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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Romandolide®

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

Director
Chemicals Notification and Assessment

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Romandolide®

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Firmenich Limited (ABN 86 002 964 794)
73 Kenneth Rd
Balgowlah NSW 2093

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer, (1 tonne or less per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication:
Identity of chemical and composition.

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)
Low volume chemical (LVC) permit issued in 2001.

NOTIFICATION IN OTHER COUNTRIES
USA (2001), EU (2000, 2002, 2004), Switzerland (2002), Philippines (2002), Canada (2002)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Romandolide®

3. COMPOSITION

DEGREE OF PURITY
> 90%

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 component (maximum 10%) of compounded fragrances.

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

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

USE
The notified chemical will be used as a fragrance ingredient in a variety of cosmetic and domestic products. It will be imported in liquid compounded fragrances, which will be reformulated in Australia to produce the final consumer products. In the final products, the concentration of the notified chemical will be a maximum of 2% in fine perfumes, and a maximum of 0.05% in other cosmetic products and domestic products.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, transport and storage

PORT OF ENTRY
The notified chemical will be imported through Sydney, by wharf or airport, as a small component of perfume preparations.

IDENTITY OF MANUFACTURER/RECIPIENTS
The fragrance preparations containing the notified chemical will be imported by Firmenich Ltd and will be reformulated locally. The fragrance preparations containing the notified chemical will initially be stored and distributed from the notifier's site. Customers (manufacturers of cosmetics, toiletries and household products) will receive the perfume compositions for blending into a wide variety of cosmetics, toiletries and household products.

TRANSPORTATION AND PACKAGING
The fragrance preparations containing the notified chemical will be transported by road from the wharf or airport of entry to the Firmenich Ltd warehouse for storage. Firmenich Ltd forwards them directly to the clients, typically by road, when needed. These fragrance preparations will be imported and distributed in tightly closed lacquered drums, typically of 180 kg size, but also 100, 50, 25, 10 or 5 kg. Final consumer products will be transported to retail stores for distribution, and will be sold in a variety of small package sizes, typical of consumer-sized containers.

5.2. Operation description

The fragrance preparations containing the notified chemical will be used to perfume cosmetics, household cleaning products and detergents. The process mainly involve a blending operation which will be highly automated and will occur in a fully enclosed environment, followed by automatic filling in containers of various sizes.
The final consumer products will be distributed to retail outlets, displayed and sold to the public.

5.3. Occupational Exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Transport workers	4	Unknown	unknown
Mixer	5	4 h/day	2 days/year
Drum handling	5	4 h/day	2 days/year
Drum cleaning	8	4 h/day	2 days/year
Maintenance	5	4 h/day	2 days/year
Quality control	1	0.5 h/day	1 day/year
Packaging	10	4 h/day	2 days/year

Exposure Details
Warehousing and transport of the notified polymer involves loading, unloading, moving, storing of packaged imported fragrance concentrate or repacking of fragrance concentrate prior to distribution. Exposure via all routes is anticipated as minimal.

Workers may potentially be exposed to fragrances containing the notified chemical during handling of the drums, production line, cleaning and sampling or analysis tasks. Exposure via all three routes is anticipated to be minimal and irregular. The number and category of workers will depend on the nature of the customers business.

The major occupational exposure to the notified chemical will be at the manufacturing plants of customers (manufacturers of cosmetics and household products), where the import containers of fragrance mixtures containing the notified chemical are opened and used.

Formulation of final consumer products (cosmetics and household cleaning products)
The products in which the fragrance compositions are added are usually produced in fully automated

systems with a few facilities not being fully automated. Hazardous components of the products mixed together as well as the size of the batches usually necessitate the use of closed lines, local exhaust ventilation where vapours or aerosols are produced and automated packing lines.

5.4. Release

RELEASE OF CHEMICAL AT SITE

As the notified substance will not be manufactured in Australia, there will be no environmental exposure associated with this process in Australia. Environmental release of the notified substance (as a component of perfume preparations) is unlikely during importation, storage and transportation except in case of accidental spill or leak of a drum.

Release of the notified chemical to the environment during blending of the cosmetic and household products is expected to be minimal. Potential sources of release include spills, equipment washing, and container residues. A total of 0.1% of waste may be generated as a result of spills. No release is anticipated from cleaning of formulation equipment. It is expected that this equipment will be cleaned using water and the aqueous solution reused for new purposes. The average amount of residue in empty containers is estimated to be < 0.1%. Therefore a total of 0.2% or up to 2 kg of waste generated each year as a result of formulation.

Empty containers of perfume compositions containing the notified chemical will either be recycled or disposed of through an approved waste management capacity.

RELEASE OF CHEMICAL FROM USE

Practically all the notified chemical (<1 tonne) will enter the sewer in commercial or domestic laundry effluent during use of the consumer products (cosmetics, toiletries, household products) when the washwater is released.

It is estimated that a maximum of 3% of the consumer product (containing maximum of 2% notified chemical) will remain in the container after use. This corresponds to 30 kg of the notified chemical imported per annum. These consumer containers will be disposed of through domestic garbage and ultimately into landfill.

5.5. Disposal

Disposal via incineration or landfill is recommended for wastes generated during the formulation of the products. The majority of the notified chemical will ultimately be disposed of in sewer (major) or landfill. The emptied imported drums may potentially be rinsed and re-used, sent to a recycler, or sent to landfill for disposal. Drum rinse water may be reused. Following use, emptied consumer product containers are disposed of through domestic garbage disposal and hence will enter landfill or recycling.

5.6. Public exposure

Public exposure to the notified chemical as imported as a component of fragrance compositions could only occur in the event of transport accident or spillage. Public exposure from the reformulation process is unlikely. Public exposure to the notified chemical will occur during repeated usage of consumer products (cosmetics, toiletries and household products) containing the notified chemical.

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa Colourless liquid

Melting Point/Freezing Point <-20ºC

METHOD EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
TEST FACILITY SafePharm Laboratories Ltd (1999a)

Boiling Point 299ºC at 100.63 to 100.78 kPa

METHOD EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks Differential scanning calorimetry
TEST FACILITY SafePharm Laboratories Ltd (1999a)

Density 1003 kg/m^3 at 20ºC

METHOD OECD TG 109 Density of Liquids and Solids.
EC Directive 92/69/EEC A.3 Relative Density.
Remarks The test was performed in duplicate using a pycnometer at 20ºC
TEST FACILITY SEPC (2000a)

Vapour Pressure 5.3 x 10^{-5} kPa at 20ºC.

