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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Romascone®

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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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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Firmenich Ltd (ABN 86 002 964 794)
73 Kenneth Road
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) permits issued in 1994, 1998 and 2001

NOTIFICATION IN OTHER COUNTRIES
USA (1992), Switzerland (1995), Canada (2003) and EU (1992, 2000)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Romascone®

3. COMPOSITION

DEGREE OF PURITY
>97 %

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 imported as a component of liquid compounded fragrances (maximum 1%), which will be reformulated in Australia to produce the final consumer products. In the consumer products, the concentration of the notified chemical will be a maximum of 0.2% in fine perfumes, and a maximum of 0.005% in other cosmetic products and domestic products.

4. INTRODUCTION AND USE INFORMATION

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

Year	*1*	*2*	*3*	*4*	*5*

Tonnes	0.050	0.075	0.100	0.125	0.150

USE
The notified chemical will be used as a fragrance ingredient in a variety of cosmetic 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
Firmenich Ltd
73 Kenneth Road
Balgowlah NSW 2093

TRANSPORTATION AND PACKAGING
The imported fragrance preparations containing the notified chemical will be transported by road from the wharf or airport of entry to the notifier's warehouse for storage. The 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. The notifier will distribute the fragrance preparations to local formulators by road. Locally manufactured consumer products will be delivered by road to retail distribution centers prior to distribution to retail outlets. The consumer products will be sold in a variety of small package sizes, typical of consumer size containers.

5.2. Operation description

The fragrance preparations containing the notified chemical will be reformulated at customer sites to produce domestic products in a continuous mixing process. A typical reformulation process will involve a regulated feed of the fragrance mixture into an automated system, followed by blending with other ingredients and packaging of the mixture. The imported fragrance preparation may require re-packaging prior to distribution.

Cosmetic products will be formulated in a batch process, which may involve open vessels and manual addition of the fragrance preparations containing the notified chemical. Usually, batches will be produced by blending all ingredients together in a large closed mixer, followed by automatic filling in containers of various sizes.

The individual consumer products will be sent to retail distribution centers for storage until distribution to retail outlets, beauticians and professional cleaners (using house hold cleaning products).

5.3. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Storage, maintenance and quality control (only if need arises to repack containers prior to distribution to local reformulators))	3	1	1
Warehouse/transport	5	2	2
Production line	5	4	2
Drum cleaning/washing	8	2	2
Maintenance	3	2	1
Quality assurance	2	0.5	1
Packaging of end-use product	8	4	2

Exposure Details

Transport and storage

Warehousing and transport of the notified chemical 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.

Formulation into end use products

Workers involved in the reformulation, and packaging of end use products may have dermal, inhalation and limited ocular exposure to the notified chemical when opening and closing fragrance containers or manually weighing and transferring the imported fragrance preparations into mixing vessels, during blending operations and when overfilling containers during packaging operations. Laboratory technicians may also be exposed to small amounts of the notified chemical when carrying out quality testing. Skin contamination of cleaners and maintenance workers can also occur when cleaning equipment and during routine maintenance.

Blending operations can be in open or closed systems, however, the process is often automated. Local exhaust ventilation is in operation during reformulation. Filling or packaging machines are enclosed and automated. Workers will wear suitable gloves, eye and face protection and protective clothing, and respiratory protection when handling the notified chemical.

Products packed in various container sizes will be sent to retail distribution centres for storage until distribution to retail outlets.

End-use products

Worker exposure to end use products may include professional cleaners (using house hold cleaning products) and beauticians (using cosmetics). These workers can be expected to use minimal PPE. However, the final concentration of the notified chemical in cleaning and cosmetic products (other than fine perfumes) will be at a maximum of 0.005%.

Except in the case of accident, workers handling the end-use products during distribution and retail would not be exposed to the notified chemical because of the closed containers, and even in the case of spills, the small packaging size and the low concentration of the notified chemical in the finished products would limit exposure.

5.4. Release

RELEASE OF CHEMICAL AT SITE

Since the notified chemical will not be manufactured locally, there will be no environmental exposure associated with this process in Australia. Environmental release of the notified substance is unlikely during importation, storage and transportation, and an accidental spill or leak is the most likely reason for environmental release. The size of the containers (180 kg and smaller) and the concentration of the notified chemical (maximum 1%) will limit the impact on the environment of accidental spills/leaks. The notifier expects a total of 0.1% of the notified chemical to be released as a result of spills.

Release of the notified chemical to the environment during blending of the cosmetic and household products is expected to be minimal due to the use of mostly automated and closed systems. Formulation equipment will be cleaned using water and the aqueous solution will be reused. After removal of the notified chemical by vacuum pump the average amount of residue in empty containers is estimated to be < 0.1%. Therefore, a total of 0.2% or up to 0.3 kg of waste notified chemical is expected to be generated each year as a result of formulation. The emptied import drums may be rinsed and re-used and drum rinse water may also be reused.

RELEASE OF CHEMICAL FROM USE

Since the notified chemical will be used in cosmetics, toiletries, household products, almost all of the notified chemical imported will enter the sewer when the products are washed off the hair and skin and due to household cleaning activities.

The percentage of notified chemical remaining in emptied consumer product containers will vary depending of size and type of the containers and the type of consumer product. It is estimated that the

notified chemical remaining in the consumer product containers to be less than 50 g per year (<0.03% of the maximum annual import volume). These containers will be mostly disposed of to landfill or recycled via domestic garbage collection.

5.5. Disposal

Disposal via incineration or landfill is recommended for wastes generated during the formulation of the products containing the fragrance preparations. The majority of the notified chemical will ultimately be disposed of in sewer with a minor amount disposed of to landfill. The emptied imported drums may potentially be rinsed and re-used, sent to a recycler, or disposed of to landfill through an approved waste management company. Drum rinse water may be reused. Emptied consumer product containers are disposed of through domestic garbage and hence will enter landfill or recycling.

