0
Control Group	5%	0	0

Remarks - Results: Necrosis at intradermal injection site was attributed to propylene glycol.

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

TEST FACILITY: Notox (1996i).

7.7. 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	Propylene glycol.
Remarks - Method	A number of minor protocol deviations were listed, but were not considered to affect the results of the study. Dosing formulations were freshly prepared and dosed at up to 40°C.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	5/sex	0	
II (low dose)	"	50	1 female
III (mid dose)	"	150	
IV (high dose)	"	1000	1 female

Mortality
Two animals died, one as a result of gavage dosing error, the other from the blood sampling procedure.

Clinical Observations
There was a decrease in food consumption in females at 150 and 1000 mg/kg/day corresponding to reduced body weight gain.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Neutrophil counts were increased and lymphocyte counts decreased among high dose males.

Effects in Organs
An irregular surface of the forestomach was observed in all males and 4 females of the high dose group.

Incidental findings among treated animals included a reduced size of the testes, thymus and epididymes, dark red (isolated) foci on the mesenteric and mandibular lymph nodes, lungs and thymus, an accented lobular pattern of the liver, sores and scab formation. These findings were considered typical for rats used in this type of study and were judged to be of no toxicological significance.

Reduced thymus weights among high dose males and increased adrenal:body weight ratios in mid and high dose females were considered to be non-specific responses to stress.

Remarks – Results
Only the effects on the forestomach were considered to be treatment related.

CONCLUSION
The No Observed Effect Level (NOEL) was established as 50 mg/kg bw/day in this study, based on reduced body weight gain and stomach irritation.

TEST FACILITY Notox (2001a).

7.8. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure.

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100.
Metabolic Activation System	Aroclor 1254 treated rat liver S9 fraction.
Concentration Range in Main Test	a) With metabolic activation: 100 - 5000 µg/plate. b) Without metabolic activation: 100 - 5000 µg/plate.
Vehicle	DMSO.
Remarks - Method	Two independent tests were performed in triplicate.

RESULTS

Remarks - Results	No increase in induced mutation frequency was observed in any strain at any dose. At the top dose precipitation was observed at the beginning but not at the end of the incubation period. No decrease in the background lawn was observed for any strain at any dose but a slight decrease in the number of revertants was observed for 333 and 1000 µg/plate and a moderate decrease at 3330 and 5000 µg/plate was an indication of toxicity. Positive and solvent controls were used and gave the expected results.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Notox (1996j).

7.9. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test. EC Directive 67/548EEC B.10: Mutagenicity: In vitro Mammalian Chromosome Aberration Test. USEPA Health Effects Test Guidelines OPPTS 870.5375 In vitro Mammalian Chromosome Aberration Test.
Cell Type/Cell Line	Human lymphocytes.
Metabolic Activation System	Aroclor 1254 treated rat liver S9 fraction.
Vehicle	DMSO.
Remarks - Method	In a first test the positive control cultures without S9 did not induce significant changes and in the presence of S9 a 50% reduction in mitotic index was not reached. Therefore only the results for the valid replicate experiment are listed below.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	333*, 380, 400, 420*, 470*, 530	3 hours	24 hours
Present			
Test 1	333*, 380*, 400*, 420, 470, 530	3 hours	24 hours

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity[a] in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	1000	≥ 333	560[b]	+

Present				
Test 1	1000	≥ 333	560[b]	+

[a] based on mitotic index; [b] preliminary test

Remarks - Results

Average percentages of cells with chromosomal aberrations (minus gaps) were:

	Control	*380*	*400*	*420*	*470*
-S9	1%			3.5%	4.5%
+S9	1%	15%	19%		

Statistically significant and dose related responses were seen following treatment with the notified chemical in the presence of metabolic activation. Positive control substances gave the expected responses.

CONCLUSION

The notified chemical was clastogenic to human lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY

Notox (2000h).

7.10. Genotoxicity – in vivo

TEST SUBSTANCE

Notified chemical.

METHOD

OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
EC Directive 2000/32/EC B.12 Mutagenicity - Micronucleus Test.
Japan Ministry of Health and Welfare Japan, MHW Ordinance No. 21
Japan Ministry of International Trade and Industry, JMITI Kikoyu No. 85
Health Effects Test Guidelines, OPPTS 870.5395, Mammalian Erythrocyte Micronucleus Test.