METHOD OECD TG 104 Vapour Pressure.
EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks The vapour pressure was determined using a gas saturation method. The test was performed at around 20ºC and 40°C. The vapour pressure was estimated by linear regression and analysed by HPLC.
The notified chemical is considered to be moderately volatile (Mensink *et al* 1995). The calculated Log H = 1.31 Pa m^3/mole based on Henry's law calculation.
TEST FACILITY INERIS (2000)

Water Solubility 0.0109 g/L at 20ºC

METHOD EC Directive 92/69/EEC A.6 Water Solubility (shake flask method).
Remarks Based on the preliminary result, the mixture of test material and water was added to three separate flasks. They were shaken at approximately 30ºC and after standing at room temperature for a period of >24 h, the contents of the flask were filtered. The concentration of the test material in the filtrate was determined by GC.
The notified chemical is moderately soluble in water (Mensink *et al* 1995).
TEST FACILITY SafePharm Laboratories Ltd (1999a)

Hydrolysis as a Function of pH

METHOD EC Directive 92/69/EEC C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH.

pH	*T (ºC)*	$t_{½}$
4	25	> 365 days
7	25	994 hours
9	25	18.1 hours

Remarks Based on a preliminary test, further tests were performed in buffers at pH 4 (50°C), pH 7 (50, 60 and 70°C) and pH 9 (35 and 50°C) under sterile conditions and protected from light. The solutions were analysed by GCMS. The results were extrapoltated to 25ºC and indicate that the notified chemical is hydrolytically stable at pH 4, hydrolytically unstable at pH 7 and rapidly hydrolysed at pH 9 at 25ºC.
TEST FACILITY CIT (2001)

Partition Coefficient (n-octanol/water) log Pow at 30ºC = 4.74 to 4.79

METHOD EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks A preliminary assessment of the partition coefficient was made based on the approximate solubilities of the test material in n-octanol and water by visual assessment. The retention times of the sample, thiourea and reference standard solutions were then determined in duplicate by HPLC. The results indicate that the notified chemical is likely to partition in the octanol layer.
TEST FACILITY SafePharm Laboratories Ltd (1999a)

Adsorption/Desorption log K_{oc} = 3.385

METHOD Estimated according to European Commission, TGD, Part III, 2003, page 26, table

4 "QSAR for soil and sediment sorption for different chemical classes.

Remarks The Log Koc was calculated using QSAR for esters. The method is recommended by the EU to calculate the Koc of various classes of organic compounds. For esters the QSAR is calculated as Log Koc = 0.49 Log Pow + 1.05 = 0.49 × 4.765 + 1.05 = 3.38485.
A corrected logKoc of 2.70 was calculated using the EPIWIN PCKOC program.

Dissociation Constant Not determined.

Remarks There are no acidic or basic groups on the molecule able to dissociate.

Surface Tension 50.6 mN/m at 20ºC

METHOD OECD TG 115 Surface Tension of Aqueous Solutions.
EC Directive 92/69/EEC A.5 Surface Tension.

Remarks The surface tension was determined using the ring method. The test concentration: was 9.81 mg/L at 90% of the limit of solubility. Three assays were performed with a thermoregulated circulator at 20º. The test substance with a surface tension of 50.6 mN/m is considered to be surface-active.

TEST FACILITY SEPC (2000c)

Particle Size

Remarks Test not conducted as the notified chemical is a liquid.

Flash Point 152ºC at 100.73 kPa

METHOD EC Directive 92/69/EEC A.9 Flash Point.
Remarks The determination was carried out using the closed cup equilibrium method.
TEST FACILITY SafePharm Laboratories Ltd (1999b)

Flammability Limits Not determined

Remarks Test not conducted since experience in use indicate that negative results would be obtained.

Autoignition Temperature 388ºC

METHOD 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
TEST FACILITY SEPC (2000b)

Explosive Properties Not determined

Remarks There are no chemical groups that would imply explosive properties, therefore the result has been predicted negative.

Reactivity

Remarks Expected to be stable under normal environmental conditions.

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral LD50 > 2000 mg/kg bw	low toxicity
Rat, acute dermal LD50 > 2000 mg/kg bw	low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	non-irritating
Guinea pig, skin sensitisation - adjuvant test	no evidence of sensitisation.
Rat, dietary, repeat dose toxicity - 28 days	NOAEL = 44 mg/kg/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 423 Acute Oral Toxicity – Acute Toxic Class Method. EC Directive 92/69/EEC B.1tris Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/Sprague-Dawley CD (Crl : CD® (SG) IGS BR)
Vehicle	None
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 females	2000	0/3
2	3 males	2000	0/3

LD50	> 2000 mg/kg bw
Signs of Toxicity	Clinical signs of systemic toxicity noted were ataxia and/or hunched posture. Male animals recovered one day after dosing and female animals recovered two days after dosing.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	None.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	SafePharm Laboratories (1999c)

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/Sprague-Dawley ICO:OFA-SD (IOPS Caw)
Vehicle	None.
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 females	2000	0/5
2	5 males	2000	0/5

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	No cutaneous reactions were noted.
Signs of Toxicity - Systemic	A reduced body weight gain was seen in 4/5 females between days 1 and 8. The overall body weight gain of the other animals was similar to that of the laboratory historical control animals.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	None.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	CIT (2000a)

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	None
Observation Period	14 days
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

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	0	0	0		
Oedema	0	0	0	0		

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

Remarks - Results	There was no evidence of skin irritation.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	SafePharm Laboratories (1999d)

7.5. 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	72 hours
Remarks - Method	No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0	0.3	0	1	24 hours	0
Conjunctiva: chemosis	0	0	0	1	1 hour	0
Conjunctiva: discharge	0	0	0	1	1 hour	0
Corneal opacity	0	0	0			0
Iridial inflammation	0	0	0			0

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

Remarks - Results	No corneal or iridial effected were noted during the study. Minimal conjunctival irritation was noted in all treated eyes 1 hour after treatment and persisted in one treated eye at the 24-hour observation. Two treated eyes appeared normal at the 24-hour observation and the remaining treated eye appeared normal at the 48-hour observation.

CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	SafePharm Laboratories (1999e)

7.6. Skin sensitisation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 406 Skin Sensitisation – Guinea Pig Maximisation Test. EC Directive 96/54/EC B.6 Skin Sensitisation – Guinea Pig Maximisation Test
Species/Strain	Guinea pig/Dunkin Hartley
PRELIMINARY STUDY	Maximum Non-irritating Concentration: intradermal: Not determined topical: 100%
MAIN STUDY	
Number of Animals	Test Group: 20 Control Group: 10
INDUCTION PHASE	Induction Concentration: intradermal injection : 25% in arachis oil topical application : 100%
Signs of Irritation	Moderate erythema was observed at the intradermal induction sites in all test animals while slight erythema was seen in control animals.
CHALLENGE PHASE	
1st challenge	topical: 75% and 50% in arachis oil
Remarks - Method	Sodium lauryl sulphate in petroleum was applied a day prior to topical induction.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	75%	0	0
	50%	0	0
Control Group	75%	0	0
	50%	0	0

Remarks - Results	One test group animal and one control group animal were killed for humane reasons unrelated to treatment during the study and therefore 19 test group animals and 9 control group animals completed the study. The absence of these animals was considered not to affect the purpose or integrity of the study.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	SafePharm Laboratories (1999f)

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/Sprague-Dawley (Crl CD® (SD) IGS BR)
Route of Administration	Oral – diet
Exposure Information	Total exposure days: 28 days;

	Dose regimen: 7 days per week; Post-exposure observation period: 14 days
Vehicle	Notified chemical mixed with the diet
Remarks - Method	An 8-day range-finding toxicity study by oral route was conducted to select the dose-levels for the main study. No urinalysis findings were reported for the main study.

RESULTS

Group	*Number and Sex of Animals*	*Concentration in ppm (mg/kg bw/day) Nominal*	*Mortality*
I (control)	5/sex	0	0/10
II (low dose)	5/sex	545 (M=44; F= 51)	0/10
III (mid dose)	5/sex	5455 (M=436; F= 482)	0/10
IV (high dose)	5/sex	10910 (M=881; F= 953)	0/10

M = Males
F = Females

Mortality and Time to Death
No deaths occurred during the study.

Clinical Observations
No notable clinical signs were observed during the treatment period in any group. However, the mid-dose and high-dose females showed a lower body weight gain correlated with lower mean food consumption values.

Laboratory Findings – Clinical Chemistry, Haematology
There were no changes in haematological parameters in treated animals receiving the low dose which could be attributed to treatment with the test substance. For the mid- and high-dose treated females, a decrease in prothrombin time and increase in protein, cholesterol and calcium plasma levels were observed. For the high-dose treated males, an increase in protein and cholesterol was noted.

Effects in Organs
Low-dose males showed a slight increase in relative kidney weights (+ 14%).
For the mid-dose animals, an increase in relative liver weight was noted in males (+ 20%) and females (+ 18%) and correlated with hepatocellular hypertrophy in all the males and 3/5 females. Increase in kidney relative weight of males was also noted (+ 21%).
For the high-dose animals, an increase in relative kidney weight in all males (+ 19%) and increase in relative liver weight (males + 29%, females + 26%) were noted.
In the high-dose group, acidophilic globules in the cortical tubular epithelium of the kidneys were seen in all treated males and this was sometimes associated with epithelial degeneration/necrosis, tubular basophilia, tubular dilatation and exfoliation. These findings were due to the accumulation of urinary protein alpha 2 μ–globulin in the tubular epithelium which is a known sex-specific effect in rats. Other effects observed were either scattered or common findings from experimental animals, and therefore were not considered to be test related.

Remarks – Results
When administered by dietary admixture for 4 weeks, the test substance induced lower body weight gain, changes in clinical pathology parameters, increased liver weight and hepatocellular hypertrophy at the mid- and high-dose levels.
The liver changes identified during the study in both sexes are generally considered to be adaptive in nature as there was no evidence of associated inflammatory or degenerative change. The kidney changes in the treated males were consistent with well-documented changes that are peculiar to the male rats in response to treatment with hydrocarbons. This effect is therefore not indicative of a hazard to human health and, for purposes of hazard evaluation, the NOAEL should be regarded as the low-dose level corresponding to 44 mg/kg/day for males and 51 mg/kg/day for females.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 44 mg/kg bw/day in this study, based on the observed increases in protein and cholesterol levels in the mid- and high-doses as well as the liver changes at higher doses.

TEST FACILITY CIT (2000b)

7.8. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

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

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100. *E. coli*: WP2 uvrA$^-$.
Metabolic Activation System	Aroclor 1254 activated S9 fraction
Concentration Range in Main Test	a) With metabolic activation: 50-5000µg/plate. b) Without metabolic activation: 50-5000 µg/plate.
Vehicle	Dimethyl sulfoxide (DMSO)
Remarks - Method	Two independent mutation tests were performed in triplicate.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in PreliminaryTest	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Present				
Test 1	5000 (TA 100, WP2 uvrA$^-$)	5000	5000	Negative
Test 2		5000	5000	Negative
Absent				
Test 1	5000 (TA 100, WP2 uvrA$^-$)		5000	Negative
Test 2			5000	Negative

Remarks - Results

A visible reduction in the growth of the bacterial lawn and reduction in revertant colony numbers in all of the Salmonella tester strains at 5000 µg/plate in the presence of Aroclor-induced rat liver S9 only, was seen. No toxicity was observed in E. coli strain WP2 uvrA$^-$, either with or without S9. The test material was, therefore, tested up to the maximum recommended dose of 5000 µg/plate. An oily precipitate was observed at 5000 µg/plate, this did not prevent the scoring of revertant colonies.

No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test material, either with or without metabolic activation.
Appropriate positive controls were used and resulted in large increases in the frequency of revertant colonies, confirming the sensitivity of the test system. The results from the negative controls were acceptable.

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

TEST FACILITY SafePharm Laboratories (1999g)

7.9. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 473 In vitro Mammalian Chromosomal Aberration Test.
Cell Type/Cell Line	Human lymphocytes
Metabolic Activation System	Aroclor 1254 activated S9 fraction
Vehicle	Dimethyl sulfoxide (DMSO)
Remarks - Method	No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Present			
Test 1	78.125, 156.25, 312.5*, 625*, 1250*, 2500, 3750, 5000	3 h	20 h
Test 2	39.06, 78.125, 156.25, 312.5*, 625, 1250, 2500	3 h	20 h - 44 h
Absent			
Test 1	78.125, 156.25, 312.5*, 625*, 1250*, 2500, 3750, 5000	3 h	20 h
Test 2	39.06, 78.125, 156.25*, 312.5*, 625*, 1250, 2500	20 h – 44 h	20 h – 44 h
Test 3	62.5, 125, 250*, 500*, 750*, 1000, 1250	20 h – 44 h	20 h – 44 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/mL) resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1 (20 h)	≥ 1250	≥ 1250	None
Test 2 (20 h)	≥ 1250	≥ 1250	None
Test 2 (44 h)	≥ 312.5	≥ 1250	None
Test 3 (20 h)	≥ 1250	≥ 1250	None
Test 3 (44 h)	≥ 500	≥ 1250	None
Present			
Test 1 (20 h)	≥ 1250	≥ 1250	None
Test 2 (20 h)	≥ 625	≥ 1250	None
Test 2 (44 h)	≥ 156.25	≥ 1250	None

Remarks - Results

In the culture medium, the dose level of 5000 μg/mL produced an emulsion. At this dose level, the pH and the osmolality were equivalent to those of the vehicle control.

