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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Cassiffix

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Director
NICNAS

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
International Flavour and Fragrances (Australia) Pty Ltd (ABN: 77 004 269 658)
301 Frankston-Dandenong Rd
Dandenong South Victoria 3175

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer, (1 tonne or less 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)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
LVC/392

NOTIFICATION IN OTHER COUNTRIES
US EPA: PMN (1995)
EC-Spain VIIA 1995-1996

2. IDENTITY OF CHEMICAL

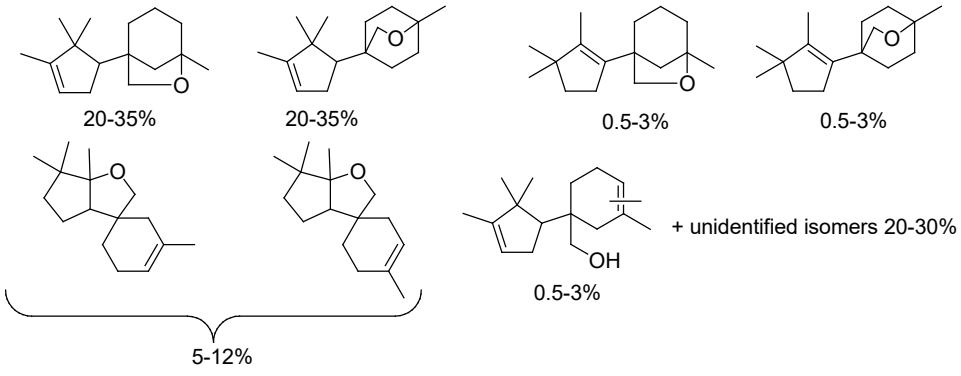
CHEMICAL NAME
3-Cyclohexene-1-methanol, 3(or 4)-methyl-1-(2,2,3-trimethyl-3-cyclopenten-1-yl)-, acid-isomerised

MARKETING NAME(S)
Cassiffix

CAS NUMBER
426218-78-2

MOLECULAR FORMULA
$C_{16}H_{26}O$

STRUCTURAL FORMULA



MOLECULAR WEIGHT

234 g

SPECTRAL DATA

METHOD	UV Visible, IR spectroscopy, NMR spectrometry
Remarks	Reference spectra were provided.
TEST FACILITY	In-house.

METHODS OF DETECTION AND DETERMINATION

METHOD	Gas Chromatography
Remarks	Reference spectra were provided.
TEST FACILITY	In-house.

3. COMPOSITION

DEGREE OF PURITY
98%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

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

ADDITIVES/ADJUVANTS

Chemical Name	p-cresol, 2,6-di-t-butyl		
CAS No.	128-37-0	*Weight %*	0.1%

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. It will be introduced as a liquid in 205 L drums at a concentration of up to 10% for reformulation into a variety of consumer products or as a component of finished consumer products..

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	0.001	1	1	1	1

USE
The notified chemical will be used as a fragrance in a variety of consumer products at 0.01-0.1% such as alcoholic perfumery, cosmetics, toiletries, household products, soaps and detergents.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, transport and storage

PORT OF ENTRY
Melbourne

IDENTITY OF MANUFACTURER/RECIPIENTS
International Flavours and Fragrances (Australia), Pty Ltd (IFF)

TRANSPORTATION AND PACKAGING

The notified chemical Cassiffix will be imported in 205 L polypropylene lined steel drums. The notified chemical will also be imported in a variety of end-use consumer products. The products containing the notified chemical will be transported by road to the warehouse for storage until required.

5.2. Operation description

The notified chemical is not manufactured in Australia. Blending or packaging of the product containing the notified chemical occurs in Australia.

Blending and packing

The 205 L drums of liquid product containing the notified chemical (up to 10%) will be transported by forklift or manually as required from the warehouse to the production area. At the blending plant the imported liquid product containing the notified chemical is transferred from the drum to the blending tank. This is typically achieved by manually opening the drum and measuring out the product containing the notified chemical. In some operations this may occur by largely automated means whereby by the drum is lanced and the contents automatically transferred by transfer lines to the blending tank. During the blending process, the product containing the notified chemical is pumped automatically through to the blending tank (closed system) to formulate a variety of consumer products that contains the notified chemical (<1%). The end-use products containing the notified chemical are characteristically packed by means of automated and enclosed filling systems into 1–2 L plastic containers.

End use

There is potential for formulated consumer products (containing 0.1%) to be used occupationally, for example by professional cleaners using cleaning products or beauticians using cosmetic products.

Cleaning products are generally applied with a cloth or sponge, by mop or brush or by spray followed by wiping. In some cases, the cleaning product will be diluted with water prior to application. The dilution factor, which is often on the label, depends on the type of surface to be cleaned, the soil loading, and the type and method of application.

5.3. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Transport and Warehouse workers	5	None	Incidental Exposure only
Reformulation			
Mixing workers	5	4 hr/day	2 days/year
Drum handling workers	5	4 hr/day	2 days/year
Drum cleaning/washing workers	10	4 hr/day	2 days/year
Maintenance workers	5	4 hr/day	2 days/year
Quality control worker	2	0.5 hr/day	2 days/year
Packager	10	4 hr/day	2 days/year

Exposure Details

Transport and warehousing

Transport, warehouse and stores personnel will wear protective equipment (overalls/ industrial clothing and gloves as appropriate) when receiving and handling consignments of the imported product containing the notified chemical (up to 10% notified chemical). The product will be handled in the warehouse by forklift handling of drums. During transport and warehousing, workers are unlikely to be exposed to the notified chemical except when packaging is accidentally breached.

Blending and packing

The main routes of exposure to the notified chemical (up to 10% notified chemical) are dermal and accidental ocular exposure during manual measuring and transferring of the imported product to the blending tank.

It is possible that dermal and accidental ocular exposure may also occur if manual intervention is

required during the automated blending and packaging operations and if the packaging is accidentally breached. Maintenance workers will have intermittent dermal and the potential for accidental ocular exposure to the notified chemical when performing maintenance/cleaning of the equipment in general.

