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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Benzenebutanenitrile,α,α,γ-trimethyl (Khusinil)

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Director

Chemicals Notification and Assessment

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FULL PUBLIC REPORT

Bezenebutanenitrile,α,α,γ-trimethyl (Khusinil)

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
International Flavours and Fragrances Australia Ltd of 301 Frankston-Dandenong Road Dandenong South VIC 3175 (ABN 77 004 269 658)

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

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: dissociation constant and reactivity

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
LVP 441, August 8, 2002

NOTIFICATION IN OTHER COUNTRIES
US EPA: Premanufacture Notification 1/22/99
EC: United Kingdom 96-00-0000-04, 1996
Environment Canada: Schedule 1, NSN 11825, August 16, 2002

2. IDENTITY OF CHEMICAL

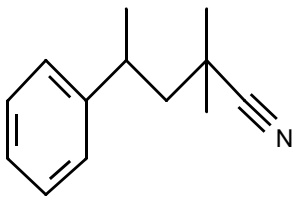
CHEMICAL NAME
Benzenebutanenitrile, α, α, γ-trimethyl

MARKETING NAME(S)
Khusinil

CAS NUMBER
75490-39-0

MOLECULAR FORMULA
$C_{13}H_{17}N$

STRUCTURAL FORMULA



MOLECULAR WEIGHT

187.14

METHODS OF DETECTION AND DETERMINATION

ANALYTICAL METHOD: UV, IR, NMR and Gas Chromatography

3. COMPOSITION

DEGREE OF PURITY
98-99.9%

HAZARDOUS IMPURITIES
None identified

NON HAZARDOUS IMPURITIES (>1% by weight)

CHEMICAL NAME	Unidentified minor closely related isomers and intermediates		
CAS No.	Unidentified	*Weight %*	≤1.7%

ADDITIVES/ADJUVANTS

CHEMICAL NAME	p-cresol-2,6-di tertiary butyl		
CAS NO.	128-37-0	*Weight %*	0.1-0.3%

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
Imported as part of a finished fragrance oil or in an end-use consumer product.

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

Year	*1*	*2*	*3*	*4*	*5*
Kilograms	150	150	350	500	500-1000

USE
The notified chemical (Khusinil) will be used as an odourant in cosmetics and household products. The concentration of Khusinil in the imported fragrance oil is at a maximum of 3%. The concentration of Khusinil in the end-use consumer products is 0.02-0.2%

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, Transport and Storage

PORT OF ENTRY
Melbourne

IDENTITY OF MANUFACTURER/RECIPIENTS
International Flavours and Fragrances Australia Ltd

TRANSPORTATION AND PACKAGING
Khusinil will be imported into Australia as a component of fragrance oils in sealed polypropylene lined steel drums (200 L). Khusinil will be transported from the docks by road to the notifier's warehouse.

5.2. Operation Description

The fragrance oil containing Khusinil will be blended with other ingredients to form end-use consumer

products such as alcoholic perfumes, cosmetics and household products. Consumer products are usually manufactured by automated systems.

5.3. Occupational Exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Mixer	5	4 hr	2 days/year
Quality control worker	2	0.5 hr	2 days/year
Packager	10	4 hr	2 days/year
Maintenance	5	4 hr	2 days/year

Exposure Details
Only workers qualified and trained in the safety of handling chemicals and chemical mixtures should be permitted to work with the mixtures containing this material.

The manufacturing of consumer products is typically automated. However, workers may have potential for exposure during mixing, packaging, cleaning of equipment and sampling for quality control purposes. They will handle both imported fragrance oil containing <3% Khusinil and the final consumer products containing 0.02-0.2% Khusinil. Coveralls, gloves and safety glasses are expected to be worn by workers at formulation facilities.

5.4. Release

RELEASE OF CHEMICAL AT SITE
Release of the chemical is not expected at the IFF warehouse site. Release from the reformulation facilities is anticipated to be extremely low given the concentration of Khusinil in the imported fragrance oils.

Release to the environment during reformulation would result from residual material in the imported containers, which would be rinsed and discharged off to the sewer. Little material is expected to be lost during the formulation into the consumer product since the processes are mainly automated.

RELEASE OF CHEMICAL FROM USE
Since Khusinil will be used in household, laundry and personal cleaning products, almost all (~97%) of Khusinil will end up in the sewer. Approximately 1% of the Khusinil imported is expected to be lost as residues in consumer containers, which are primarily landfilled.