A slight to moderate emulsion was observed at the end of the treatment period at dose levels ≥1250 μg/mL.

In the experiment without S9 mix, the test substance demonstrated slight to very strong toxicity, depending on the dose levels and the treatment time. Therefore, on the basis of International Guidelines and in order to reach a more adequate level of toxicity than that obtained in the second experiment (more than 50% decrease in the mitotic index), a third experiment was performed under the same experimental conditions, using a closer range of dose levels.

In experiment with S9 mix, the test substance demonstrated slight to very strong toxicity, depending on the dose levels and the harvest times.

The frequency of cells with structural chromosome aberrations of the vehicle and positive controls were consistent with acceptance criteria. The study was therefore considered valid.

CONCLUSION

The notified chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY

CIT (2000c)

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

8.1.1.1. Manometric respirometry test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	A mixed population of activated sewage sludge micro-organisms from the aeration stage of a sewage treatment plant which treats predominantly domestic sewage.
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Biological oxygen demand (BOD) was monitored daily.
Remarks – Method	The notified chemical was exposed to activated sewage sludge micro-organisms at a concentration of 100 mg/L with culture medium in sealed culture vessels in the dark at 21°C for 28 days. The degradation of the test material was assessed by the measurement of daily oxygen consumption. Control solutions with inoculum and the standard material, aniline (100 mg/L), together with a toxicity control, were used for validation purposes. The percent degradation of the test item was based on BOD/ThOD. ThOD was determined from the structural formula.

RESULTS

Test substance		*Aniline*	
Day	*% degradation*	*Day*	*% degradation*
1	4	1	1
2	15	2	9
5	39	5	74
6	45	6	79
10	52	10	85
17	51	17	84
23	53	23	87
28	54	28	87

Remarks – Results	The test material attained 54% degradation after 28 days and therefore cannot be considered as readily biodegradable. However, the test material exhibited the potential for relatively rapid degradation. The toxicity control attained 70% degradation after 28 days thereby confirming the test substance was not inhibitory to the activated sludge. The reference substance, aniline, attained 87% degradation after 28 days thus confirming the validity of the test.
CONCLUSION	The notified chemical is not considered to be readily biodegradable based on this test.
TEST FACILITY	SafePharm Laboratories (1999h)

8.1.1.2. Closed Bottle Test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test.
Inoculum	A mixed population of activated sewage sludge micro-organisms from the aeration stage of a sewage treatment plant which treats predominantly domestic sewage.
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Measurement of dissolved oxygen over a 28-day test period.

Remarks – Method

The test contained two inoculum control groups, two reference groups, and two treatment groups. Each group contained 10 replicate test chambers. The inoculum control chambers were used to measure the dissolved oxygen consumption of the inoculum and were not dosed with a carbon source. The reference chambers were dosed with sodium benzoate, a substance known to be biodegradable, at a concentration of 2 mg/L. The test chambers within the treatment group were used to evaluate the test substance at 2 mg/L. Measurements of oxygen consumption were performed on two test chambers from the control, reference, and treatment groups on days 0, 7, 14, 21 and 28.

The test was performed using: a) freshly collected inoculum and b) inoculum that was pre-exposed to the test substance for 31 days prior to start of the test. Pre-exposure was performed in two replicate semi-continuous activated sludge (SCAS) units.

RESULTS

	Test substance *% degradation after 28 days*	*Sodium benzoate (Reference substance)* *% degradation after 28 days*
Freshly collected sludge inoculum at 28 days of exposure	68	145
Pre-exposed sludge inoculum at 28 days of exposure	19	111

Remarks – Results

The results indicate that the freshly collected and pre-exposed inoculum were active by degrading sodium benzoate within the acceptable range confirming the validity of the results. The notified chemical met the OECD criteria (~68% degradation after 10-day window) for ready biodegradability in the freshly collected sludge inoculum as the degradation occurred slowly up to 22 days at 10 % degradation and reached 68% degradation within 10-day window However, this did not occur in the pre-exposed sludge inoculum. The notifier indicates that the difference could be explained on the basis that degradation rates are influenced by microbial biomass concentrations. Since the pre-exposed inoculum contained fewer viable bacteria, the decrease in degradation rate with the pre-conditioned medium is not unexpected. The notifier also indicates that during the pre-exposure period, the relatively low concentration of test substance as compared to the nutrient level of the synthetic sewage may have not been sufficient to provide the conditions needed to increase the percentage of bacteria capable of degrading the test substance. Instead it has resulted in a decrease in total biomass and thus the degradation rate.

CONCLUSION

The notified chemical can be classified as readily biodegradable.

TEST FACILITY

Wildlife International (2000)

8.1.2. Bioaccumulation

Not determined. The low water solubility and high Log Pow suggest a potential for the notified chemical to cross biological membranes and bioaccumulate. However, the low import volume and dispersed use suggest that exposure will not be significant and will limit this potential. A BCF value of 536.7, calculated using the EPIWIN BCF program (v2.14), indicates a relatively low potential for bioaccumulation.

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

8.2.1.1. Acute toxicity to fish – Initial test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test - Semi-static. EC Directive 92/69/EEC C.1 Acute Toxicity for Fish - Semi-static.
Species	Rainbow trout (*Oncorhynchus mykiss*),
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	150 mg $CaCO_3$/L
Analytical Monitoring	Samples were analysed by HPLC with UV detection at 210 nm.
Remarks – Method	Eight fish per concentration were exposed to the test substance. Preliminary (limit and range-finding) and definitive tests were performed. In the definitive test, 6 concentrations of the notified chemical and one control were used. Fish were observed at 0, 2, 4, 24, 48, 72, and 96 hours. Animals were inspected for mortality and sub-lethal effects such as animals swimming at the surface of solutions, minor and severe loss of equilibrium, hyperactive swimming behaviour, spasmodic swimming, animals lying at the bottom of the aquarium, colour change, abnormal respiratory rate and immobilisation before death. The pH, temperature, water hardness and oxygen concentrations remained within acceptable limits during the test.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*2 h*	*24 h*	*48 h*	*72 h*	*96 h*
control	< LOQ	8	0	0	0	0	0
0.313	< LOQ	8	0	0	0	0	0
0.625	< LOQ	8	0	0	0	0	0
1.25	< LOQ	8	0	0	0	0	0
2.5	< LOQ	8	0	0	0	0	0
5	0.89	8	0	0	0	0	0
10	1.78	8	0	0	3	3	8

LC50	Time-weighted mean measured: 1.26 mg/L at 96 hours.
NOEC	Time-weighted mean measured: 0.89 mg/L at 96 hours.
Remarks – Results	All results are reported as measured concentrations. Concentrations at 0.313 to 2.5 mg/L were not analysed because these concentrations were <LOQ. No mortalities were observed at concentrations 0-5 mg/L (nominal) at the end of 96 hours. Sub-lethal effects were observed at the 2.5, 5, and 10 mg/L (nominal).
CONCLUSION	The notified chemical is considered toxic to rainbow trout.
TEST FACILITY	CIT (2000d)

8.2.1.2. Acute toxicity to fish – Repeat test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static. EC Directive 92/69/EEC C.1 Acute Toxicity for Fish – Semi-static.
Species	Rainbow trout (*Oncorhynchus mykiss*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	100 mg $CaCO_3$/L
Analytical Monitoring	GC.