All workers involved in handling the imported product and blended product are expected to wear personal protective equipment (PPE) such as safety glasses, safety boots, gloves, protective clothing, if necessary. The blending operations are likely to occur in a closed system under local exhaust ventilation (LEV). All production operators are expected to be trained in the appropriate operational procedures and precautions.

Once the formulated cleaning products are packaged for distribution, no further worker exposure is expected except when packaging is accidentally breached.

End-use
While the notifier gives no details, it is estimated that a large number of retail workers may potentially be exposed to the notified chemical (<1%) by means of end-use products. Retail workers would only be exposed to the notified chemical (<1%) in the case of inadvertent breach of the packaging or when demonstrating consumer products. Dermal exposure is expected to be the main route of exposure but inhalation exposure to aerosols could occur if products include perfumes and/or spray cleaning products. Dermal or inhalations exposure is expected to be greatest when used occupationally, for example by professional cleaners using cleaning products or beauticians using cosmetic products. In the event of an accident, spills will be removed in accordance with the manufacturers instructions

5.4. Release

RELEASE OF CHEMICAL AT SITE
The notified chemical will be manufactured overseas and will be imported in 205 L steel drums at <10% concentration. On arrival in Australia, the notified chemical will be transported to the notifier's storage facility. With the exception of accidental spills during transport and storage, release at this point is not expected. Spills are expected to be physically contained, collected and subsequently disposed of to landfill.

At the formulation facilities, the batch process will be used. Following each batch, cleaning of blending equipment may result in the generation of wastewaters containing the notified chemical. The quantity of notified chemical remaining in the wash water may approximate up to 1% of the import volume. The disposal route for these wastewaters may include disposal to on-site wastewater treatment plants and/or sewer.

Residual notified chemical remaining within import containers may approximate up to 1% of the import volume. The disposal route for container rinsate may include disposal to on-site wastewater treatment plants and/or sewer.

RELEASE OF CHEMICAL FROM USE
Since the notified chemical will be used in household, laundry and personal cleaning products, almost all (~97%) will be released to sewer after use. Approximately 1% of the imported quantity of notified chemical is expected to remain as residual within consumer containers and it is expected that this will be disposed of to domestic landfill.

5.5. Disposal

Emptied imported drums containing residual quantities of the notified chemical may be rinsed and re-used, sent to a metal recycler, or sent to a landfill for disposal. Drum rinsate will be discharged to on-site wastewater treatment plants and/or sewer. Following use, emptied product containers are expected to be disposed of through domestic garbage disposal and then to landfill or a recycling program.

5.6. Public exposure

The notified chemical will be used in the formulation of numerous consumer products, which will be available to the general public. Public exposure will be widespread and will result through the use of consumer products containing up to 0.1% notified chemical. Members of the public will make dermal contact and possibly accidental ocular and/or inhalation exposure with products containing the notified chemical.

Since the consumer products will be stored and used in a domestic environment, there is the possibility of accidental ingestion by a child.

Public exposure during transport, storage and retail distribution is unlikely unless the packaging is breached.

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa Clear colourless liquid.

Freezing Point <–25ºC

METHOD EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks Statement of GLP.
TEST FACILITY Huntingdon (1994a)

Boiling Point 301.5–309.5ºC at 101.3 kPa

METHOD EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks Statement of GLP.
Determined using a reduced scale distillation method.
TEST FACILITY Huntingdon (1994a)

Density 9859 kg/m^3 at 20ºC

METHOD EC Directive 92/69/EEC A.3 Relative Density.
Remarks Statement of GLP.
Density was determined using a pycnometer.
TEST FACILITY Huntingdon (1994a)

Vapour Pressure 0.015 kPa at 25ºC

METHOD EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks Statement of GLP.
Determined using the isoteniscope method. Two runs were performed and the was value taken from the more degassed run.
TEST FACILITY University of Leeds (1994)

Surface Tension 54.7 mN/m at 19.5ºC

METHOD EC Directive 92/69/EEC A.5 Surface Tension.
Remarks This determination was carried out using a torsion/tension balance and a procedure based on the OECD harmonised ring method. The surface tension of the sample solution was measured at intervals until a constant reading was obtained three times in succession.
TEST FACILITY Huntingdon (1994a)

Water Solubility 11 mg/L at 20ºC

METHOD EC Directive 92/69/EEC A.6 Water Solubility.
Remarks Statement of GLP.
The determination was carried out using the Flask method. Based on the preliminary test, 20-30 mg of the test material was combined with 100 mL distilled water. After stirring continuously at 30 degrees C (pre-equilibration) and for 5 days (equilibration) at 20 degrees C the flask was allowed to stand for 1 hour, before the solution was centrifuged and analysed. The concentration of the test material in the sample was determined by GC.

TEST FACILITY Huntingdon (1994a)

Hydrolysis as a Function of pH Half-life: 710 h at pH 4, 520 h at pH 7, and 830 h at pH 9

METHOD EC Directive 92/69/EEC C. Method C7, Abiotic degradation: hydrolysis as a function of pH.

Remarks Under preliminary test conditions, the notified chemical was found to undergo greater than 10% hydrolysis after a 5-day period at pH 4, 7 and 9, which indicated that Test 1 (ambient temperature) and either Test 2 or Test 3 (elevated temperatures) would be required at each pH value.

It could not be concluded with certainty from Test 1 results, performed at 50°C in aqueous solution at pH 4,7 and 9 whether Test 2 or Test 3 would be required. Therefore, Test 2 was performed in aqueous solution at pH 4, 7 and 9 at 25°C.

Q TEST FACILITY Huntingdon (1995a)

Partition Coefficient (n-octanol/water) log Kow > 3.66

METHOD OECD TG 117 Partition Coefficient (n-octanol/water).
EC Directive 92/69/EEC A.8 Partition Coefficient.

Remarks Statement of GLP.
The shake-flask method was used in the test. 0.22444 g of test material was added to 200 mL of water saturated octanol to make the stock solution. The solvent was prepared by mixing equal volumes of octanol and water for 24 hours, after which, the phases were transferred to separating funnels and left to stand for 4 hours. Three tests and 1 blank were used. 1) 10 mL of the stock solution and 50 mL of the water saturated with octanol were combined and shaken for 15 minutes. 2) 10 mL of the stock solution and 20 mL of the octanol test solution were combined and shaken for 15 minutes. 3) 10 mL of the stock solution and 40 mL of the octanol test solution were combined and shaken mechanically for 15 minutes. After separation, aliquots of both phases were centrifuged at 300 rpm for 15 minutes then taken for analysis. The concentration of the test material in the sample solution was determined by GC.