For the portion of Khusinil that reaches the sewerage treatment plants, the proportion which partition to the different environmental compartments were estimated using the STP Fugacity Model. These estimates based on the chemical having a calculated Henry's Law Constant of 1.27×10^{-5} atm m^3/mol indicate that Khusinil would be expected to partition to air, water and sewage sludge as follows:

Air: 0%
Water ~90%
Sludge ~10%

5.5. Disposal

Any spills of the notified chemical will be contained using absorbent material, placed into sealed containers and disposed of in accordance with current applicable laws and regulations.

The notified chemical will ultimately be disposed of in either the sewer (major) or landfill. The emptied import drums may potentially be rinsed and re-used, sent to a recycler, or sent to landfill for disposal. Drum rinse waters may be reused, discharged to an on-site wastewater treatment plant and/or the sewer. Following use, emptied consumer product containers are expected to be disposed of through domestic garbage disposal from where they will enter landfill or a recycling program.

5.6. Public Exposure

Public exposure from transport, storage, reformulation or disposal is negligible.

Cosmetics and household products are designed to be sold to the public. The general public will repeatedly make dermal contact and possibly accidental ocular contact with Khusinil via a number of different consumer products. Due to its low level of presence in the products, the overall daily exposure to Khusinil will be low.

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa Clear, colourless liquid with characteristic aroma.

Melting Point/Freezing Point < -25 ºC

METHOD EEC Directive 92/69/EEC, Annex V, Part A, Method A.1, in accordance with British Standard 4633:1970.
TEST FACILITY Huntingdon Life Sciences Ltd (1996a).

Boiling Point Decomposes at 268.5-276ºC at 101.3 kPa

METHOD EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks The test substance darkened slightly when boiling commenced, with the distillate of a colourless liquid as the same colour as the original sample. The last remaining drops of the test substance decomposed to a dark brown liquid with the emission of white fumes, which distilled as a light yellow liquid.
TEST FACILITY Huntingdon Life Sciences Ltd (1996a).

Density 939.05 g/m^3

METHOD EC Directive 92/69/EEC A.3 Relative Density.
TEST FACILITY Huntingdon Life Sciences Ltd (1996a).

Vapour Pressure $7.5x10^{-4}$ kPa at 25ºC

METHOD EEC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks The vapour pressure was determined using a vapour pressure balance, which measured mass differences at several temperatures. Three runs were completed with Run 2 yielding a curved vapour pressure relationship; therefore the rounded mean of runs 1 and 3 were used to give the above value. The result indicates that the notified chemical is moderately volatile (Mensink e*t al*. 1995).

An estimated boiling point value of 287.51ºC (by the adapted Stein and Brown Method) and an estimated melting point value of 48.08ºC (the mean of estimates from the Adapted Joback Method and the Gold and Ogle Method) were used to estimate the vapour pressure using MPBPWIN v1.40. Three vapour pressure estimates were derived using the Antoine Method, Modified Grain Method and Mackay Method and the results of the Modified Grain method was selected ($3.09x10^{-4}$ kPa).

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 = 1.29 Pa m^3/mol, also indicates that the substance is moderately volatile (Mensink e*t al*. 1995).

The Henry's Law constant estimate derived using the notifier's estimate of vapour pressure was $1.6x10^{-4}$ Pa m^3/mol, which is significantly smaller than the above value based on the measured vapour pressure value. Three vapour pressure runs were completed. Run 2 yielded a curved vapour pressure relationship; therefore the rounded mean of runs 1 and 3 were used to give the reported vapour pressure

value.

TEST FACILITY University of Leeds, Leeds, England (1996).

Water Solubility 109 mg/L at 20ºC

METHOD EC Directive 92/69/EEC A.6 Water Solubility (Stir-Flask Method)

Remarks About 0.05 g of the test substance was added to 100 mL distilled water and the samples were stirred at 30±0.5ºC up to 3 days followed by equilibration for one day at 20±0.5ºC before centrifuging at 12,000 rpm for 10 minutes. The concentration of the test substance in the aqueous phase was determined by gas chromatography.

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

A water solubility estimate of 38.7 mg/L was also obtained by applying estimated and measured log P_{ow} values to the QSAR program WSKOW (v1.40).

TEST FACILITY Huntingdon Life Sciences Ltd (1996a).

Hydrolysis as a Function of pH The half-life times at 25ºC are greater than one year at pH 4 and 7, and between one day and one year at pH 9.