5.6. Public exposure

Public exposure to the notified chemical as imported as a component of fragrance composition could only occur in the event of transport accident or spillage. The packaging will protect the contents from being released during normal handling. Similarly, public exposure during the reformulation process is unlikely.

However, widespread and repeated exposure to the public may occur as a result of day-to-day 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

Freezing Point < -21ºC

METHOD EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
TEST FACILITY SafePharm Laboratories Ltd (1997a)

Boiling Point 205 to 210ºC at 98.7 kPa

METHOD EC Directive 92/69/EEC A.2 Boiling Temperature.
TEST FACILITY Toxicol Laboratories Ltd (1992)

Density 962 kg/m^3 at 20ºC

METHOD EC Directive 92/69/EEC A.3 Relative Density.
Remarks Density was measured using the pycnometer method.
TEST FACILITY SafePharm Laboratories Ltd (1997a)

Vapour Pressure 0.027 kPa at 25ºC

METHOD EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks The vapour pressure was measured using an isoteniscope system. The temperature and pressure readings were obtained between 157°C and 212°C during a sequence of 3 runs. Linear regression was used to calculate the vapour pressure at 25ºC. The result indicates that the notified chemical is volatile (Mensink e*t al*, 1995).

The Henry's Law constant (H) was calculated from the molecular weight, the measured water solubility, and the measured vapour pressure according to the following equation: H = MW (g/mol) X Vapour Pressure (Pa)/Water Solubility (mg/L). H = 58.97 Pa m^3/mol, indicates that the substance is moderately volatile from water or moist soil (Mensink e*t al,* 1995).
TEST FACILITY SafePharm Laboratories Ltd (1997b)

Water Solubility 8.346 X 10^{-2}g/L at 20°C

METHOD EC Directive 84/449/EEC A.6 Water Solubility (Flask method).

Remarks The test report does not provide details of the method and results other than that mass concentration of the test substance in solution was determined by gas chromatography.

Based on Mensink e*t al* (1995) the results show that the test substance is moderately soluble.

TEST FACILITY Toxicol Laboratories Ltd (1992)

Fat Solubility Soluble in all proportions with standard fat (coconut oil) at 37°C

METHOD EC Directive 84/449/EEC A.6 Water Solubility (Flask method).

Remarks The proportions tested were 1:1, 1:3, 3:1, 1:5, 5:1, 1:9 and 9:1 by volume. No other details on the test were provided.

TEST FACILITY Toxicol Laboratories Ltd (1992)

Hydrolysis as a Function of pH Half-life >1 year

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

pH	*Estimated half-life at 25 °C*
4	>1 year
7	>1 year
9	>1 year

Remarks Sample solutions were prepared at a nominal concentration of 8 X 10^{-3} g/L in 3 buffer (filtered) solutions. A preliminary test and the definitive test were performed by maintaining the sample solutions at pH 4, 7 and 9 for a period of 5 days. The solutions were shielded from light whilst maintaining the temperature at 50°C.

The concentrations of the sample solutions were determined by gas chromatography. Less than 10% hydrolysis after 5 days at 50°C measured at each pH level was determined to be equivalent to a half-life greater than 1 year at 25°C.

TEST FACILITY SafePharm Laboratories Ltd (1999)

Partition Coefficient (n-octanol/water) Log P_{ow} = 4.10

METHOD EC Directive 92/69/EEC A.8 Partition Coefficient (HPLC Method).

Remarks A preliminary assessment of the $\log_{10} P_{ow}$ was made based on the approximate solubilities of the test substance in n-octanol and water (by visual assessment).

The dead time was determined by measuring the retention time of a solution of thiourea in methanol. Retention times of the sample solution, thiourea solution and six reference standards solutions, all in methanol, were measured and a calibration curve was constructed.

The high P_{ow} value indicates a high affinity for the organic component of soils and sediments.

TEST FACILITY SafePharm Laboratories Ltd (1997a)

Adsorption/Desorption Log K_{oc} = 3.06 (Estimated)

METHOD EC Directive 93/67/EEC

Remarks The log K_{oc} was calculated using the method to calculate QSAR for esters recommended by the EEC for various classes of organic compounds (European

Commission, TGD, Part III, 2003).

For esters, the QSAR is calculated as follows:

$$\text{Log } K_{oc} = 0.49 \text{ Log } P_{ow} + 1.05$$
$$= 3.06$$
$$K_{oc} = 1145.5$$

According to the Koc value the notified chemical has a low mobility (Mensink et al, 1995).

Dissociation Constant Not determined.

Remarks There are no groups likely to dissociate.

Surface Tension 69.5 mN/m at 21.0 ± 0.5°C
(For the 3.67 X 10^{-2} to 8.13 X 10^{-2} g/L solution).

METHOD EC Directive 92/69/EEC A.5 Surface Tension (Modified as mentioned below)

Remarks The determination was carried out using a surface tensiometer (based on the ISO 304 ring method), which complied with the above method except for the following deviation, which was not considered to have affected the integrity of the test. The surface tension result was not corrected using the Harkins-Jordan correction table, as the correction is not applicable to the apparatus used.

Surface tension readings were made at intervals until a constant reading (of the minimum force required to detach the ring from the surface of the liquid) was obtained. The sample solution analysis determined by HPLC showed loss of test substance during the study.

The test substance is not considered to be a surface-active material.

TEST FACILITY SafePharm Laboratories Ltd (1997a)

Particle Size Not determined

Remarks The notified chemical is a liquid.

Flash Point 78ºC

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

Remarks The determination was carried out using the Pensky-Martens Closed Tester according to the ASTM-IP method (ASTM D93-77-IP34/80).

TEST FACILITY Toxicol Laboratories Ltd (1992)

Flammability Limits Not determined

Remarks Based on the vapour pressure, the notified chemical is not expected to be a flammable liquid but is expected to be a combustible liquid.