TEST FACILITY Huntingdon (1994a)

Adsorption/Desorption log K_{oc} = 3.55

METHOD Estimated using EPIWIN, using the following SMILES string:
CC1(C)C(C)=CCC1C2(C3)CCCC3(C)OC2

TEST FACILITY EPI Suite v3.12

Dissociation Constant Not applicable

Remarks The notified chemical does not contain any functional groups expected to dissociate in water

Particle Size Not applicable

Flash Point 144.5ºC at 101.3 kPa

METHOD EC Directive 92/69/EEC A.9 Flash Point.

Remarks Statement of GLP.
Determined using the Pensky-Martens closed cup method. The notified chemical is classified as a C1 combustible liquid according to NOHSC *National Code of Practice for the Storage and Handling of Workplace Dangerous Goods* (NOHSC 2001).

TEST FACILITY Huntingdon (1994a)

Flammability Not flammable

METHOD EC Directive 92/69/EEC A.12 Flammability (Contact with Water).
Remarks Statement of GLP. No gas evolved during the test.
TEST FACILITY Huntingdon (1994a)

Autoignition Temperature 240°C

METHOD 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks Statement of GLP.
TEST FACILITY Huntingdon (1994a)

Explosive Properties Not Explosive

METHOD EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks There was no reaction of any kind with the shock test. The test substance ignited on the heat test, but no explosions or deformations to any of the tubes were recorded. A test of mechanical sensitivity with respect to friction is not required for liquids. From examination of the structure, there are no chemical groups that would infer explosive properties.
TEST FACILITY Huntingdon (1994a)

Reactivity

Remarks Stable under normal conditions of use.

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint	*Result and 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	moderately irritating
Rabbit, eye irritation	irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Skin sensitisation human volunteers	no evidence of sensitisation
Skin sensitisation human volunteers	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL 150 mg/kg bw/day
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosome aberration	non genotoxic

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/Sprague-Dawley
Vehicle	Test substance administered as supplied.
Remarks - Method	There were no significant protocol deviations, however details of specific clinical observations made were not reported. Statement of GLP included. A preliminary study indicated the LD50 > 800 mg/kg bw

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	2/sex	800	0/4
II	5/sex	2000	0/10

LD50	> 2000 mg/kg bw
Signs of Toxicity	Pilo-erection was observed in all rats within three minutes of dosing and throughout the remindar of Day 1, recovery was complete by Day 2. There were no other clinical signs.
Effects in Organs	No adverse macroscopic observations at necropsy.
Remarks - Results	There were no remarkable body weight changes during the study period.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Huntingdon (1994b)

7.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test. EC Directive 84/449/EEC B.3 Acute Toxicity (Dermal) – Limit Test.
Species/Strain	Rat/Sprague-Dawley
Vehicle	Test substance administered as supplied.
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations. Statement of GLP included.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	5/sex	2000	0/10

LD50	>2000 mg/kg bw
Signs of Toxicity - Local	Slight erythema was observed in all test animals on Day 2 only. Residual brown staining from the test substance was noted on all animals from Days 2 to 6. There were no other dermal changes.
Signs of Toxicity - Systemic	There were no notified chemical-related systemic reactions.
Effects in Organs	No adverse macroscopic observations at necropsy.
Remarks - Results	Slightly low bodyweight gains were recorded for all five males and one female on Day 8 and in four males and one female on Day 15. There were no deaths or notified chemical related clinical signs or during the study period.

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

TEST FACILITY Huntingdon (1994c)

7.3. Acute toxicity – inhalation

Not Determined

7.4.1 Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Directive 84/449/EEC B.4 Acute Toxicity (Skin Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 females
Vehicle	Test substance administered as supplied.
Observation Period	13 days.
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations. Statement of GLP included.

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	2	-	1.67	4	< 13 days	0
Oedema	2	3	0.67	3	< 12days	0

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

Remarks - Results	Exposure to the notified chemical resulted in very slight to well defined erythema with desquamation, blanching and/or necrosis in the treated skin areas of the rabbits, which had resolved within 9, 13 or 6 days. Exposure to the notified chemical resulted very slight to moderate oedema in the treated skin areas of the rabbits, which had resolved within 8, 12 days or 48 hours. Small scabs were observed in one animal up to day 13.

CONCLUSION The notified chemical is moderately irritating to the skin.

TEST FACILITY Huntingdon (1994d)

7.5. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
EC Directive 84/449/EEC B.5 Acute Toxicity (Eye Irritation).

Species/Strain Rabbit/New Zealand White
Number of Animals 3 females
Observation Period 7-14 days
Remarks - Method No significant protocol deviations.
Statement of GLP included.

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	2	1.3	2.7	3	< 14 days	0
Conjunctiva: chemosis	2.3	1	3	3	< 14 days	0
Conjunctiva: discharge	-	-	-	-	-	-
Corneal opacity	0	0	0	0	0	0
Iridial inflammation	0	0	0	0	0	0

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

Remarks - Results Instillation of the notified chemical resulted in effects on the conjunctivae. Redness of the conjunctivae was observed among all animals within 1 hour and had resolved within 72 hours, 7 days or 14 days. Chemosis of the conjunctivae was observed among all animals within 1 hour and had completely resolved within 72 hours, 7 days or 14 days. No corneal damage or iridal inflammation was observed.

CONCLUSION The notified chemical is irritating to the eye.

TEST FACILITY Huntingdon (1994e)

7.6.1 Skin sensitisation

TEST SUBSTANCE Notified chemical

METHOD OECD TG 406 Skin Sensitisation - < Magnusson and Kligman >.
EC Directive 84/449/EC B.6 Skin Sensitisation - < Magnusson and Kligman >.