Species/Strain: Mouse/CD-1.
Route of Administration: Intraperitoneal.
Vehicle: Mazola corn oil (dried).
Remarks - Method: Doses were based on a preliminary toxicity test.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	5 males		24, 48
II (low dose)	”	31.3	24
III (mid dose)	“	65	24
IV (high dose)	“	125	24, 48
V (positive control, CP)	“	65	24

CP=cyclophosphamide. M=mitomycin C.

RESULTS

Doses Producing Toxicity: Via the i.p. route: 200 mg/kg for males, 320 mg/kg for females.
Genotoxic Effects: None.
Remarks - Results: Residual chemical in the abdominal cavity was observed in some animals of the high dose group.

CONCLUSION

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

TEST FACILITY

Central Toxicology Laboratory (2001).

7.11. Dermal Absorption

TEST SUBSTANCE	Dioic acid
METHOD	OECD Draft Guideline 428 (2000) for Dermal Delivery and Percutaneous Absorption: In vitro Method.
Remarks - Method	Dermatomed pig skin, 0.4 mm thick was used to determine the penetration of 4 oil and water emulsions. A mixture of ^{3}H-labelled and unlabelled dioic acid was applied and the amount of radiolabel in the receptor fluid was measured at times up to 24 hour post-administration.
RESULTS	Transfer of label across the skin was 4.9 – 6.9% of the applied dose.
Remarks - Results	There was little difference between formulations and there was no indication the barrier function of the skin was compromised.
CONCLUSION	Dermal absorption of less than 10% of the applied dose of notified chemical is predicted from the experimental results.
TEST FACILITY	Central Toxicology Laboratory (2002)

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE: Notified chemical.

METHOD: OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test (Modified Sturm Test)

Inoculum	Fresh activated sludge from municipal sewage treatment plant
Exposure Period	28 days
Auxiliary Solvent	None.
Analytical Monitoring	Titration remaining Ba(OH) with 0.05M HCl.
Remarks - Method	Test concentration 12 mg total carbon/L Reference Substance – sodium acetate Treatments: – test substance and inoculum (duplicates) – inoculum control (duplicates) – positive control (reference substance and inoculum) (single test) – toxicity control (test substance, reference substance and inoculum) (single test) Titrations were done every 2 or 3 days for first 10 days then every 5 days. Theoretical CO_2 production could not be determined. Therefore total carbon was determined for a sample of the pure test substance. The pH was measured before the test started and on day 28.

RESULTS

Test substance		*Positive control*		*Toxicity control*	
Day	*% degradation*	*Day*	*% degradation*	*Day*	*% degradation*
2	1.5, 5.8 av. = 3.7	2	17.1	2	4.5
5	36.7, 30.7 av. = 33.7	5	55.4	5	16.9
9	44.3, 42.7 av. = 43.5	9	75.9	9	30.4
14	55.0, 52.1 av. = 53.6	14	81.5	14	32.8
23	72.9, 69.6 av. = 71.3	23	95.5	23	41.7
29	76.3, 71.3 av. = 73.8	29	96.7	29	42.4

Remarks - Results: On day 14, the reference substance had degraded by 81.5% and on day 28/29 it reached 96.7% degradation, thus satisfying the 60% degradation by day 14 criterion.

The toxicity control reached 32.8% degradation on day 14, thus indicating that test material was not inhibitory to the sewage sludge organisms.

The temperature range during the study was 20.5 to 22°C, while the pH ranged from 7.6 to 8.0.

CONCLUSION: While the degradation of the notified chemical exceeded 60%, the 10 day window (60% degradation within 10 days of reaching 10%) was not achieved. Therefore the notified chemical is not readily biodegradable.

TEST FACILITY: Notox (1996k).

8.1.2. Bioaccumulation

Remarks	The bioaccumulation of the notified chemical was not studied. Due to its molecular size it has the potential to bioaccumulate, however, it is unlikely to do so due to its likely inherent biodegradability.