Autoignition Temperature 342ºC

METHOD 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).

TEST FACILITY SafePharm Laboratories Ltd (1997c)

Explosive Properties Not explosive

METHOD EC Directive 92/69/EEC A.14 Explosive Properties.

Remarks A negative result was obtained for sensitivity to shock and to heat. The test for friction is not applicable to liquids.

TEST FACILITY SafePharm Laboratories Ltd (1997c)

Reactivity

Remarks	The notified chemical is expected to be stable under normal environmental conditions. The notified chemical does not have oxidising properties or other unusual reactivity based on the chemical structure.

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	moderately irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	limited evidence of sensitisation
Rat, repeat dose oral route toxicity – 28 days.	NOAEL 15 mg/kg bw
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro Mammalian Chromosome Aberration Test	non genotoxic

7.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 401 Acute Oral Toxicity. EC Directive 84/449/EEC B.1 Acute Toxicity (Oral).
Species/Strain	Rat/Crl:CD(SD)Br (VAF plus)
Vehicle	Polyethylene Glycol (PEG 400)
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	2000	0/10

LD50	> 2000 mg/kg bw
Signs of Toxicity	Piloerection was observed in all animals and hunched posture in most of them on the day of dosing but recovery had generally occurred by day 2. No effect on bodyweight.
Effects in Organs	At necropsy no abnormalities were found in any animal.
Remarks - Results	None.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Toxicol Laboratories Ltd (1991a)

7.2. Acute toxicity - dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity. EC Directive 84/449/EEC B.3 Acute Toxicity (Dermal).
Species/Strain	Rat/Crl:CD(SD)Br (VAF plus)
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 per sex	2000	0/10

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	
Signs of Toxicity - Systemic	Perinasal staining was noted in all animals, periorbital staining occurred in one female and piloerection was observed in all the males. All animals had recovered from the apparent effects of treatment by day 15. No effect on bodyweight.
Effects in Organs	There were no treatment related necropsy findings.
Remarks - Results	None.

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

TEST FACILITY Toxicol Laboratories Ltd (1991b)

7.3. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD EC Directive 84/449/EEC B.4 Acute Toxicity (Skin Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	4 females
Vehicle	Used as supplied
Observation Period	14 days
Type of Dressing	Semi-occlusive.
Remarks - Method	Additional assessments were carried out 7 and 14 days after dosing to determine if the skin responses were reversible.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Erythema/Eschar	1.44	3	14 days	2
Oedema	1.625	3	14 days	1

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

Remarks - Results

Erythema and oedema were noted on the backs of all animals 24 hours after the end of the dosing period. These skin responses developed progressively until the 72 hour observation period with erythema developed from well defined or moderate to severe, and oedema from slight to moderate.

At the 7 day observation period, oedema was reduced or absent in all animals and the severity of erythema had lessened in 2 of the 4 treated rabbits. Skin thickening was also noted in 3 animals.

At the 14 day observation period, erythema and oedema were absent in 3 of the rabbits but persisted, albeit at a reduced level, in the remaining rabbit. Slight skin thickening was evident in one rabbit.

CONCLUSION The notified chemical is irritating to the skin.

TEST FACILITY Toxicol Laboratories Ltd (1991c)

7.4. Irritation - eye

TEST SUBSTANCE	Notified chemical.
METHOD	EC Directive 84/449/EEC B.5 Acute Toxicity (Eye Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	4 females
Observation Period	72 hours
Remarks - Method	One animal was treated initially as a pilot.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	1.33	3	72 hours	0
Conjunctiva: chemosis	0.42	3	48 hours	0
Conjunctiva: discharge	0	2	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 ALL animals.

Remarks - Results	Administration of the test article produced an eye reaction characterised by conjunctival hyperaemia, chemosis and discharge in the treated eye of all 4 rabbits from one hour after dosing. This conjunctival irritation gradually reduced in intensity during the 72 hours following dosing and, by day 8, the treated eye of all 4 rabbits was free from apparent irritation. No corneal or iridial irritation was apparent in the treated eye of any animal at any examination during the study.
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	Toxicol Laboratories Ltd (1991d)

7.5. Skin sensitisation

TEST SUBSTANCE	Notified chemical
METHOD	EC Directive 84/449/EC B.6 Skin Sensitisation – Maximisation Test.
Species/Strain	Guinea pig/Albino, Dunkin-Hartley
PRELIMINARY STUDY	Maximum Non-irritating Concentration: intradermal: 25% in liquid paraffin topical: 100%
MAIN STUDY	
Number of Animals	Test Group: 20 Control Group: 10
INDUCTION PHASE	Induction Concentration: intradermal: 25% in liquid paraffin topical: 100%
Signs of Irritation	
CHALLENGE PHASE	
1st challenge	topical: 100% and 50% in ethanol
2nd challenge	topical: 100% and 50% in ethanol
Remarks - Method	Two dose range-finding studies via the intradermal route were performed to determine the appropriate concentrations for the main test.

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	100%	0/20	0/20	0/20	0/20
	50%	0/20	0/20	2/20	2/20
Control Group	100%	0/10	0/10	0/10	0/10
	50%	0/10	0/10	0/10	0/10

Remarks - Results: Two challenge applications were made. Following the first challenge, responses were zero for all test and control animals. The second application was made as it was noted during the first application that a number of patches became prematurely detached from the application sites. Following the second challenge, responses were zero for all test and control animals at the treated site of the undiluted test article, but 2 test animals exhibited responses scored as 1, at the application sites of the 50% concentration of test article.

CONCLUSION: There was limited evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY: Toxicol Laboratories Ltd (1991e)

7.6. Repeat dose toxicity

TEST SUBSTANCE: Notified chemical

METHOD: EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).