Species/Strain Guinea pig/ Dunkin Hartley strain
PRELIMINARY STUDY Maximum Non-irritating Concentration:
intradermal: 7.5% v/v in Alembicol D (irritation observed at all doses tested)
topical: 100% (mild-moderate irritation observed up to 7.5%)
MAIN STUDY
Number of Animals Test Group: 10 females Control Group: 5 females
INDUCTION PHASE Induction Concentration:
intradermal: 7.5% v/v in Alembicol D (with and without Freund's complete adjuvant)
topical: 100% v/v notified chemical

Signs of Irritation	Intradermal: The intradermal injections with Freund's Complete Adjuvant (with and without notified chemical) caused necrsosis. All test animals showed slight irritation following treatment with the notified chemical 7.5% v/v in Alembicol D and very slight irritation was observed in control animals receiving Alembicol D only. Topical: Very slight erythema was observed in test animals following topical plication with Cassiffix, as supplied. Very slight erythema was also seen in the control guinea-pigs.
CHALLENGE PHASE	
1st challenge	topical: 50% v/v in Alembicol D
2nd challenge	Not conducted.
Remarks - Method	Statement of GLP. Sodium lauryl sulfate pre-treatment before induction was performed as highest topical concentration in preliminary test did not produce irritation. No significant protocol deviations.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*			
		1st challenge		*2nd challenge*	
		24 h	*48 h*	*24 h*	*48 h*
Test Group	50%	0/10	0/10	-	-
Control Group	50%	0/5	0/5	-	-

Remarks - Results	Drying and sloughing of the epidermis was evident in one test animal 48 and 72 hours after the challenge application. The degree and duration of this reaction was not considered to represent evidence of skin sensitisation.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Huntingdon (1994f)

7.6.2 Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (concentration 1%)
METHOD	In-house method. Multiple application of 24 hr occlusive patch test according to Consumer Product Testing was used.
Study Design	Induction Procedure: Ten induction procedures (3 per week), with 24 hour or 48 hour rest periods between topical applications. Participants were instructed to remove these patches after 24 hours. Evaluation of the test site occurred prior to re application of the test item. Rest Period: 14 days Challenge Procedure: A challenge patch was applied to the treatment site and a virgin site. Each site was evaluated at 24, 48 and 72 hours after application
Study Group	6 M & 50 F human volunteers (3 F volunteers did not complete the study)
Vehicle	Alcohol : Diethyl phthalate (3:1)
RESULTS	
Remarks - Results	*Induction* One subject exhibited a mild response to both the control and test material at the second and fifth observation. The treated areas were negative for the remindar of the test phase. One subject exhibited a mild response to both the control and test item at

the third observation. This was an isolated occurrence.
No other dermal responses were noted throughout the induction period.
Challenge
No dermal responses were noted throughout the challenge phase.

CONCLUSION — A human repeat patch insult test was conducted using the notified chemical diluted with alcohol:diethyl phthalate to 1% under occlusive dressing. The notified chemical was considered to be non-irritating and non-sensitising under the conditions of the test.

TEST FACILITY — Consumer Product Testing (1993a)

7.6.3 Skin sensitisation – human volunteers

TEST SUBSTANCE — Notified chemical

METHOD — In-house method.
Multiple application of 24 hr occlusive patch test according to Consumer Product Testing was used.

Study Design — Induction Procedure: Ten induction procedures (3 per week), with 24 hour or 48 hour rest periods between topical applications. Participants were instructed to remove these patches after 24 hours. Evaluation of the test site occurred prior to re application of the test item.
Rest Period: 14 days
Challenge Procedure: A challenge patch was applied to the treatment site and a virgin site. Each site was evaluated at 24, 48 and 72 hours after application

Study Group — 8 M & 40 F human volunteers (8 F volunteers did not complete the study)

Vehicle — Alcohol

RESULTS

Remarks - Results

Induction
One subject exhibited a mild transitory response on the to both the control and test substance on the 6th and 7th induction exposures.
No other dermal responses were noted throughout the induction period.
Challenge
No dermal response was exhibited at the original test site, however a mild response in two subjects at 72 hours were observed when treated with the test material. In the control no dermal responses were observed at the original test site, however one subject showed a mild dermal response at the virgin site following challenge at 72 hours.
Rechallenge
The subjects that showed responses in the challenge phase were rechallenged. No dermal responses were observed in any of the test subjects.

CONCLUSION — A human repeat patch insult test was conducted using the notified chemical diluted with alcohol:diethyl phthalate to 1% under occlusive dressing. The notified chemical was considered to be slightly irritating and non-sensitising under the conditions of the test.

TEST FACILITY — Consumer Product Testing (1993b)

7.7. Repeat dose toxicity

TEST SUBSTANCE — Notified chemical

METHOD — OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
EC Directive 87/18/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).

Species/Strain	Rat/Sprague-Dawley
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7/7 days per week Post-exposure observation period: 0
Vehicle	Corn oil
Remarks - Method	Statement of GLP. A preliminary 7 day repeat dose oral toxicity study was conducted at 500, 750 and 1000 mg/kg bw/day (3/sex) to determine the highest dose level tolerable for the 28 day study. This study indicated 1000 mg/kg bw/day was acceptable as the highest dosage. Protocol deviations include: 1. Functional observations not conducted 2. Organ weights not measured: heart, thymus 3. No post-exposure observation period

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	5/sex	0	0/10
II (low dose)	5/sex	15	0/10
III (mid dose)	5/sex	150	0/10
IV (high dose)	5/sex	1000	0/10

Mortality and Time to Death

All animals survived until scheduled necropsy.

Clinical Observations

Increased salivation after dosing and associated wet fur was seen on the majority of occasions throughout the study in male and female rats in the high dose group. Increased salivation was also seen sporadically during the study for rats in the mid dose group and in one male rat of the low dose group. Post-dose brown perioral staining was noted in one male rat in the mid dose group on Day 10.

Paddling of the forepaws was observed immediately following administration of the test substance in two female rats in the high dose group on isolated occasions.

Greasy fur was noted in all rats (test and control). This finding was attributed to the vehicle corn oil.

These findings are considered to be attributed to the unpalatability of the test substance and are therefore not of toxicological significance.

Food Consumption: No significant findings.