Remarks – Method

A repeat of the initial test was conducted as a result of a request from the French Competent Authorities to meet the test criteria for the analytical method.
Ten fish per concentration were exposed to the test substance. The test material solutions for the definitive test were prepared by stirring an excess (100 mg/L) of test material in dechlorinated tap water at a temperature of 14°C for 24 hours and then filtered to remove undissolved test material, in order to give a saturated solution of 10 mg/L. This was then further diluted to produce the test series for the definitive test. The water temperature (14.6-14.9°C), pH (7.6-7.9) and dissolved oxygen concentrations (8.5-8.9 mg O_2/L) were recorded daily throughout the test and were within acceptable limits.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	<LOQ	10	0	0	0	0	0
1.0	0.51	10	0	0	0	0	0
1.8	0.92	10	0	0	0	0	0
3.2	1.6	10	0	0	1	4	5
5.6	2.5	10	0	0	10	10	10
10	9.0	10	0	10	10	10	10

LC50

Time-weighted mean measured: 1.6 mg/L (CL: 1.3–1.8 mg/L) at 96 hours.

NOEC

Time-weighted mean measured: 0.51 mg/L at 96 hours.

Remarks – Results

Sublethal effects of exposure were observed at nominal test concentrations of 1.8 mg/L and above. These responses were increased pigmentation, swimming at the surface with increased pigmentation, swimming at the bottom with increased pigmentation, loss of equilibrium with increased pigmentation and the presence of moribund fish with increased pigmentation.

The test material preparations were observed to be clear and colourless solutions throughout the duration of the test.

After 3 h exposure 8 out of 10 fish and then after 4 hours all the remaining fish were observed to be moribund with increased pigmentation at 10 mg/L. After 30 h exposure 1 out of 10 fish and 2 out of 10 fish were observed to be moribund with increased pigmentation at 3.2 and 5.6 mg/L, respectively. After 32 h exposure 1 out of 8 fish and then after 47 hours all the remaining fish were observed to be moribund with increased pigmentation at 5.6 mg/L. After 70 h exposure 3 out of 9 fish and then after 73.5 h 1 out of 6 fish were observed to be moribund with increased pigmentation at 3.2 mg/l. All the above fish were killed due to the approach of the substantial severity limit (Animals Scientific Procedures) Act 1986) and were classed as mortalities.

Chemical analysis of the freshly prepared test media sampled at 0, 24, 48 and 72 h showed the measured test concentrations to range from 87% to 108% of the nominal test concentrations. However, analysis of the old or expired test media sampled at 24, 48, 72 and 96 h showed a marked decline in the measured test concentrations which were shown to range from 2% to 46% of the nominal values with the exception of the 10 mg/L test concentration at 24 h which showed a measured value of 82% of nominal. The notifier indicates that the marked decline was attributed to degradation of the test material as degradation peaks were shown in the chromatographic profile of the old or expired test media samples. Further losses may have been incurred by the suspected volatile nature of the test material and adsorption and/or bioaccumulation in the test fish was

considered likely to be a factor in the marked decline shown in the measured test concentrations of the old test media.

CONCLUSION — The notified chemical is considered toxic to rainbow trout.

TEST FACILITY — SafePharm Laboratories (2003)

8.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE — Notified chemical

METHOD — OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Semi-static.
EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia – Semi-static.

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	272 mg $CaCO_3$/L
Analytical Monitoring	HPLC with UV detection at 210 nm.
Remarks – Method	A preliminary test which included a limit test and a range-finding test preceded the definitive test. For both limit and range-finding tests, test solutions were changed 24 h after the beginning of the assay. In the definitive test, twenty daphnids (four groups of five each group) were exposed to each concentration for 48 h and immobilisation was recorded at 0, 24 and 48 h. The pH (7.73 to 8.42), temperature (18.6°C to 19.8°C) and dissolved oxygen concentrations (6.3 to 9.1 mg/L) were within acceptable limits.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0	< LOQ	20	0	0
0.313	< LOQ	20	0	0
0.625	< LOQ	20	0	0
1.25	< LOQ	20	0	0
2.5	< LOQ	20	0	0
5	1.64	20	0	0
10	2.02	20	0	0
10*	3.16	20	0	3

*Limit test

LC50	>3.16 mg/L at 48 hours
NOEC	2.02 mg/L at 48 hours
Remarks – Results	No immobilisation was observed at any of the concentrations tested.

All effects were based on geometric means of measured concentration throughout the test, calculated as 3.16 mg/L for the limit test solution and as 1.64 and 2.02 mg/L for the definitive test solution at 5 and 10 mg/L, respectively.

A translucent colourless solution was obtained in all test concentrations.

After 48 hours, 15% immobilisation was observed in the limit test. The slight toxicity difference at 10 mg/L in the preliminary and definitive tests could be explained by a higher level of test substance in the limit test solution than in the definitive test solution (based on geometric means of measured concentrations in these solutions, 3.16 mg/L versus

2.02 mg/L).

CONCLUSION — The notified chemical is considered to be potentially toxic to *Daphnia magna*.

TEST FACILITY — CIT (2000e)

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	*Scenedesmus subspicatus*
Exposure Period	96 hours
Concentration Range	
Nominal	10 mg/L
Actual	3.73 - 4.19 mg/L
Auxiliary Solvent	None
Water Hardness	34 mg $CaCO_3$/L
Analytical Monitoring	HPLC.
Remarks – Method	The study includes a limit test at 10 mg/L and a range-finding test at 0.01, 0.1, and 1 mg/L of the notified chemical under the same conditions of light and temperature. At the beginning, nominal algae cell density was ca. 10^4 cells/mL. The growth of the cell culture was monitored by counting the number of cells at 24, 48, 72 and 96 h. The pH range (7.39 to 9.04) and temperature (23.4°C to 23.6°C) were within acceptable limits.