Species/Strain: Rat/Sprague-Dawley Crl:CD BR

Route of Administration: Oral – gavage.

Exposure Information: Total exposure days: 28 days;
Dose regimen: 7 days per week;
Post-exposure observation period: none

Vehicle: Arachis oil BP

Remarks - Method: No significant protocol deviations.

RESULTS

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

Mortality and Time to Death

There were no deaths during the study.

Clinical Observations

Animals treated with 1000 mg/kg/day showed increased salivation approximately two minutes after initial dosing and approximately 1 hour after dosing together with associated signs including red/brown staining of the external body fur, and fur wetting, which continued through out the study.

Bodyweights and bodyweight gains were unaffected by administration of the test article. Food and water consumption were not affected by treatment.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

No treatment related changes were detected in the haematological parameters measured. Females treated with 1000 mg/kg/day showed a slight but statistically significant reduction in bilirubin levels. No other changes in the clinical chemistry parameters were observed. Urinalysis was not conducted.

Effects in Organs

Animals treated with 1000 mg/kg/day showed an increase in liver weight, both absolute and relative to terminal bodyweight, in comparison with controls. A similar, but less marked effect on liver weight was detected for males treated with 150 mg/kg/day. Centrilobular hepatocyte enlargement was observed in animals treated with 1000 mg/kg/day with males from this group also showing an increase in the severity of periportal glycogen vacuolation of hepatocytes. Hepatocyte enlargements were also present in other treated groups and in one animal in the control group but in isolated occurrences.

Absolute and relative kidney weights were also elevated in males in the high dose group. Males in the high and mid dose groups showed speckled kidney at terminal kill. At necropsy, accumulations of globular eosinophilic material (hyaline droplets) were observed in male high and mid dose groups, and in one male in the low dose group.

Several incidents of dark areas, dark foci or pale areas on the lungs were observed in high dose animals.

Females treated with 150 and 15 mg/kg/day showed no treatment related changes in the organ weights measured.

Remarks – Results

The clinical observations are commonly reported following gavage administration of a test material formulation, and are considered to be attributable to an unpleasant tasting or slightly irritant formulation rather than an indication of systemic toxicity.

The reduction of bilirubin levels in high dose females is unlikely to be of toxicological importance since all individual values were within the normally expected range for animals of this strain.

Hepatocyte enlargement at mid and low dose groups were occasional and such effect is commonly observed in the rodent liver following administration of xenobiotics, and in the absence of associated inflammatory or degenerative change, is generally considered to be adaptive in nature.

The kidney finding is consistent with the appearance of hydrocarbon nephropathy, which results from excessive accumulation of α_2-microglobulin in renal proximal tubular epithelial cells, which is specific to male rats only.

CONCLUSION	The No Observed Adverse Effect Level (NOAEL) was established as 15 mg/kg bw/day in this study, based on liver treatment-related effects, which were confined to minor but predominantly adaptive liver changes at the high dose groups, and on the lack of human relevance of the renal observations in the male rats.
TEST FACILITY	SafePharm Laboratories Ltd (1998)

7.7. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100.
Metabolic Activation System	Rat liver S9 fraction from animals pretreated with β-naphthoflavone and sodium phenobarbitone
Concentration Range in Main Test	a) With metabolic activation: 1.6 to 1000 µg/plate. b) Without metabolic activation: 0.32 to 200 µg/plate.
Vehicle	Dimethylsulphoxide (DMSO)
Remarks - Method	A preliminary test was performed in TA98 to find the appropriate concentrations for the main test. Toxicity was observed at 200 µg/plate without S9 and at 1000 µg/plate with S9. Therefore these concentrations were the highest concentrations tested in the main test. Two independent mutation tests were performed for the main test.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥200 (TA98)	none	none	none
Test 2		none	none	none
Present				
Test 1	≥1000 (TA98)	1000 (TA100)	none	none
Test 2		none	none	none

Remarks - Results	In Test 1, a significant decrease in the number of revertant colonies in TA100 with S9 at the highest concentration was observed, which suggests that the test substance is toxic at this level. A statistically significant increase in revertant colonies (1.8 fold) compared with the relevant solvent control was also reported in TA1535 at 1.6 µg/plate without S9. Since the increase is non-dose response and non reproducible, the effect was considered as an artefact. No significant increase in the number of revertant colonies was recorded for any of the other bacterial strains at any dose, either with or without metabolic activation. Appropriate control values were within the background historical ranges, indicating that the test conditions were optimal and that the test system responded appropriately.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Toxicol Laboratories Ltd (1991f)

7.8. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test. EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.
Cell Type/Cell Line	Human lymphocytes

Metabolic Activation System	Rat liver S9 fraction from animals pretreated with Arochlor 1254
Vehicle	DMSO
Remarks - Method	An intermediate level of 170.63 µg/mL was used in all treatment groups in Test 2 to achieve an approximate 50% mitotic inhibition.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 14.22, 28.44*, 56.88*, 113.75*, 227.5, 455, 910 and 1820	4 hours	16 hours
Test 2a	0*, 14.22, 28.44*, 56.88*, 113.75*, 170.63* and 227.5	4 hours	16 hours
Test 2b	0*, 56.88, 113.75*, and 170.63	4 hours	40 hours
Present			
Test 1	0*, 14.22, 28.44*, 56.88*, 113.75*, 227.5, 455, 910 and 1820	4 hours	16 hours
Test 2a	0*, 14.22, 28.44*, 56.88*, 113.75*, 170.63* and 227.5	4 hours	16 hours
Test 2b	0*, 56.88, 113.75, and 170.63*	4 hours	40 hours

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*		
	Cytotoxicity in Preliminary	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	≥ 227.5	none	none
Test 2a	≥ 227.5	none	none
Test 2b	≥ 170.63	none	none
Present			
Test 1	≥ 227.5	none	none
Test 2a	≥ 227.5	none	none
Test 2b	≥ 170.63	none	none

Remarks - Results

Similar toxicity was observed in Test 1 and Test 2a, with greater toxicity observed at the extended time point (Test 2b).