Body Weight: Body weight gains decreased in males of the mid (11%, $p<0.05$) and high dose (11%, $p<0.05$) groupand females in the high dose group (10%, not significant) when compared to controls. Individual values with the exception of one mid dose and one high dose male were within the range of individual control values. No dose response relationship was observed and the findings were not considered toxicologically relevant.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Clinical Chemistry: Significant ($P<0.05$) decreases in glucose levels for high dose males (29%) and high dose females (16%) were observed. Alkaline phosphatase levels were decreased in high dose males and females (17% and 23%, not significant).

Cholesterol levels were significantly higher than control for male rats treated in the mid (35%) and high (37%) dose groups. No dose-response relationship was observed for this parameter but for rats in the mid dose group the mean value was elevated by two particularly high values. No corresponding histopathological changes in the mid-dose group were observed.

Significant ($P<0.05$) decreases in calcium concentration were observed in all male treatment groups (low dose,

2.6%, mid dose 3.6%, high dose 1.8%). No dose-response relationship was observed for this parameter and with minimal difference from the control variation and within expected range.

There were no other significant findings.

Haematology: The monocyte count was significantly lower ($P<0.05$) than the control for males in the high dose group. The neutrophil count was decreased (not significant) in the low and high dose group of females (57%, 37% respectively) when compared with controls. The neutrophil count was lower (not significant) in males of the low and mid dose group (32%, 5% respectively) when compared with controls. The lymphocytes count was decreased (not significant) in males and females of the high dose group (32%,14% respectively) when compared with controls.

Urinalysis: Not performed.

Effects in Organs

Organ Weights: Significant ($P<0.01$) increases in liver weights (bodyweight adjusted) were observed for high dose male (36.6%) and females (47%). Liver weight (bodyweight adjusted) was significantly ($P<0.01$) higher than control for female rats in the mid (14%) and low (14%) dose group. Individual values were within stated historical control and not accompanied by histopathological changes at the mid and low dose and thus not considered to be treatment related.

Kidney weights (bodyweight adjusted) were significantly increased ($P<0.05$) for male (10%) and female (11%) rats in the high dose group and for males in the mid dose group ($P<0.05$, 16%). Minor histopathological changes accompanied males in the high dose group however given the absence of a dose-response relationship the effect was determined not to be treatment related.

The adrenal weights for all male rats receiving treatment were significantly ($P<0.05$, high dose 15%, mid dose 21% and low dose 21%) lower than the control. However, all values were within the stated historical control data and the resultant finding was considered to be caused by a particularly high group mean control value.

Ovary weights for high dose female rats were significantly ($P<0.01$, 34%) higher than the control. This was considered to be caused by a particularly high individual value and not treatment related.

Macroscopic Findings: No significant findings.

Histopathological Findings: Minimal hepatocyte enlargement was seen in centrilobular zones in all males and was generalised in females of the high dose groups. This change was associated with the higher liver weights recorded for these treatment groups.

A marginal increase in incidence and degree of eosinophilic inclusion in proximal tubular epithelium was seen in males of the high dose group.

The changes to ovary and adrenal organ weight were not accompanied by any histopathological findings.

Remarks – Results

The histopathological evidence of accumulated eosinophilic material within the renal proximal tubules of high males is consistent with α2-microglobulin nephropathy. Male animals exhibited characteristics of α2-microglobulin nephropathy, a phenomenon known to occur only in adult male rats; as such, this finding is without any interspecies toxicological significance.. This syndrome is specific to male rats and is a common finding observed in certain compounds. This finding, whilst treatment related in not considered predictive for similar effects in humans.

CONCLUSION

The No Observed (Adverse) Effect Level (NO(A)EL) was established as 150 mg/kg bw/day in this study, based on the observed effects such as elevated liver and kidney weights in high dose animals and corresponding histopathological changes in high dose animals and biochemical changes.

TEST FACILITY Huntingdon (1995b)

7.8. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 79/831/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1538, TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	Aroclor 1254 induced rat liver S9 – homogenate
Concentration Range in Main Test	Test 1 a) With metabolic activation: Test 1: 0 - 500 µg/plate b) Without metabolic activation: Test 1: 0 - 500 µg/plate Test 2 a) With metabolic activation: Test 1: 0 - 500 µg/plate b) Without metabolic activation: Test 1: 0 - 500 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks - Method	No significant protocol deviations. No precipitation was recorded. Doses selected were based on cytotoxicity observed in preliminary dose range finding study.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 500	≥ 500, ≥ 125 (TA100, TA1538)	-	Negative
Test 2	≥ 500	≥ 500, ≥ 125 (TA100, TA1538)	-	Negative
Present				
Test 1	≥ 500	≥ 500, ≥ 250 (TA1538)	-	Negative
Test 2	≥ 500	≥ 500, ≥ 500, ≥ 250 (TA100, TA1538)	-	Negative

Remarks - Results	The test substance did not cause a marked increase in the number of revertants per plate of any of the tester strains, either in the presence or absence of activation in either test. Positive controls confirmed the sensitivity of the test system.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Huntingdon (1994g)

7.9. Genotoxicity – in vitro

TEST SUBSTANCE	
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test. EC Directive 84/449/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.
Cell Type/Cell Line	Cultured human lymphocyte
Metabolic Activation System	Aroclor 1254 induced rat liver S9-homogenate
Vehicle	Dimethyl sulfoxide

Remarks - Method

No significant protocol deviations.
Statement of GLP.
Doses selected based on precipitation observed at 3 µg/mL in preliminary test.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	1.0, 2.0, 3.9, 7.8*, 15.6, 31.3*, 62.5*, 125, 250, 500	3	18
Test 1- repeat	25, 31.3, 50*, 62.5*, 75	3	18
Test 2	1.0, 2.0, 3.9*, 7.8, 15.6*, 31.3*, 62.5, 125, 250, 500	3	32
Present			
Test 1	1.0, 2.0, 3.9, 7.8, 15.6, 31.3, 62.5, 125, 250, 500	3	18
Test 2	15.6, 31.3, 62.5, 125, 150, 175, 200, 250, 300, 500	3	18
Test 3	10, 20*, 30, 40 50, 60, 80*, 100, 150*, 200, 250, 300	3	18
Test 4	1.0, 2.0, 3.9, 7.8*, 15.6, 31.3*, 62.5*, 125, 250, 500	3	32