RESULTS

Biomass		*Growth*	
E_bC50 mg/L at 96 h	*NOEC mg/L at 96 h*	*E_rC50 mg/L at 96 h*	*NOEC mg/L at 96 h*
> 3.73	3.73	> 3.73	3.73

Remarks – Results — The measured concentration in the limit test solution was 4.74 mg/L. After 96 h it corresponded to 43% and 50% of the initial value with or without algae, respectively. Furthermore, measured concentrations in the solution without algae were systematically higher than those in the solution with algae. This indicates that the test substance may be adhering to the surface of the algae or being degraded by it. All effects are based on geometric means of measured concentrations at 10 mg/L without algae, calculated as 3.73 mg/L for the 96 h exposure.

CONCLUSION — The notified chemical is considered potentially toxic to algae.

TEST FACILITY — CIT (2000f)

8.2.4. Inhibition of microbial activity

TEST SUBSTANCE — Notified chemical

METHOD — OECD TG 209 Activated Sludge, Respiration Inhibition Test.

Inoculum — A mixed population of activated sewage sludge micro-organisms from the aeration stage of a sewage treatment plant which treats predominantly domestic sewage.

Exposure Period	3 hours
Concentration Range	
Nominal	1 - 100 mg/L
Remarks – Method	The test solutions were prepared by using 2 control solutions at concentration of 1.6 g/L, 5 test substance solutions at concentrations of 1, 3.16, 10, 31.6 and 100 mg/L and 3 reference substance (3,5-Dichlorophenol) at concentrations of 4, 12 and 36 mg/L. The oxygen consumption of these solutions was measured for approximately 10 minutes after an aeration of 3 hours. The EC50 of the test substance and reference substance was determined considering the oxygen consumption of the controls as 100%.
RESULTS	
EC50	>100 mg/L at 3 h
Remarks – Results	The respiration rate of the test solution at 100 mg/L was equivalent to the respiration rate of the control. As a result the oxygen consumption rate of the remaining solutions were not determined. The 3 h EC50 of the reference substance was determined to be 16.6 mg/L which is in the range of 5-30 mg/L and the difference between the two controls were <15% thus confirming the validity of the test.
CONCLUSION	The notified chemical is considered not toxic to sewage micro-organisms.
TEST FACILITY	CIT (2000g)

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The notified chemical is moderately volatile and loss to the atmosphere is likely to be from sewers and the aquatic environment. It is considered readily biodegradable (68% after 28 days in a closed bottle test). It is moderately soluble in water (10.9 mg/L) and has a hydrolysis half-life of greater than 1 year at pH 4, 994 h at pH 7 and 18.1 h at pH 9. It has a log Pow of 4.74-4.79 and a log Koc of 3.38 indicating that it has the potential to bioaccumulate and the ability to bind tightly to organic matter in soil.

Following its use in Australia, practically all the notified chemical will eventually be released into the aquatic environment. A calculated worst-case scenario daily PEC in the sewer effluent is 0.68 µg/L (Environment Australia, 2003). In calculating the PEC, the following were assumed: (1) usage of the maximum import volume is evenly distributed over a 365 day period; (2) usage is nationwide, with a population of 20 million contributing 200 L of water per person per day to the sewer, (3) there is no adsorption or degradation in the sewer prior to release. However, data provided by the notifier indicate some biodegradation may take place in the sewer, and as the notified chemical has some affinity to organic matter (calculated log Koc = 3.385), some losses may also occur through adsorption to suspended solids in the sewer, thereby decreasing the PEC.

Using the SIMPLETREAT model for modelling partitioning and losses in sewage treatment plants (European Commission, 2003), the percentage removal from solution by STP approximates 0% through volatilisation, 47% adsorption in sludge, and 45% biodegraded. This is based on the Henry's Law Constant Log H of 0.12, log K_{0w} of 4.77 and ready biodegradability. Hence, approximately 8% of the inflow concentration of the notified chemical may potentially remain in solution, passing through the STP. The resulting PEC concentrations in treated effluents will be reduced to 0.68 µg/L X 0.08 = 0.054 µg/L.

Based on the respective dilution factors of 1 and 10 for rural areas and coastal discharges of effluents, the PECs of the notified chemical in rural areas and coastal water may approximate 0.054 and 0.0054 µg/L, respectively.

Partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 3.4 mg/kg (dry wt), assuming 47% attenuation in sludge during the STP process. This is based on the assumption that 0.1 tonne of biosolids is generated for each ML of STP effluent and the consumption of 4000 ML/day for total population per year. Biosolids are applied to agricultural soils, with an assumed average rate of 10 t/ha/year. Assuming a soil bulk density of 1000 kg/m^3 and a soil mixing zone of 0.1 m, the concentration of the notified chemical may approximate 0.34 mg/kg in the applied soil, assuming accumulation of the notified chemical in soil for 10 years under repeated biosolids application.

The effluent re-use (eg. irrigation purposes) concentration of the notified chemical may potentially approximate 0.054 µg/L, assuming 8% remains in solution during the STP process. STP effluent re-use for irrigation in Australia occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 0.1 m of soil (density 1000 kg/m^3). Using these assumptions, irrigation with a concentration of 0.33 µg/L may potentially result in a soil concentration of approximately 5.4 µg/kg assuming accumulation of the notified chemical in soil for 10 years under repeated irrigation.

The worst-case PECs values are summarised below:

Sewage effluent/coastal city = 0.068 µg/L
Sewage effluent/rural areas = 0.68 µg/L.

The mitigated PECs values are summarised below after taking into account the SIMPLETREAT model
Sewage effluent/coastal city = 0.0054 µg/L
Sewage effluent/rural areas = 0.054 µg/L.
Soil concentrations after 10 years application of biosolids = 0.34 mg/kg
Soil concentrations following 10 years irrigation with effluent = 5.4 µg/kg.

9.1.2. Environment – effects assessment

The results of the ecotoxicological data indicate that the notified chemical is toxic to aquatic life. The most sensitive species are fish, where the acceptable acute 96 h LC50 is 1.6 mg/L.

Organism	***Duration***	***Endpoint***	***Concentration (mg/L)***
Rainbow trout* (*Oncorhynchus mykiss*)	96 h	LC50	1.26
		NOEC	0.89
Rainbow trout (*Oncorhynchus mykiss*)	96 h	LC50	1.6
		NOEC	0.51
Waterflea (*Daphnia magna*)	48 h	EC50	> 3.16
		NOEC	2.02
Alga (*Scenedes-mus subspicatus*)	96 h	E_bC50	>3.73
		E_rC50	>3.73

*The analytical method criteria were not met in this test and the test was repeated.

The Predicted No Effect Concentration (PNEC) is 16 µg/L, using a safety factor of 100, and the lowest acceptable acute 96 h LC50 for rainbow trout of 1.6 mg/L.