No statistically significant increases in the frequency of cells with aberrations or polyploid cells were observed either in the presence or absence of metabolic activation and any dose level.

Appropriate positive controls induced large increases in the number of aberrant cells, indicating that the test system responded appropriately.

CONCLUSION

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

TEST FACILITY

SafePharm Laboratories Ltd (1997d)

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test and EC Directive 92/69/EEC C4.D.

Inoculum

A mixed population of activated sewage sludge micro-organisms from the aeration stage of a sewage treatment plant, which predominantly

	treats domestic sewage.
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Dissolved organic carbon (DOC) analysis on all control and reference material solutions and measuring daily oxygen consumption to determine the biological oxygen demand (BOD).
Remarks - Method	The test material was dispersed in culture medium with the aid of ultrasonic disruption and 2 mL of innoculum was added to give a final test concentration of 50 mg/L. This concentration is lower than that recommended in the Guideline of 100 mg/L of test substance/L giving at least 50-100 mg ThOD/L. In an initial experiment using a test substance concentration of 100 mg/L, the toxicity control failed to attain the ≥ 25% biodegradation by day 14 indicating that the test substance was inhibitory to the sewage sludge microorganisms at this concentration. Therefore, the test was repeated at the lower test substance concentration. In addition to the test sample, blank and toxicity control samples and samples containing a reference substance (aniline at 100 mg/L) were measured. DOC analysis of the test substance dispersions was not possible due to the insoluble nature of the test substance in water.

RESULTS

	% degradation	
Day	*Test substance**	*Aniline**
7	0	60
14	0	83
28	0	90

* Calculated from the oxygen consumption values.

Remarks - Results	The test substance attained 0% degradation after 28 days. The toxicity control attained 36% and 42% degradation after 14 and 28 days confirming that the test substance was not inhibitory to activated sludge bacteria under the test conditions. Degradation of the reference substance confirmed the suitability of the innoculum and validity of test conditions. The degradation rate for the reference material on day 28 (96%) calculated based on the DOC analysis was higher than that based on the oxygen consumption value of 90%. The report noted that this was considered to be due to incorporation of the reference material into the microbial biomass prior to degradation.
CONCLUSION	The notified chemical cannot be considered to be readily biodegradable according to the OECD criteria.
TEST FACILITY	SafePharm Laboratories (1997e)

8.1.2. Bioaccumulation

No bioaccumulation data were provided. The moderate water solubility, low molecular weight and high log Pow suggest a potential for the notified chemical to cross biological membranes and bioaccumulate (Connell 1990). However, the low import volume and dispersed use suggest that exposure will not be significant and this will limit the potential of the notified chemical to bioaccumulate.

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical

METHOD

OECD TG 203 Fish, Acute Toxicity Test and EC Directive 92/69/EEC C.1 Acute Toxicity for Fish – Semi-static.

Species: Rainbow trout (*Oncorhynchus mykiss*).

Exposure Period: 96 hours

Auxiliary Solvent: Dimethylformamide

Water Hardness: 100 mg $CaCO_3$/L

Analytical Monitoring: The concentration and stability of test substance in test solutions were verified by gas chromatography (GC) using an external standard technique. Duplicate samples from the solvent control and test solution vessels were obtained at 0, 24, 48, 72 and 96 hours (both fresh and old media as relevant).

Remarks – Method: A single concentration of 2.0 mg/L was selected for the definitive test following a preliminary range-finding study. A solvent stock solution was prepared in dimethylformamide. An aliquot of this solution was dispersed in dechlorinated tap water to give the test concentration.

The report stated that 2.0 mg/L was the highest attainable test concentration due to the limited solubility of the test substance in water and auxiliary solvent, and having due regard for the amount of auxiliary solvent permitted in the test under the OECD guidelines. At higher concentrations marked precipitation of the test substance occured when the solvent stock solution was added to water. This is inconsistent with the water solubility test result (summarised in Section 6) for the test substance of 83.46 mg/L (note few details provided).

A pre-study analysis of test solutions in open and closed vessels to assess losses of test substance due to volatalisation and a dosing trial to determine the suitability of dynamic, continuous flow conditions for the definitive study was performed. Oil globules were observed on the solution surface of the 2 mg/L concentration therefore, a semi-static regime was selected.

A significant loss (26%) of the test substance was observed in open vessels due to volatility. Each test vessel in the definitive study was completely filled to reduce headspace and sealed to reduce losses.

Oxygen content (7.0 to 9.8 mgO_2/L in control and 6.9 to 9.8 mgO_2/L in the test substance solutions), pH (7.3 to 7.5 in control and 7.2 to 7.5 in test solutions) and temperature (13.5 to 14°C in control and test solutions) were all satisfactorily maintained.

RESULTS

Concentration mg/L		*Number of Fish*	*Cumulative Mortality*				
Nominal	Time weighted mean measured		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	0	10	0	0	0	0	0
2.0	0.88 – 2.04	10	0	0	0	0	0

LC50: >1.5 mg/L at 96 hours (based on time weighted mean measured concentrations)

NOEC: 1.5 mg/L at 96 hours.

Remarks – Results: No abnormalities or sub-lethal effects were observed in the control or test media.

Analysis of the fresh test media showed the measured test concentrations to be in excess of the required 80% of nominal values except for in one replicate (at 0 hours) with a measured concentration of 67% of nominal.

This low value was considered to be due to sampling and/or analytical variation.

A marked decline in concentrations was observed for the 24 hour old test media ranging between 44% and 69% of nominal value, which was attributed to the suspected volatile nature of the test material. Therefore it was considered justifiable to base the results on the measured test concentrations.

CONCLUSION — The notified chemical is at worst toxic to fish.