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 203 Fish, Acute Toxicity Test - static EC Directive 92/69/EEC C.1 Acute Toxicity for Fish – static.
Species	Carp (*Cyprinus carpio*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	None
Remarks – Method	Limit test. The medium was mixed with test substance to a loading of 100 g/L. The solution was stirred for 4 days and then observed to be glassy with lumps of test material. A proportion of the solution was filtered through a paper filter, with the filtrate being a homogeneous glassy solution. A 16 -hour daily photoperiod was maintained throughout. Dissolved oxygen, pH and temperature were measured daily. At the start of the study the pH was 8.0.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*3.5 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control (0 mg/L)	-	7	0	0	0	0	0
100 mg/L filtered	-	7	0	0	0	0	0
100 mg/L unfiltered	-	7	0	0	0	0	0

LC50	> 100 mg/L (nominal) at 96 hours.
NOEC (or LOEC)	≥ 100 mg/L (nominal) at 96 hours.
Remarks – Results	Before commencing the study the test media/solution was aerated until saturation was reached then aeration ceased. However, aeration was commenced half way through the study and continued until the end due to a drop in dissolved oxygen concentration to 6.3 mg/L. Dissolved oxygen concentration ranged from 5.2 to 9.1 mg/L during the study. Temperature ranged from 20.6 to 21.8°C and pH ranged from 7.2 to 8.0. In the unfiltered sample, undissolved test substance was observed as deposits and a layer on the surface of the solution. No mortality was observed in the control or in either test vessel.
CONCLUSION	Under the test conditions, the notified chemical is not toxic to carp up to the level of its water solubility.
TEST FACILITY	Notox (2001b).

8.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE

Notified chemical.

METHOD

ISO International Standard 6341: Water quality – Determination of the inhibition of the mobility of *Daphnia magna* Straus- Acute toxicity test third ed 1996-4-1 - Static.
OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - Static.
EC 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: None.
Remarks - Method: Test material (100.9 mg) was added to 1000 mL of ISO-medium and the solution was stirred for 72 hours. The resultant solution was glassy and turbid containing small lumps of the test substance. The solution was filtered through a paper filter with the resultant filtrate being slightly less turbid. The test concentrations were prepared by diluting the filtrate to 2.2 to 100% nominal concentration. All concentrations were done in duplicate with 10 Daphnia per test vessel.

There was no feeding or aeration during the study and a 16-hour photoperiod was maintained. Dissolved oxygen and pH were measured at the start and end of the study.

Reference test conducted with potassium dichromate.

RESULTS

Concentration of test material mg/L		*Number of D. magna*	*Number Immobilised*			
Nominal	*Actual*		*24 h*		*48 h*	
(% of filtrate prepared at 100 mg/L)			*A*	*B*	*A*	*B*
Control	-	10 + 10 = 20	0	0	0	0
2.2	-	20	0	0	0	0
4.5	-	20	0	0	0	0
10	-	20	0	0	0	0
22	--	20	0	0	0	0
45	-	20	0	0	0	0
100	-	20	3	2	5	4

LC50: ≥ 100 mg/L (filtered) nominal at 48 hours
NOEC (or LOEC): 45% of filtrate prepared at 100 mg/L (nominal).
Remarks - Results: In the control the pH began at 7.9 and ended 8.1 and the dissolved oxygen concentration was 8.0 and 8.2 mg/L. In the test solutions the starting pH ranged from 7.9 to 6.6 and the dissolved oxygen concentration ranged from 8.0 to 5.4, while at the end of the study the pH range was 8.1 to 7.7 and the dissolved oxygen concentration ranged from 8.7 to 7.5. The low pHs and dissolved oxygen concentrations occurred at the higher concentrations.

The results given by the reference substance, potassium dichromate, were within the expected range of results, giving a 48 h EC_{50} of 0.57 mg/L, thus indicating that the validity of the study conditions.

CONCLUSION

Under the study conditions the notified chemical appears to show some toxicity to Daphnia below the level of its water solubility (< 0.7 mg/L). Since the 100 mg/L test filtrate was slightly turbid the observed results may be due to physical distress.

TEST FACILITY Notox (2001c).

8.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical.

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

Species *Selenastrum capricornutum*
Exposure Period 72 hours
Concentration Range
Nominal A range of dilutions containing 2.2 to 100% of filtered 100 mg/L (nominal) preparation.
Actual Not determined.
Auxiliary Solvent None.
Water Hardness 24 mg $CaCO_3$/L.
Analytical Monitoring Varian Cary 50 single beam spectrophotometer with immersion probe at 720 nm.
Remarks - Method The medium was mixed with test substance to a loading of 100 g/L. The solution was stirred for 4 days and then observed to be glassy with lumps of test material. A proportion of the solution was filtered through a paper filter, with the filtrate being a homogeneous glassy solution. The test concentrations were prepared by diluting the filtrate to 2.2 to 100% nominal concentration.
Treatments:
- 3 replicate of each test concentration
- 6 replicates of the blank control
- 1 replicate of each test concentration without algae.