9.1.3. Environment – risk characterisation

Location	**PEC (µg/L)**	**PNEC (µg/L)**	**Risk Quotient (RQ)**
Australia-wide STPs (worst case)			
Ocean outfall	0.068	16	4.3 X 10^{-3}

Inland river	0.68	16	4.3×10^{-2}
After mitigation using SIMPLETREAT model*			
Ocean outfall	0.0054	16	3.4×10^{-4}
Inland river	0.054	16	3.4×10^{-3}

* 8%of the notified chemical remains in solution

Both sets of risk quotients indicate an acceptable risk (Q<1) for both marine and fresh water organisms.

The low Q values indicate that there is unlikely to be an environmental risk to the aquatic compartment. The low import volumes and the anticipated nationwide use of the notified chemical indicate that the levels of release of the chemical to the environment will be low and hence the notified chemical is unlikely to pose an unacceptable risk to the environment.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

Transport and Storage

Occupational exposure to the notified chemical during transport and storage of fragrance preparations containing the notified chemical is low considering the handling of sealed packages of imported fragrance preparations containing the notified chemical. Similarly, distribution, warehouse and retail workers will also have low exposure as these workers will only handle sealed products containing low concentrations of the notified chemical.

Formulation into end-use products

During reformulation of fragrance preparations containing the notified chemical into cosmetics and household products, dermal contact is the most likely route of exposure. Ocular exposure may also occur due to accidental splashes. Exposure may occur when workers open drums containing up to 10% notified chemical, when weighing and transferring, during blending operations and when cleaning up spills and the equipment. Blending operations can be in open or closed systems, however, the process is often automated and local exhaust ventilation is usually employed. All workers handling perfume preparations containing the notified chemical and involved in open mixing operations should wear suitable gloves, eye and face protection and protective clothing.

Dermal and inhalation exposure during formulation was estimated using the EASE model (HSE, 1994). Assuming non-dispersive use and intermittent direct-handling, the estimated dermal exposure during formulation is 0.1-1 mg/cm^2/day of the fragrance preparation containing up to 10% notified chemical. This equates to 0.01-0.1 mg/cm^2/day of the notified chemical. Absorption of the notified chemical may be significant, as the substance has a high $LogP_{ow}$, so ready diffusion across membranes would be expected. Therefore, for a 70 kg worker with surface area for hands at 820 cm^2 and forearms at 1140 cm^2, and assuming 100% absorption, systemic dermal exposure is estimated to be 0.28-2.8 mg/kg bw/day. This exposure would be substantially reduced by the use of protective clothing and gloves.

The atmospheric concentration of notified chemical during formulation was estimated using three different scenarios as tabulated below:

Scenario	ppm	mg/m^3	Fragrance prep with 10% notified chemical (mg/m^3)	Inhalation exposure (mg/kg bw/day)*
Open system, non-dispersive use, aerosol formation, LEV	10-50	110.8-554	11.08-55.4	1.646-8.23

Open system, non-dispersive use, no aerosol formation, LEV	0.5-3	5.54-33.2	0.554-3.32	0.082-0.493
Closed system, with or without aerosol formation	0-0.1	0-1.108	0-0.1108	0-0.016

* For a 70 kg worker, with an inhalation rate of 1.3 m^3/hour, an 8-hour exposure time (maximum worker exposure/day) and 100% bioavailability.

As exposure to the notified chemical is reported to be for a maximum of 4 hours per day, 2 days per year, for any individual worker the dermal and inhalation exposure will be proportionately reduced. Inhalation exposure to the notified chemical can be further reduced by the use of personal respiratory equipment.

End use products

Occupational exposure to end use consumer products containing the notified chemical may occur, for example, with professional cleaners using cleaning products, or beauticians using cosmetic products. These workers are less likely to use extensive personal protective equipment (PPE); however, the concentration of notified chemical in end use products will be 0.05% (except for fine fragrances, where it is up to 2%). While the products containing the notified chemical are likely to be used regularly, actual applications (eg dermal or aerosol) will only normally occur for very brief periods.

Using the EASE model, assuming wide dispersive use with extensive direct handling and continuous use of the products, the estimated dermal exposure to end use products is 5-15 mg/cm^2/day. This equates to 0.0025-0.0075 mg/cm^2/day for cosmetics and domestic products containing 0.05% notified chemical, and 0.1-0.3 mg/cm^2/day for fine fragrances containing 2% notified chemical. Therefore, for a 70 kg worker with affected area of 1960 cm^2 and assuming 100% absorption, systemic dermal exposure is therefore estimated to be 0.07-0.21 mg/kg bw/day for 0.05% notified chemical and 2.8-8.4 mg/kg bw/day for 2% notified chemical.

The estimated atmospheric concentrations of the notified chemical in the end use products are tabulated below:

Scenario	ppm	mg/m^3	Fine fragrance with 2% notified chemical (mg/m^3)	Cosmetic/domestic products with 0.05% notified chemical (mg/m^3)
Wide-dispersive use, aerosol formation, uncontrolled direct handling	500-1000	5540-11081	110.8-221.62	2.77-5.54
Wide-dispersive use, no aerosol formation, uncontrolled direct handling	200-500	2216-5540	44.32-110.8	1.108-2.77

For a 70 kg worker, with an inhalation rate of 1.3 m^3/hour, an 8-hour exposure time (maximum worker exposure/day) and 100% bioavailability, inhalation exposure is estimated to be 0.412 – 0.823 mg/kg bw/day for a wide dispersive use, direct handling and with aerosol formation; and 0.165 – 0.412 mg/kg bw/day for a wide dispersive use, direct handling and without aerosol formation.

9.2.2. Public health – exposure assessment

It is expected that during import, transport, storage, reformulation of fragrance compositions containing the notified chemical, exposure of the general public will be limited, except in the event of an accidental spill.

Consumer products containing the notified chemical (cosmetics/domestic products) will be sold in the public domain, consequently there is a potential for widespread public exposure. Exposure will be principally via dermal route. Systemic exposure to the notified chemical for cleaning products and cosmetics other than fine fragrances for a 70 kg person is similar to that of workers exposed to the end use products, which is estimated to be 0.07-0.21 mg/kg bw/day. As a worst case, inhalation exposure to the notified chemical when used as a fine fragrance is up to 32.9mg/kg bw/day and as a cosmetic/domestic product is up to 0.823 mg/kg bw/day. However, these assume 8 hour exposure, and the episodic nature of actual use will proportionately decrease exposure.

9.2.3. Human health – effects assessment

The notified chemical was of low acute oral and dermal toxicity in rats. In rabbits, the notified chemical is non-irritating to the eye or the skin. The notified chemical is not a skin sensitiser in an adjuvant study in guinea pigs. It is not mutagenic in bacteriological testing, and not clastogenic to human lymphocytes.