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	*Cytotoxicity in Preliminary Test**	*Cytotoxicity in Main Test**	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	≥ 62.5	≥ 125	Equivocal
Test 1 - repeat	-	≥ 62.5	75	Negative (insufficient metaphase figures for analysis at the highest dose level)
Test 2	-	> 31.3	≥ 125	Negative
Present				
Test 1	-	≥ 250	≥ 250	Not possible to determine (insufficient metaphase figures for analysis)
Test 2	-	≥ 62.5	≥ 62.5	Not possible to determine (insufficient dose levels for analysis)
Test 3	-	≥ 150	≥ 80	Negative
Test 4	-	> 125 (one culture highly toxic at this dose level)	≥ 250	Negative

*Based on ≥50% decrease in mitotic index

Remarks - Results

In the absence of metabolic activation the notified chemical caused a statistically significant increase ($P<0.05$) in aberrant cells at 62.5 mg/mL in Test 1. However this increase, to 6.5% lies just outside the historical control range. Furthermore, a repeat test did not cause a statistically significant increase in the number of aberrant cells at 62.5 mg/mL. No statistically significant increase was observed at a later harvest time (32 hours). Therefore the response seen in the initial 18 hour harvest is not considered to be treatment related.

Although there were statistically significant increases ($P<0.05$) in the proportion of aberrant cells observed in the presence of metabolic activation, at the 18 hour harvest (2.5%) and at the 32 hour harvest (2.0%) when gap damage was included. The increases lie well within the historical control range (0-5.25% without gaps and 0-6.25% with gaps). In addition, the mean frequencies of aberrant cells in the solvent control cultures were relatively low (0.25%, for both harvest times) when compared with the mean historical control values (0.98% excluding gaps and 1.20% including gaps).

	Positive controls confirmed the sensitivity of the test system.
CONCLUSION	The notified chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.
TEST FACILITY	Huntingdon (1995bc)

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test. Directive 92/69/EEC Method C.4-E
Inoculum	Activated Sewage Sludge Bacteria
Exposure Period	28 days
Auxiliary Solvent	Chloroform
Analytical Monitoring	Temperature, dissolved oxygen.
Remarks - Method	The test substance was dissolved in chloroform to give a stock solution of 560 mg/10 mL. 10 µL aliquots of stock solution were placed on individual pieces of Whatman GFA glass filter paper and the solvent allowed to evaporate to dryness. One piece of paper was placed in each test bottle prior to filling with inoculated medium. Filter paper blanks were prepared in the same manner, using solvent only. Sodium benzoate standards were prepared by dissolving the sample directly in nutrient medium.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
5	0	5	94
15	0	15	90
28	3	28	88

Remarks - Results	Cultures containing both test and standard substances combined showed the same oxygen depletion value as that anticipated on the basis of results from separate cultures. Consequently, the notified chemical is not considered to have had an inhibitory effect on sewage bacteria under the conditions of the test.
CONCLUSION	The notified chemical cannot be termed as readily biodegradable under the strict test conditions.
TEST FACILITY	Huntingdon (1995c)

8.1.2. Bioaccumulation

Based on the relatively low molecular weight and water solubility, the notified chemical may bioaccumulate, however the relatively low use volume and diffuse release pattern will mitigate this.

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 203 Fish, Acute Toxicity Test – dynamic (flow-through). EC Directive 92/69/EEC C.1 Acute Toxicity for Fish – dynamic (flow-through).
Species	Rainbow Trout *Oncorhynchus mykiss*
Exposure Period	96 h
Auxiliary Solvent	10% Tween 80-Acetone
Water Hardness	165 ± 9 mg $CaCO_3$/L

Analytical Monitoring	Temperature, oxygen saturation
Remarks – Method	The test substance was dissolved in 10% Tween 80-acetone to give a series of stock solutions of 199, 112, 64, 36, 20 and 11 mg/mL. Test concentrations were verified by chemical analysis at 0, 24 and 96 hours. Animals were exposed to the test or control (including solvent control) conditions for a period of 96 hours under continuous flow conditions. Solvent stock solutions were dispensed by Braun Perfusor (Secura) syringe pumps at the rate of 0.3553 mL/h into a diluent stream of 118 mL/vessel/min provided by a Watson Marlow multichannel peristaltic pump. The LC50 values and 95% confidence limits were calculated according to the method of Thompson and Weil.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	0	10	0	0	0	0	0
0.56	0.52	10	0	0	0	0	0
1.0	1.0	10	0	0	0	0	0
1.8	1.6	10	0	0	0	0	0
3.2	2.9	10	0	0	1	1	2
5.6	5.4	10	0	3	5	8	9
10	10	10	6	10	10	10	10

LC50	3.8 mg/L at 96 hours (95% Confidence Limits: 3.0 – 4.9 mg/L)
NOEC	0.52 mg/L at 96 hours.
Remarks – Results	Environmental parameters remained within acceptable limits throughout the duration of the study. Marked reactions to exposure (other than death) were increased pigmentation and respiration, loss of equilibrium, lethargy and moribundity. These reactions rose with increasing concentration from 1.0 mg/L

CONCLUSION — The notified chemical was found to be toxic to fish under the strict test conditions.

TEST FACILITY — Huntingdon (1995d)

8.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE — Notified chemical

METHOD — OEC D TG 202 Daphnia sp. Acute Immobilisation Test - Static.
EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia - Atatic.

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	10% Tween 80-Acetone
Analytical Monitoring	Temperature, oxygen saturation, pH
Remarks - Method	The test substance was dispersed in 10% Tween 80-acetone to give an initial stock solution of 100 mg/mL. Subsequent dilutions of this stock with 10% Tween 70 acetone gave a series of stock solutions, from which 2000 µL aliquots were taken and added to 2 L of Elendt M7 medium to give the desired test exposure levels. Test concentrations were verified by chemical analysis at 0 and 48 hours. *Daphnia* were exposed to the test or control conditions for a period of 48 hours without renewal of test media.