Initial cell density 10^4 cell/mL.
Continuous illumination – 70 to 94 μE/m^2/s.
pH was measured at the start and end of the study.
Reference test was conducted with potassium dichromate.

RESULTS

Concentration of test material (% of filtrate prepared at 100 mg/L) Nominal mg/L	*Biomass Percentage reduction 0-72 h*	*Growth Percentage reduction*
Control	-	-
2.2	5.4	1.3
4.5	-2.3	–0.2
10	-10.5	–2.2
22	-23.0	–4.9
45	-4.4	–1.1
100	81.9	44.8

Biomass E_bC_{50} mg/L at 0-72 h	*Growth E_rC_{50} mg/L at 0-72 h*	*Growth NOEC mg/L at 72 h*
74% (95% C.I: 71-78%) of filtered solution prepared at 100 mg/L	> 100% of filtered solution prepared at 100 mg/L	45% of filtered solution prepared at 100 mg/L

Remarks - Results The temperature at the start of the study was 22.5ºC, which increased to 23.0ºC at the end of the study. At the beginning of the study the pH ranged from 8.1 to 6.7 and at the end it was 9.1 to 8.4. At both times the pH decreased with increasing test concentrations. These variations are within acceptable limits.

	The cell density increased in the control by a factor of greater than 16 within 3 days, thus validating the test conditions. The reference test with potassium dichromate validated the sensitivity of the algal species and test conditions. The E_bC_{50} at 0 – 72 h was 0.64 mg/: and the E_rC_{50} at 0 – 72 hours was 0.96 mg/L.
CONCLUSION	Under the test conditions the notified chemical was slightly toxic to the growth of the algae.
TEST FACILITY	Notox (2001d).

8.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Micro organisms in activated sludge
Exposure Period	30 mins
Concentration Range Nominal	46, 100, 220, 600 and 1000 mg/L
Remarks – Method	Reference substance – 3,5-dichlorophenol
RESULTS	
30 min IC50	>1000 mg/L
NOEC	220 mg/L
Remarks – Results	At test concentrations 46 to 600 there was no significant inhibition of respiration, while at 1000 mg/L there was an 18% inhibition of respiration. With the difference in the respiration rates in the two controls being 12%, and the EC_{50} of the reference substance being 8 mg/L (95% C.I: 0 to 168 mg/L), the conditions of the test were validated.
CONCLUSION	Under the conditions of the test some toxicity to micro-organisms was shown, however with an EC_{50} greater than 1000 mg/L the notified chemical is not toxic to micro-organisms (Mensink, 1995). Note that this figure may have been lower if the usual 3 hour test time was used.
TEST FACILITY	Notox (2001e)

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The majority of the notified chemical (up to 9700 kg annually) will eventually be released into the environment via discharge into sewerage systems mainly during personal washing. It is expected that up to 100 kg per annum will remain in the consumer product containers and will be disposed of to landfill, along with 200 kg from end-user product formulation.

The notified chemical has limited water solubility and has a high log P_{ow}, therefore it is likely to become associated with sediment and sludge and be immobile in soil and sediment. It will not readily hydrolyse in natural waters at environmental pH values and is not readily biodegradable. However, the notified chemical will be degraded through biological and abiotic processes to water and oxides of carbon.

As the majority of the notified chemical in the skin care products will eventually be released into the aquatic environment via the sewerage systems the predicted environmental concentration (PEC) in the aquatic environment is estimated using a worst-case scenario assuming all the notified chemical is released to sewer, where there is no removal and it is used across Australia:

Amount released to sewer	10000 kg
Population	20 million
Water use per person	200 L
Number of days used	365
PEC_{sewer}	10 000 000 000 365 x 200 x 20 000 000 = 0.0068 mg/L = 6.8 µg/L
PEC_{inland} (dilution factor 1)	6.8 µg/L
PEC_{ocean} (dilution factor 10)	0.68 µg/L