In a 28-day repeat dose oral toxicity study in rats, the NOAEL was 44 mg/kg bw/day, based on liver treatment related effects, which were confined to minor but predominantly adaptive changes at the higher dose groups. Hydrocarbon nephropathy as a result of excessive accumulation of α_2-microglobulin in renal proximal epithelial cells was observed in all treated male rats. However, this effect is a well-documented effect, peculiar to the male rat, which occurs in response to treatment with certain hydrocarbons, and such effect is not manifested in humans.

Based on the available data, the notified chemical is not classified as a hazardous substance in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2002).

9.2.4. Occupational health and safety – risk characterisation

The imported fragrance preparation containing the notified chemical will be reformulated into cosmetics, domestic products and fine fragrances. The formulation process is largely automated in a fully enclosed environment but manual intervention may also be required.

It should be noted that there is no inhalation study available, hence the following margin of exposure (MOE) calculations are based on the NOAEL (44 mg/kg bw/day) from the repeat dose oral study. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences.

For the reformulation of the fragrance preparation (10% notified chemical), the MOE for inhalation is tabulated below:

Scenario	Inhalation exp. (mg/kg bw/day)*	MOE
Open system, non-dispersive use, aerosol formation, LEV	1.646-8.23	5.3-26.7
Open system, non-dispersive use, no aerosol formation, LEV	0.082-0.493	89.2-536.6
Closed system, aerosol formation	0-0.016	>2750

* For a 70 kg worker, with an inhalation rate of 1.3 m^3/hour, an 8-hour exposure time (maximum worker exposure/day) and 100% bioavailability.

The scenario of reformulation in a closed system is the most relevant to the reformulation processes described for the notified chemical, the risk of which is acceptable, using modelled

worker data. However, the risk is not acceptable for workers handling the notified chemical in an open system. Occupational risk due to inhalation exposure can be further limited by the use of respiratory protection. The risks of chronic exposure are also limited by the predicted exposure frequency, which for reformulation workers is up to 2 days/year.

Based on the NOAEL of 44 mg/kg bw/day, the MOE for dermal exposure is calculated to be 15.7-157.1. Therefore, the use of PPE and appropriate engineering controls for workers handling the fragrance preparation is highly recommended.

For inhalation exposure to the end use products (2% notified chemical in fine fragrances and 0.05% notified chemical in cosmetic/domestic products), the MOE is tabulated below:

Scenario	Inhalation exp. of 2% notified chemical (mg/kg bw/day)*	MOE (for 2% notified chemical)	Inhalation exp. of 0.05% notified chemical (mg/kg bw/day)*	MOE (for 0.05% notified chemical)
Wide-dispersive use, aerosol formation, uncontrolled direct handling	16.46-32.9	1.3-2.7	0.412-0.823	53.5-106.8
Wide-dispersive use, no aerosol formation, uncontrolled direct handling	6.58-16.46	2.7-6.7	0.165-0.412	106.8-266.7

* For a 70 kg worker, with an inhalation rate of 1.3 m^3/hour, an 8-hour exposure time (maximum worker exposure/day) and 100% bioavailability.

In the case of the fine fragrances, aerosol formation is more relevant and should be used as the worst-case inhalation exposure. Though the risk to workers handling the fine fragrance without the use of PPE and engineering controls would seem unacceptable, it should be noted that an 8-hour inhalation exposure time to the fine fragrance would be unlikely and the exposure will be via short intermittent applications.

In the case of cosmetics and domestic products, no aerosol formation is the more likely scenario. With an MOE of greater than 100 for this type of exposure, the risk of systemic inhalation toxicity using modelled worker data is therefore acceptable.

The MOE for dermal exposure to the fine fragrances containing 2% notified chemical is calculated to be 5.2-15.7, and 209.5-628.6 for the cosmetic/domestic products with 0.05% notified chemical. Therefore, the risk to chronic systemic dermal toxicity using modelled worker data is not acceptable for wide dispersive use and uncontrolled direct handling of the fine fragrances containing the notified chemical, but acceptable for the other end use products. However, again, the dermal exposure to the fine fragrance will be through short intermittent applications, which should be taken into consideration in interpreting the calculated MOE.

A range of exposure scenarios has been covered above. Controls indicated by the notifier suggest that actual exposure conditions will approximate the scenario of enclosed systems with little to no dermal exposure. In addition, exposure is expected to be much less frequent than has been assumed in the calculations. However, in the absence of suitable engineering controls, the risk of high peak exposures would exist. Under the conditions specified by the notifier for reformulation and end use, the risk from exposure to the notified chemical, both dermal and by inhalation, will be low.

9.2.5. Public health – risk characterisation

It is expected that public exposure to the fragrance preparation containing up to 10% notified chemical for industrial use would be minimal except in the rare event of an accidental spill.

Public exposure will be through the use of the fine fragrances (2% notified chemical), domestic

and cosmetic products (0.05% notified chemical). Using the same toxicity data (NOAEL 44 mg/kg bw/day), the MOE for inhalation and dermal exposure will be similar to that calculated for workers handling the end use products. However, due to the low concentrations, the low quantities of product used, and the low frequency of use, public exposure will be further reduced compared with the worst-case occupational exposures predicted for the end use product. Hence, the public risk from exposure to the notified chemical through all phases of its life cycle 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 not classified as a hazardous substance under the NOHSC *Approved Criteria for Classifying Hazardous Substances*.

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.

According to the United Nations (2003) Globally Harmonised System for the Classification and Labelling of Chemicals, the notified chemical is categorised as **Chronic II** based on fish toxicity data.

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

10.3.2. Public health

There is Negligible Concern to public health when used as a fragrance ingredient in a variety of cosmetic and domestic products.

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

CONTROL MEASURES

Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical:
  - Closed system during mixing and blending of ingredients with fragrance preparations containing the notified chemical, particularly if aerosol formation is likely.
  - Local exhaust ventilation during mixing and blending of ingredients with fragrance preparations containing the notified chemical.

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical:
  - Prevent splashes and spills.

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:
  - Chemical resistant gloves, protective overalls and goggles/faceshield.
  - Personal respiratory equipment during mixing and blending of ingredients with fragrance preparations containing the notified chemical.

  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

- Do not allow material or contaminated containers to enter drains, sewers or water courses.

Disposal

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

Emergency procedures

- Gross spillages should be contained by the use of sand or inert powder and disposal of these materials should be in accordance with Local, State and Federal government regulations.
- Any absorbent used for cleaning up spillage should be disposed of promptly, preferably by incineration.

12.1. Secondary notification

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

(1) Under Section 64(2) of the Act
  – The importation volume of the notified chemical exceeds one tonne per annum.

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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