EC50 values were calculated using a logistic model (Berkson, 1944) for which 95% confidence limits were estimated by the likelihood ratio method (Williams, 1986). The "no-effect level" is the highest concentration at and below which the incidence of immobilisation is equal to or less than 10%. Immobilisation was considered if the daphnids were unable to swim for approximately 15 seconds after gentle agitation.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h]*
0	0	20	0	0
0.10	0.08	20	1	0*
0.18	0.15	20	1	0*
0.32	0.28	20	0	3
0.56	0.48	20	3	2*
1.0	0.85	20	1	4
1.8	1.7	20	2	9
3.2	2.8	20	16	20
5.6	5.0	20	20	20
10	11	20	20	20

*Numbers of immobilised *Daphnia* decreased due to apparent recovery of a few individuals during the 24 – 48 h test period.

LC50	1.3 mg/L at 48 hours (95% Confidence Limits: 1.0 – 1.6)
NOEC	0.15 mg/L at 48 hours
Remarks - Results	Although there was no indication of poor stability from the results of preliminary investigations, effective test concentrations declined during the 48 hour exposure period. This is not considered to have invalidated the results of the test, however, since the losses were generally in the region of only 20% and the geometric means of fresh and expired media concentrations have been used for all subsequent calculations. Individual pH, temperature and dissolved oxygen values remained within acceptable limits throughout the duration of the study.
CONCLUSION	The notified chemical was found to be toxic to *Daphnia* under the strict test conditions.
TEST FACILITY	Huntingdon (1994e)

8.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	*Selenastrum capricornutum*
Exposure Period	72 hours
Concentration Range	Nominal: 0, 3.125, 6.25, 12.5, 25, 50 mg/L Actual: 0, 1.2, 2.6, 7.8, 13, 31 mg/L
Auxiliary Solvent	20% Tween 80 acetone
Water Hardness	Not given
Analytical Monitoring	Temperature, oxygen saturation, pH
Remarks - Method	The test substance was dissolved in the auxiliary solvent 20% Tween 80 acetone to give a preliminary stock solution of 500 mg/mL. The solution was further diluted with auxiliary solvent to give a series of 250, 125, 62.5, 31.25 mg/mL. 10 µL of these stock solutions were added to 100 mL

of algal preculture to give the final test series. Test concentrations were verified by chemical analysis at 0 and 72 hours. The samples were not filtered to remove algal cells prior to analysis.

RESULTS

Biomass		*Growth*
E_bC_{50} *mg/L at 72 h*	*NOEC mg/L*	E_rC_{50} *mg/L at 72 h*
8.6 (95% CI: 7.5 – 9.9)	2.6	13 (95% CI: 11 – 15)

Remarks - Results: All test and control cultures were inspected microscopically at 72 hours. There were no abnormalities detected in the control and test cultures except at 7.8, 13, and 31 mg/L treatment levels where the cells appeared turgid. No cultures showed any signs of contamination by foreign algal cells or protozoa.

CONCLUSION: The notified chemical was found to be toxic to algae under the test conditions.

TEST FACILITY: Huntingdon (1995f)

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: A mixed population of activated sewage sludge micro-organisms.
Exposure Period: 3 hours
Concentration Range: Nominal: 0, 10, 18, 32, 56 and 100 mg/L
Remarks – Method: The test substance was dispersed in 20% Tween 80 acetone to give a stock solution of 500 mg/mL. Subsequent dilutions of this stock with 20% Tween 80 acetone gave a stock series of 500, 280, 160, 80 and 50 mg/mL. These stocks were added at the rate of 100 µL to 300 mL to give the final test series concentrations. 3,5-dichlorophenol was used as a reference substance at concentrations of 3.2, 10, and 32 mg/L.

RESULTS
IC50: >100 mg/L
NOEC: 100 mg/L
Remarks – Results: The validation criteria for control culture respiration and respiration inhibition by the reference substance were fulfilled during this study.

CONCLUSION: The notified chemical did not significantly inhibit respiration up to the maximum concentration (100 mg/L) tested.

TEST FACILITY: Huntingdon (1995g)

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

Since most of the notified chemical will be washed into the sewer, under a worst-case scenario with no removal of the notified chemical in the sewage treatment plant, the resultant Predicted

Environmental Concentration (PEC) in sewage effluent on a nationwide basis is estimated as follows:

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	20.496	million
Removal within STP	0%	
Daily effluent production:	4,099	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.67	µg/L
PEC - Ocean:	0.07	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/yr). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 0.1 m of soil (density 1000 kg/m^3). Using these assumptions, irrigation with a concentration of 0.67 µg/L may potentially result in a soil concentration of approximately 6.7 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in applied soil in 5 and 10 years may be approximately 33.5 and 67 µg/kg respectively.

9.1.2. Environment – effects assessment

The following Predicted No-Effect Concentration has been calculated using the EC50 value for Daphnids.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Invertebrates).	1.30	mg/L
Assessment Factor	100.00	
PNEC:	13.00	µg/L

9.1.3. Environment – risk characterisation

Based on the above calculated PEC and PNEC values, the following Risk Quotients (Q) have been derived.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River:	0.67	13	0.051
Q - Ocean:	0.07	13	0.005

As the PEC/PNEC ratio is considerably less than 1 for both river and ocean, there should be an acceptable risk to aquatic organisms.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

Blending and packing

Dermal and possibly ocular exposure to the notified chemical could occur during the transfer of imported product containing the notified chemical to the blending vessel. The level of exposure would vary from site to site depending on the level of automation of the formulation process. The estimated dermal exposure is 42 mg/day, based on the EASE model using reasonable worst case defaults for the exposure scenario 'manual addition of liquids' (European Commission, 2003) and assuming the notified chemical is present at concentration of 10%. Therefore, for a 70 kg worker and a 100% dermal absorption factor, systemic exposure is estimated to be 0.6 mg/kg

bw/day.

Exposure would be limited by the use of PPE.

Following formulation of the end use products, exposure to the notified chemical is expected to be very low due to the low concentration of the notified chemical (up to 0.1%) and the expected use of PPE.

End use
Workers may be exposed to the notified chemical during final application of the formulated cosmetic products or during their addition to water if dilution is required. Although the level and route of exposure will vary depending on the method of application and work practices employed, exposure is considered to be low due to the low concentration of the notified chemical (up to 0.1%).