The ready biodegradability test results showed that the notified chemical was biodegradable but not readily biodegradable since it did not satisfy the 10-day window. The SIMPLETREAT model (European Commission, 2003) for modelling partitioning and losses in sewage treatment plants (STP) was used to estimate the proportions of the chemical partition into the different environmental compartments under the provisions that it passed the 28 day biodegradation but not the 10 day criteria. The estimated log Henry's constant is 2.2 and the partition coefficient was a range (log P_{ow} 2.4 to 5)

log P_{ow} = 2.4	log P_{ow} = 5.0
36% to air	17% to air
19% to water	12% to water
1% to sludge	49% to sludge
45% degraded	22% degraded
81% removed from aqueous phase	88% removed from aqueous phase

The results indicate that when the chemical is released into the aqueous phase of a STP it is likely that some components will partition into the water compartment and others will partition to the sludge and that there will be significant removal (partly due to degradation). Thus, if there is 81% removal the above estimated PECs become 1.3 µg/L and 0.13 µg/L.

STP effluent re-use for agricultural irrigation occurs throughout Australia The following calculation is undertaken assuming an application rate of 1000 L/m^2/year (10 ML/ha/year) and that any notified chemical in the water is assumed to infiltrate and accumulate in the top 0.1 m of soil (density 1000 kg/m^3).

Concentration in effluent	1.3 µg/L
Soil concentration, PECsoil (mg/kg) (assumes no degradation)	
1 year	0.013
5 years	0.065
10 years	0.13

There is a potential for the notified chemical to bioaccumulate but this is not likely due to its biodegradability.

9.1.2. Environment – effects assessment

The results of the aquatic toxicity tests are listed below.

Organism	*Duration*	*End Point*	*mg/L (nominal concentration)*
Fish	96 h	LC_{50}	> 100
Daphnia	48 h	EC_{50}	> 100
Algae	96 h	EC_{50}	74% of 100 mg/L preparation = 74
Microbial activity	6 h	EC_{50}	> 1000

Using the lowest EC_{50} of 74 mg/L for algae and a safety factor of 1000 (OECD), since in the

ecotoxicity studies the actual concentrations were not determined and therefore the results may underestimate the toxicity, a predicted no effect concentration (PNEC for aquatic ecosystems) of 0.074 mg/L has been estimated (EC_{50}/1000).

9.1.3. Environment – risk characterisation

The risk of the release of all the imported notified chemical can be estimated by determining the aquatic risk quotient (RQ = PEC/PNEC).

Location	PEC	PNEC	Risk Quotient (RQ)
Australia-wide STPs			
Aquatic			
Ocean outfall	0.13 µg/L	0.074 mg/L = 74 µg/L	0.002
Inland River	1.3 µg/L	0.074 mg/L = 74 µg/L	0.02

Since the RQ values are less than 1, the proposed use of the notified chemical is unlikely to pose an unacceptable risk to the aquatic life.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

The highest level of exposure for workers will be when weighing out and transferring the notified chemical to the mixing vessel. Inhalation exposure is unlikely as the notified chemical is in a non dusting form. Typically, in factories involved in manufacturing personal care products on a large scale, local exhaust ventilation is employed and workers are provided with personal protective equipment such as gloves, goggles and protective clothing. Some limited exposure may be possible from quality control sampling, cleaning of equipment or machine maintenance. Filling of consumer type containers will normally be automatic and exposure will be limited.

Exposure of transport and storage workers may occur in the event of an accident involving breach of containers.

9.2.2. Public health – exposure assessment

The maximum concentration of the notified chemical in personal care products is 1% with a worst case 5%. If it is assumed that each application is a maximum of 8 g, is applied once a day, is not washed off and dermal absorption of the notified chemical is 10%, systemic exposure can be calculated as:

0.005 x 8 x 1000 (mg/g)/ 60 kg = 0.67 mg/kg/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 case). It was a slight skin irritant and a severe eye irritant in rabbits and was not a skin sensitiser in guinea pigs. The NOEL in a 28-day repeat dose oral toxicity study in rats was 50 mg/kg/day but the effects were mainly stomach irritation with no other organ toxicity identified at the top dose of 1000 mg/kg/day. The notified chemical was neither mutagenic in bacteria nor genotoxic in a mouse bone marrow micronucleus test in vivo but was clastogenic as judged by induction of chromosomal aberrations in human lymphocytes in vitro with the main effect in the presence of added microsomal enzyme fraction.

In common with other members of this class of chemicals, the notified chemical is predicted to be readily absorbed and metabolised. However, this prediction is found to be false for the notified chemical, at least regarding dermal absorption, as an in vitro study revealed there was less than 10% absorption through pig skin.