METHOD EEC Directive, 92/69/EEC, Annex V, Method C.7

Remarks After 5 days at 50ºC under the preliminary test conditions (50 mg/L), no significant hydrolysis of Khusinil occurred at pH 4, but 12% and 19% hydrolysis occurred at pH 7 and 9, respectively. Three further tests were performed with test 1 used to determine the order of reaction of hydrolysis and test 2 used for non-first order behaviour. Under test 1 conditions, Khusinil was found to undergo a pseudo first order reaction, therefore test 3 was carried out at 60 and 70ºC at pH 7 and 9. Rate constants were then calculated and extrapolated to 25ºC.

TEST FACILITY Huntingdon Life Sciences Ltd (1996b).

Partition Coefficient (n-octanol/water) log Pow at 20ºC = 3.34

METHOD EC Directive 92/69/EEC A.8 Partition Coefficient (Shake-Flask Method).

Remarks The stock solution used in the tests contained 0.35285 g of test substance in 200 mL water saturated n-octanol (concentration 1764.3 µg/mL). Tests were performed by shaking 10, 20 and 40 mL of the stock solution (each in duplicate) with 50 mL of octanol-saturated water for 20 minutes at 20±0.5ºC. The test phases were separated by centrifuging the samples for 15 minutes at 2500 rpm. Aliquots of both phases were analysed by gas chromatography.

The high P_{ow} value indicates a high affinity for the organic phase.

TEST FACILITY Huntingdon Life Sciences Ltd (1996a).

Adsorption/Desorption log K_{oc} = 3.38 (estimated using PCKOC Program v1.66)
log K_{oc} = 3.05-3.38 (estimation)*

METHOD The log K_{oc} value was estimated using PCKOC Program (v1.66).

* Sources of this range of values were indicated to be Kenaga/Goring Correlation (1980), Hodson/Williams Correlation (1988) and Computer Estimation, Syracuse Research Corporation, however, reports or references to these sources werenot provided.

Remarks Khusinil appears to have a Koc greater than 1000 indicating that it would be highly bound to organic matter in soil.
According to the estimated K_{oc} value, the notified chemical is slightly mobile (Mensink e*t al*. 1995).

TEST FACILITY Huntingdon Life Sciences Ltd (1996a).

Dissociation Constant Not determined.

Remarks Khusinil is expected to be stable in water and is not subject to dissociation, as it does not contain any dissociable group.

Particle Size Not applicable. This material is a liquid.

Flash Point 126ºC at 1012 mbar

METHOD EC Directive 92/69/EEC A.9 Flash Point.
Remarks A flash point of 126 ºC was recorded for both tests at an atmospheric pressure of 1012 mbar. A blue halo was observed around the test flame at 110 ºC and 114 ºC (Test 1 and 2 respectively).
TEST FACILITY Huntingdon Life Sciences Ltd (1996a).

Flammability Limits Khusinil was found not to possess flammable properties

METHOD EC Directive 84/449/EEC A.12 Flammability (Contact with Water) and A.13
TEST FACILITY Huntingdon Life Sciences Ltd (1996a).

Autoignition Temperature 446ºC

METHOD 92/69/EEC /A.15 Auto-Ignition Temperature
TEST FACILITY Huntingdon Life Sciences, Ltd (1996a).

Explosive Properties Not possess explosive properties under the condition of the tests.
METHOD EC Directive, Annex V, Part A, A.14 Explosive Properties.
TEST FACILITY Huntingdon Life Sciences Ltd (1996a).

Reactivity Khusinil is expected to be stable in water and air under normal conditions of temperature and pressure.

Surface Tension 57.9mN/m at 19ºC

METHOD EC Directive 92/69/EEC A.5 Surface Tension.
Remarks The surface tension of a 90% saturated aqueous solution of the notified chemical was determined using a surface tension/torsion balance and the OECD harmonised ring method. Measurements were made at two minute intervals until a constant reading was obtained three times in succession to within 0.1 mN/m.

The results indicate that the notified chemical is marginally surface active.
TEST FACILITY Huntingdon Life Sciences Ltd (1996a).

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral	Harmful, LD50 = 1693 mg/kg bw
Rat, acute dermal	Low toxicity, LD50 > 2000 mg/kg bw
Rabbit, skin irritation	Non-irritating
Rabbit, eye irritation	Slightly irritating
Guinea pig, skin sensitisation - adjuvant test	No evidence.
Rat, oral repeat dose toxicity - 28 days.	NOEL=15 mg/kg/day, NOAEL=150 mg/kg/day
Genotoxicity - bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro Chromosome aberration	non clastogenic

7.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 401 Acute Oral Toxicity – Limit Test. EC Directive 92/69/EEC B.1 Acute Toxicity (Oral)
Species/Strain	Rat/CD Rat – Sprague-Dawley origin
Vehicle	None

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 Male	2000	3
2	5 Female	2000	4
3	5 Female	1600	2
4	5 Female	1000	0

LD50: 1693 mg/kg bw

Signs of Toxicity: Two females at 1600 mg/kg and 3 males and 4 females at 2000 mg/kg died during the study. Deaths occurred from within 4 hours of treatment until day 2.