TEST FACILITY — SafePharm Laboratories (1997f)

8.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE — Notified chemical

METHOD — OECD TG 202 Daphnia sp. Acute Immobilisation Test – Semi-static referenced as Method C.2 of EC Directive 92/69/EEC

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Dimethylformamide
Water Hardness	270 mg $CaCO_3$/L
Analytical Monitoring	The concentrations of test substance in test solution were verified by gas chromatography (GC) using an external standard technique. Duplicate samples for analysis were obtained at 0 and 48 hours
Remarks - Method	Based on a preliminary range-finding test the test solution for the definitive test was prepared using the same method used in the fish toxicity study (8.1.1). A single concentration of 2.0 mg/L was used, as it was the highest attainable test concentration with marked precipitation occurring at higher concentrations when solvent stock solution added to water (detailed above under Section 8.2.1). This is inconsistent with the water solubility test result (summarised in Section 6) for the test substance of 83.46 mg/L. Oxygen content (7.9 to 8.1 mgO_2/L in control and 8.0 to 8.2 mgO_2/L in the test substance solutions), pH (7.6 to 7.7 in control and test solutions) and temperature (21.0°C in control and test solutions) were all satisfactorily maintained.

RESULTS

Concentration mg/L Nominal	*Number of D. magna*	*% Immobilised*	
		24 h	*48 h*
Control	20	0	0
2	40	0	0

LC50	>2 mg/L at 48 hours
NOEC	2 mg/L at 48 hours
Remarks - Results	No immobilisation in daphnids exposed to the test solution was observed during the test period. Analysis of the fresh test media showed the measured test concentrations to be in excess of the required 80% of nominal values. No abnormalities or sub-lethal effects were reported in the control or test media.

CONCLUSION — The notified chemical is at worst toxic to *Daphnia magna.*

TEST FACILITY	SafePharm Laboratories (1997g)

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	72 hours
Concentration Range	
Nominal	2.0 mg/L
Actual	0.04 to 2.56 mg/L
Auxiliary Solvent	Dimethylformamide
Water Hardness	Standard medium was used.
Analytical Monitoring	The concentrations of test substance in test solutions at 0 and 72 hours were verified by gas chromatography (GC) using an external standard technique.
Remarks - Method	Based on a preliminary range-finding test the test solution for the definitive test was prepared using the same method used in the fish toxicity study (8.1.1). A single concentration of 2.0 mg/L was used, as it was the highest attainable test concentration. Marked precipitation (with oil globules forming on the water surface) occurred at higher concentrations when solvent stock solution added to water (detailed above under Section 8.2.1). This is inconsistent with the water solubility test result (summarised in Section 6) for the test substance of 83.46 mg/L.

RESULTS

Biomass		*Growth*	
E_bC_{50}* *mg/L at 72 h*	*NOEC** *mg/L*	E_rC_{50}* *mg/L (0-24) h*	*NOEC** *mg/L*
>0.63	0.63	>0.63	0.63

* Based on the time-weighted mean measured test concentrations.

Remarks - Results	The pH values increased from 7.5 at the beginning of the test up to 9.1 in the control and solvent control solutions and up to 9.2 in the test solutions. This increase exceeded the recommended maximum increase of 1.5 pH units but was attributed to the rapid growth of algal cells. This deviation from the guideline was not considered to have affected the integrity of the study results. The test temperature was maintained at 24°C. No cell abnormalities were observed in control or test cultures. Analysis of test solutions at 72 hours showed a marked decline in test concentrations (2% and 3% of nominal), therefore, the results are based on time-weighted mean measured test concentrations. Given that the test vessels were sealed with ground glass stoppers and the pre-study stability analysis showed the test material to be stable over the study period, the decline in measured test concentrations is considered to be due to adsorption to algal cells and possible loss due to volatility.
CONCLUSION	The notified chemical is at worst very toxic to green algae.
TEST FACILITY	SafePharm Laboratories (1997h)

8.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 87/302/EEC Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	A mixed population of activated sewage sludge micro-organisms from a sewage treatment plant, which predominantly treats domestic sewage.
Exposure Period	3 hours
Concentration Range Nominal	180, 320, 560, 1000 and 1800 mg/L
Remarks – Method	The test concentrations were determined based on the results of a preliminary range finding study. A reference material (3,5-dichlorophenol) was also tested at 3.2, 10 and 32 mg/L.
RESULTS	
EC50	900 mg/L at 3 hours
NOEC	180 mg/L at 3 hours
Remarks – Results	The EC50 of the reference substance at 3 hours was 12 mg/L, thus validating the test. These test results are not consistent with the results of the initial experiment conducted during the biodegradation study (Section 8.1.1), which indicated that the test substance is inhibitory to sewage sludge micro-organisms at 100 mg/L.
CONCLUSION	The notified chemical does not inhibit the respiration of activated sludge. However, considering the inconsistency mentioned above, the results of this study should be interpreted with caution.
TEST FACILITY	SafePharm Laboratories (1997i)

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

Nearly all of the imported notified chemical will eventually be released into the aquatic environment via the sewerage systems through formulation and use (washing off the skin, hair etc or cleaning activities) of the cosmetic and household products. Less than 1 kg per annum is expected to be disposed of to landfill as residue in empty consumer containers via domestic garbage.

The notified chemical is volatile and moderately volatile from water or moist soil, therefore, in part will dissipate into air from the surfaces to which the products containing it is applied (eg. skin, sewer, aquatic and terrestrial environments). It is moderately soluble in water but not expected to readily hydrolyse in natural waters at environmental pH values. There is an inconsistency between the water solubility test result of 83.46 mg/L and the highest water solubility attained (with the aid of a solvent) of 2 mg/L during the toxicity tests for fish, daphnia and algae (summarized under Section 8).