9.2.2. Public health – exposure assessment

Since the notified chemical will be in products sold to the general public, widespread public exposure to the notified chemical at a concentration up to 0.1% is expected. Based on exposure to a range of household, personal care and cosmetic products in Europe (SDA, 2005), public exposure (dermal and inhalation) to the notified chemical through use of a wide range of products containing the notified chemical, is estimated to be 0.61 mg/kg bw/day, assuming a bodyweight of 60 kg, a 100% dermal absorption factor, a concentration of 0.1% and that product usage (amount used per use and frequency of use) is similar in Australia to Europe. This estimate is considered to be an overestimate as it assumes all products (household, personal care and cosmetic) used by one person contain the notified chemical and uses the maximum 'product amount used' from the range in the dataset.

Based on exposure to a range of household, personal care and cosmetic products in Europe (SDA, 2005), maximum single product use exposure is expected for the products; fragrance cream, facial moisturiser, body lotions, hand moisturiser and fragrance. Assuming a bodyweight of 60 kg, a 100% dermal absorption factor, a concentration of 0.1% and that product usage (amount used per use and frequency of use) is similar in Australia to Europe, exposure to the notified chemical in these products is as follows:

Fragrance cream: 0.02 mg/kg bw/day
Facial moisturiser: 0.03 mg/kg bw/day
Body lotion: 0.095 mg/kg bw/day
Hand moisturiser: 0.093 mg/kg bw/day
Fragrances – pour form: 0.1 mg/kg bw/day

If the notified chemical is used in baby care products, a child's exposure is estimated to be 0.33 mg/kg bw/day assuming a bodyweight of 15 kg, a 100% dermal absorption factor, a concentration of 0.1% and that product usage (amount used per use and frequency of use) is similar in Australia to Europe. Since products containing the notified chemical are stored and used in a domestic environment, there is the possibility of accidental ingestion by a child.

9.2.3. Human health – effects assessment

Acute toxicity
The notified chemical is of low acute toxicity via the oral route and of low acute toxicity via the dermal route.

Irritation
The notified chemical is considered to be moderately irritating in the rabbit skin irritation test. The notified chemical is also considered to be irritating in rabbit eye irritation test.

Sensitisation
The notified chemical is not considered to be a sensitiser at up to 100%w/v, based on the guinea pig maximisation skin sensitisation assay results. The notified chemical is not considered to be a sensitiser at 1% w/v based on two human repeat patch insult test.

Based on human repeat patch insult test the notified chemical was slightly irritating at a concentration of 1%, but only in a limited number of individuals.

Repeated Dose Toxicity
The No Observed (Adverse) Effect Level (NO(A)EL) was established as 150 mg/kg bw/day in this study, based on the observed effects such as elevated liver and kidney weights in high dose animals and corresponding histopathological changes in high dose animals and biochemical changes.

Genotoxicity
The notified chemical was found to be non-mutagenic in the Ames tests. The notified chemical was not clastogenic in an *in vitro* chromosomal aberration tests in cultured human lymphocyte cells.

Hazard classification for health effects
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 2004).

9.2.4. Occupational health and safety – risk characterisation

Reasonable worst-case exposure to the notified chemical during formulation was estimated to be 0.6 mg/kg bw/day. Based on a NOAEL of 150 mg/kg bw/day, derived from a 28-day rat oral study, the margin of exposure (MOE) is calculated as 246. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. Therefore, the risk of systemic effects using modelled worker data is acceptable for formulation workers.

There is a risk of skin and eye irritation effects in formulation workers. The severity of effects would be limited by the concentration (<10%) of the notified chemical. The risk would also be minimised by the use of PPE.

Following formulation of the end products, exposure is expected to be very low and as such the risk to workers is also considered to be low.

9.2.5. Public health – risk characterisation

Based on a NOAEL of 150 mg/kg bw/day, derived from a 28-day rat oral study the margin of exposure (MOE) from a number of exposure scenarios is calculated as follows:

Product(s) used	*Adult/Child*	*Estimated Exposure <mg/kg bw/day>**	*MOE*
Wide range of household, personal care and cosmetic products.	Adult	0.61	246
Fragrance cream	Adult	0.02	7500
Facial moisturiser	Adult	0.03	5000
Body lotion	Adult	0.095	1579
Hand moisturiser	Adult	0.093	1612
Fragrances – pour form	Adult	0.1	1500
Baby care products	Child	0.33	455

*SDA (2005)

MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. As the all the calculated MOEs are ≥ 100, the risk to public health is considered to be low.

Since products formulated with the notified chemical will be stored and used in a domestic

environment, there is also the possibility for children to be exposed to the notified chemical by accidental ingestion. However, as the notified chemical is considered to be of low acute toxicity and given the low concentration of the notified chemical in the formulated products, the risk of lethal effects as a result of accidental ingestion is considered to be 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 classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances*. The classification and labelling details are:
Irritant Xi: R36 Irritating to eyes
Irritant Xi: R38 Irritating to skin

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. The notified chemical may be classified as:

	Hazard category	*Hazard statement*
Eye Irritation	2A	Irritating to eyes
Skin Corrosion/Irritation	3	Causes mild skin irritation
Acute hazards to the aquatic environment	2	Toxic to aquatic life
Chronic hazards to the aquatic environment	2	Toxic to aquatic life with long-lasting effects.

10.2. Environmental risk assessment

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

10.3.2. Public health

There is Low Concern to public health when used in the proposed manner.

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 Office of the ASCC, Department of Employment and Workplace Relations (DEWR), should consider the following health classification for the notified chemical:
  - R36/38 Irritating to eyes and skin.

  Use the following safety phrases for products/mixtures containing the notified chemical:

  - S24/25 Avoid contact with skin and eyes
  - S26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
  - S28 After contact with skin, wash immediately with plenty of water.
  - S37/39 Wear suitable gloves and eye/face protection.

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - Concentration ≥20%: R36/38

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced:
  - Avoid contact with skin and eyes

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:
  - Coveralls
  - Impervious gloves
  - Eye protection

  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.

Disposal

- The notified chemical should be disposed of by incineration or to landfill.

Emergency procedures

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

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 importation volume exceeds one tonne per annum notified chemical; or

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.

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