For the induction of chromosomal aberrations in human lymphocytes an expert opinion was provided which noted the lack of pH or osmolality data. Given the negative micronucleus test the risk of mutagenic effects at the concentration of notified chemical present in typical personal care products is low.

Based on the available data, the notified chemical is classified as a hazardous substance in

accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2002) with respect to eye irritant effects but would not be classified as a hazardous substance in terms of mutagenic effects.

9.2.4. Occupational health and safety – risk characterisation

The main areas of concern for the notified chemical based on the submitted toxicological data are eye irritation and genotoxicity. Severe eye irritation is possible when the imported solid flakes are weighed out and transferred to the mixing vessel in which personal care products are made. Particles may enter the eye either directly or through transfer from hands or gloves.

Although the clastogenic effects of the notified chemical are not well proven, and may be mitigated by metabolism should flakes be accidentally ingested or in the event of transfer across the skin, there may be a low risk of genotoxic effects.

Considering the other endpoints, there is unlikely to be a risk of skin irritation or sensitisation or either acute or chronic toxic effects.

9.2.5. Public health – risk characterisation

Although the NOEL is 50 mg/kg/day, this is based on stomach irritation that may have led to reduced bodyweight gain. Therefore, for effects relevant to skin absorption, the no effect level can be considered to be > 1000 mg/kg/day. The margin of safety, therefore, is > 1000/0.67 or > 1500. Adding a safety factor of 100 reduces this to 15. Therefore, the risk of systemic effects from the notified chemical following prolonged use of personal care products containing the notified chemical is low.

The induction of chromosomal aberrations in vitro in human lymphocytes in the presence of metabolic activation was considered equivocal in the risk assessment accompanying the notification dossier submitted to the Dutch competent authority and was questioned in an expert opinion on the basis that pH measurements were not conducted on the culture medium and the possibility exists that the chromosomal aberrations were induced by low pH. The fact that the notified chemical was not mutagenic in bacteria and was negative in a mouse bone marrow micronucleus test (administered by intraperitoneal route) reduces the likelihood that it would be a clastogen in vivo and that the test itself was valid. It is stated in the submission that the likely maximum concentration of the notified chemical in typical personal care products is 1% with a worst case of 5%. Given the likely dermal absorption of 10% (maximum) genotoxic effects are unlikely.

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

10.1. Hazard classification

Based on the available data the notified chemical is classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances*. The classification and labelling details are:

R41: Risk of serious eye damage; and

As a comparison only, the classification of notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations, 2003) is presented below. This system is not mandated in Australia and carries no legal status but is presented for information purposes.

GHS classification: Eye irritant Category 1 (irreversible effects on the eye).
Environment: Chronic category 3

10.2. Environmental risk assessment

On the basis of the PEC/PNEC ratio, the chemical is not considered to pose a risk to the environment based on its reported use pattern.

10.3. Human health risk assessment

10.3.1. Occupational health and safety

There is Moderate Concern to occupational health and safety under the conditions of the occupational settings described based on the risk of eye damage during transfer of the notified chemical to mixing vessels.

10.3.2. Public health

There is No Significant 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 provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 2003). It is 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 provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994). The accuracy of the information on the label remains the responsibility of the applicant.

12. RECOMMENDATIONS

REGULATORY CONTROLS

Hazard Classification and Labelling

- The NOHSC Chemicals Standards Sub-committee should consider the following health hazard classification for the notified chemical:
  - R41: Risk of serious eye damage.

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - Concentration ≥ 10%, R41 Risk of serious eye damage;
  - 5% ≤ Concentration ≤ 10%, R36 Irritating to eyes.

CONTROL MEASURES

Occupational Health and Safety

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:
  - Chemical safety googles.

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

- 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

- The following control measures should be implemented by reformulator to minimise environmental exposure during reformulation of the notified chemical:

- Process areas should be bunded with all drains leading a treatment plant or collection point

Disposal

- The notified chemical should be disposed of to landfill.

Emergency procedures

- Spills/release of the notified chemical should be handled by containment, collection (manually) and then place in sealable labelled container. The material should be reused if not contaminated. If contaminated then it should be disposed of to 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(1) of the Act; if

- the concentration of notified chemical in imported products is likely to be greater than 10%;

or

(2) 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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