The high Pow indicates a high affinity for the organic component of the soils and sediments. The estimated high Log Koc indicates that the notified chemical will not be mobile in either the aquatic or terrestrial compartment. Therefore, the notified chemical has a potential to adsorb to particulate organic material and accumulate in sediments due to sorption and settlement. It is not readily biodegradable, however, when disposed of in landfill, the chemical can be expected to eventually become associated with soil and sediment and will slowly degrade through biological and abiotic processes.

Based on maximum annual imports of 150 kg per annum, and assuming a worst-case scenario that all of this is eventually released to sewer and not removed during sewage treatment processes, the daily release on a nationwide basis to receiving waters is estimated to be 0.41 kg/day. Assuming a national population of 20 million and that each person contributes an average 200 L/day to overall sewage flows, the worst-case predicted environmental concentration (PEC) in sewage effluent on a nationwide basis is estimated as 0.1027 µg/L (Environment Australia 2003). Based on the respective dilution factors of 0 and 10 for inland and ocean discharges of effluents, the PECs of the notified chemical in freshwater and marine water may approximate 0.1027 and 0.0103 µg/L, respectively.

The notified chemical is not readily biodegradable. The fate of the chemical in sewage treatment plants (STP) was examined using the SIMPLETREAT 3.0 model (European Commission 2003), which models partitioning and losses in STPs. The results indicate that when the chemical is released into the aqueous phase of a STP, about 42% (63 kg) released to air through volatilisation, 36% (54 kg) partitioned to water and 22 % (33 kg) partitioned to biosolids.

Based on these results assuming that 36% of the notified chemical (54 kg) remains in solution, the worst-case PEC for the aquatic environment resulting from the nationwide release of the notified chemical into the sewage systems is reduced to 0.037 µg/L prior to any dilution and the respective concentrations in freshwater and marine water may approximate 0.037 and 0.0037 µg/L.

Partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 0.2260 mg/kg (dry wt). 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 2.3×10^{-3} mg/kg in applied soil. This assumes that no degradation of the notified chemical occurs in the soil within 1 year from application. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated biosolids application, the concentration of notified chemical in the applied soil in 5 and 10 years may approximate 1.15×10^{-2} mg/kg and 2.3×10^{-2} mg/kg, respectively.

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 0.1 m of soil (density 1000 kg/m^3). Using these assumptions, irrigation with a concentration of 0.037 mg/L may potentially result in a soil concentration of approximately 4×10^{-4} mg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 2×10^{-3} mg/kg and 4×10^{-3} mg/kg, respectively.

There is potential for the notified chemical to bioaccumulate due to its high log P_{ow} and the moderate water solubility but this will be limited due to the low volume imported and diffuse release to the sewer Australia wide.

9.1.2. Environment – effects assessment

The results of the aquatic toxicity tests are listed below. The most sensitive species was algae with 72 hour EbC50 and ErC50 values of >0.63 mg/L.

Organism	Duration	End Point	mg/L
Fish	96 h	LC_{50}	>1.5 (mean measured)
Daphnia	48 h	EC_{50}	>2.0 (nominal)
Algae	72 h	E_bC_{50}	>0.63 (time-weighted mean measured)
		E_rC_{50}	>0.63 (time-weighted mean measured)

A predicted no effect concentration (PNEC - aquatic ecosystems) of >6.3 X 10^{-3} mg/L (>6.3 µg/L) has been derived by dividing the end point of >0.63 mg/L by a worst-case scenario uncertainty (safety) factor of 100 (as toxicity data are available for three trophic levels).

9.1.3. Environment – risk characterisation

Location	PEC µg/L	PNEC µg/L	Risk Quotient (RQ)
Australia-wide STPs			
Ocean outfall	0.0103*	>6.3	$<1.6 \times 10^{-3}$*
	0.0037#		$<5.9 \times 10^{-4}$#
Inland River	0.1027*	>6.3	$<1.6 \times 10^{-2}$*
	0.037#		$<5.9 \times 10^{-3}$#

* PEC and RQ values calculated assuming no removal in STP

\# PEC and the RQ values calculated assuming 22% and 36% of the notified chemical partitioned into biosolids and water, respectively (estimated based on the SIMPLETREAT model) during the STP process.

The RQ values (PEC/PNEC) for the aquatic environment, assuming nationwide use and that the chemical is not removed in STP, are below 1 for both freshwater and marine water, indicating no immediate concern to the aquatic compartment. Further, a large part of the notified chemical can be expected to be removed due to adsorption to sludge in STP and through volatilisation. considerably reducing the PEC and the RQ values. The RQ values based on the SIMPLETREAT model (assuming 42%, 36% and 22% will partition to air, water and sludge in STPs) as shown in the table above have been considerably reduced for both freshwater and marine water. Further amounts of the notified chemical can be expected to be adsorbed to sediments in aquatic environment reducing the PEC and the risk quotients.

Based on the proposed use pattern the notified chemical is not expected to pose an unacceptable risk to the health of aquatic life. Bioaccumulation is not expected from the diffuse use pattern and low import volume.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

Transport & 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 domestic cleaning products, dermal contact is the most likely route of exposure. Ocular exposure may also occur due to accidental splashes. Exposure to the notified chemical during filling of consumer product containers is expected to be minimal, as the filling of consumer containers is typically automated.

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 fragrance preparations containing up to 1% of the notified chemical. This equates to 0.001-0.01 mg/cm^2/day of the notified chemical. Absorption of the notified chemical may be significant, as the substance has a high Log P_{ow} and fat solubility 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 exposure is estimated to be 0.028-0.28 mg/kg bw/day of the notified chemical. This exposure would be substantially reduced by the use of protective clothing and gloves.

The estimated atmospheric concentration of notified chemical during formulation (1% notified chemical in fragrance preparations) is 7.5-15 mg/m^3 for an open system (non-dispersive use), with aerosol formation, and local exhaust ventilation (LEV). If no aerosols are formed, the estimated atmospheric concentration for an open system (non-dispersive use) with LEV is 0.4-0.7 mg/ m^3. For a closed system, even if aerosols are formed, the estimated atmospheric concentration is 0-0.007 mg/m^3. Therefore for a 70 kg worker, assuming an inhalation rate of

1.3 m^3/hour, a 4 hour exposure time (maximum worker exposure/day) and 100% bioavailability, inhalation exposure is estimated to be 0.56-1.11 mg/kg bw/day for an open system with aerosol formation and LEV; 0.030-0.052 mg/kg bw/day for an open system with LEV and no aerosol formation; and 0-0.0005 mg/kg bw/day for a closed system. Inhalation exposure to the notified chemical would 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 0.005% (except for fine fragrances, where it is up to 0.2%).

Using the EASE model, and assuming wide dispersive use with extensive, direct handling, the estimated dermal exposure to the end use product is 5-15 mg/cm^2/day. This equates to 0.0002-0.0008 mg/cm^2/day of notified chemical at 0.005% in most end use products. (The exception is fine fragrances, which contain up to 0.2% of notified chemical, and therefore would expose workers to 0.01-0.03 mg/cm^2/day of notified chemical. However, fine fragrances are not likely to be used occupationally.) For a 70kg worker with exposed surface area of 1960 cm^2 (hands and forearms) and assuming 100% absorption (as above), systemic exposure is therefore estimated to be 0.006-0.022 mg/kg bw/day of the notified chemical for cleaning products and cosmetics other than fine fragrances.

Based on the above results obtained from the modelled worker data, 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 being handled.

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, toiletries, household cleaning 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 70kg person is similar to that of workers exposed to the end use products, which is estimated to be 0.006-0.022 mg/kg bw/day.

Exposure to the notified chemical is considered minimal given the small amount of notified chemical in the final consumer products (maximum 0.005% other than fine fragrances, which have maximum 0.2%), and the intermittent exposure during use. For fine fragrances, the overall systemic exposure will be limited by the small volumes and skin areas involved.

9.2.3. Human health – effects assessment

The notified chemical is of low acute oral and dermal toxicity in rats. In rabbits, the notified chemical is a skin irritant but only a slight eye irritant. The notifier classified the notified chemical as a skin irritant due to irritation effects which were reversible within 14 days.

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 4-week repeat dose oral toxicity study in rats, the NOAEL was 15 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 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 preparations containing the notified chemical will be reformulated into cleaning and cosmetic products. The formulation process is largely automated but manual intervention may also be required. The notifier classified the notified chemical as a skin irritant.

During formulation, chronic systemic dermal exposure to the notified chemical was estimated to be 0.028-0.28 mg/kg bw/day. The margin of exposure (MOE) for chronic toxicity is based on a NOAEL of 15 mg/kg bw/day. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. For dermal exposure, the MOE is calculated to be greater than >536 during formulation. Therefore, the risk of chronic systemic toxicity using modelled worker data is acceptable for formulation workers handling fragrance preparations containing up to 1% notified chemical. Occupational risk due to dermal exposure can be further limited by the use of PPE specified in the MSDS.

Chronic systemic inhalation exposure during formulation was estimated to be 0.56-1.11 mg/kg bw/day for an open system with aerosol formation and LEV, 0.030-0.052 mg/kg bw/day for an open system with LEV and no aerosol formation, and 0-0.0005 mg/kg bw/day for a closed system. Based on a NOAEL of 15 mg/kg bw/day, the MOE for inhalation exposure is calculated to be 14--27 for an open system with aerosol formation and LEV, 288-500 for an open system with LEV and no aerosol formation, and more than 30000 for a closed system. Therefore, the risk using modelled worker data is acceptable for workers handling the notified chemical in an open system if no aerosols are formed; or, if aerosols are formed in a closed system. The risk using modelled worker data is not acceptable for workers handling the notified chemical in an open system if aerosols are formed. 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.

Dermal exposure to end use products containing up to 0.005% notified chemical is estimated to be 0.006-0.022 mg/kg bw/day. Using the same toxicity data (NOAEL of 15 mg/kg bw/day), the MOE is calculated to be greater than 681. Therefore the risk to workers handling end use products in the absence of PPE is acceptable.

9.2.5. Public health – risk characterisation

It is expected that public exposure to compounded fragrances containing up to 1% notified chemical for industrial use will be minimal except in the rare event of an accidental spill.

Public exposure will arise from using the cleaning and cosmetic products containing up to 0.005% notified chemical, and fine fragrances at 0.2% notified chemical. The exposure is expected to be widespread and repeated.

As a worst case scenario, systemic dermal exposure to end use products containing the highest concentration of the notified chemical (up to 0.2% in fine fragrances) is estimated to be 0.0056-0.056 mg/kg bw/day. Using the same toxicity data (NOAEL of 15 mg/kg bw/day), the MOE is calculated to be greater than 267. Therefore, the risk to public using the end use products without dermal protection is acceptable. Consequently 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

The notifier has indicated that the notified chemical is classified as hazardous. The classification and labelling details are:
R38 – Irritating to skin.

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.

Skin Corrosion/Irritation Category 3
Symbol: None
Signal word: Warning
Hazard statement: Causes mild skin irritation

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, provided closed systems or personal respiratory equipment are used for any reformulation operations.

10.3.2. Public health

There is No Significant Concern to public health when used as an ingredient in consumer products as described in the notification.

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

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - ≥ 20%: R38 - Irritating to skin

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 during formulation of fragrance preparations containing it into consumer products:
  - 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.

Disposal

- The notified chemical should be disposed of to landfill.

Emergency procedures

- Gross spillages should be contained by the use of sand or inert powder. Any absorbent rags used for cleaning up spills should be disposed of promptly, preferably by incineration.

- Do not discharge directly into drains, soil or the aquatic environment.

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

(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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