Piloerection was observed in all rats within 5 minutes of dosing and throughout the remainder of Day 1. This sign persisted and was accompanied on day 1 and/or at later intervals by

- hunched posture in all rats at 1000 and 1600 mg/kg, and in 5 animals at 2000 mg/kg
- abnormal gait in all rats at 1000 mg/kg
- lethargy in all rats at 1000 mg/kg and in 3 males 2000 mg/kg
- decreased respiratory rate in 4 rats at 1000 mg/kg and in 1 male and 1 female at 2000 mg/kg
- partially closed eyelids in 2 rats at 1600 mg/kg and in 1 female at 2000 mg/kg
- pallor of the extremities in all rats at 1000 mg/kg and in 2 rats at 1600 mg/kg
- tonic convulsions in 1 rats at 1000 mg/kg and in 2 rats at 1600 mg/kg
- increased lachrymation in 1 rat at 1000 mg/kg
- soft to loose faeces in all females at 2000 mg/kg
- clonic convulsions in 1 male and 2 females at 2000 mg/kg
- increased salivation in 1 rat at 1000 mg/kg and in all rats at 1600 and 2000 mg/kg
- walking on toes in 4 males at 2000 mg/kg
- unsteadiness in 2 rats at 1000 mg/kg and in 4 males and 5 males at 2000 mg/kg
- body tremors in 4 rats at 1000 mg/kg, 1 rat at 1600 mg/kg and in 4 males and 5 females at 2000 mg/kg
- hyperactivity in 2 females at 2000 mg/kg
- protruding eyes in 3 rats at 1000 mg/kg and in 3 males and 4 females at 2000 mg/kg
- excitable behaviour in 2 rats at 1000 mg/kg and in all females at 2000 mg/kg
- prostration in 2 rats at 1600 mg/kg and in 1 male at 2000 mg/kg

Recovery of surviving rats, as judged by external appearance and behaviour, was complete by either Day 3 (1600 mg/kg and females at 2000 mg/kg) or by day 4 (1000 mg/kg and males at 2000 mg/kg). Satisfactory bodyweight gains were achieved throughout the study by all surviving rats.

Effects in Organs	Macroscopic examination of all decedents at 2000 mg/kg revealed a darkened appearance of the liver. No macroscopic abnormalities were observed for animals killed on day 15.
CONCLUSION	Khusinil is harmful via the oral route.
TEST FACILITY	Huntingdon Research Centre Ltd (1996a).

7.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 402 Acute Dermal Toxicity EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal)
Species/Strain	Rat/CD Rat-Sprague-Dawley
Vehicle	None
Type of dressing	Occlusive

RESULTS

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

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	There were no signs of dermal irritation at any of the application sites of Khusinil.
Signs of Toxicity - Systemic	There were no signs of systemic reaction to treatment
Effects in Organs	Terminal autopsy revealed no macroscopic abnormalities.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	Huntingdon Research Centre Ltd (1996b).

7.3. Irritation – skin

TEST SUBSTANCE	Notified chemical.
METHOD	EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation). OECD Guideline for Testing of Chemicals No. 404, Acute Dermal Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White
Number of Animals	Three
Vehicle	None
Observation Period	Four days
Type of Dressing	Semi-occlusive.
RESULTS	Draize scores for both erythema/eschar and oedema were zero for all the test animals during the study.
CONCLUSION	The notified chemical is non-irritating to skin.
TEST FACILITY	Huntingdon Life Sciences Ltd (1996c).

7.4. Irritation – eye

TEST SUBSTANCE — Notified chemical.

METHOD — EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).
OECD Guideline for Testing of Chemicals No. 405, Acute Eye Irritation/Corrosion

Species/Strain — Rabbit/New Zealand White
Number of Animals — Three
Observation Period — Fourteen days

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	0.33	1.0	1.0	2	3	0
Conjunctiva: chemosis	0	0	0	3	1	0
Corneal opacity	0	0	0	0	0	0
Iridial inflammation	0	0	0	0	0	0

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

CONCLUSION — The notified chemical is slightly irritating to the eye.

TEST FACILITY — Huntingdon Life Sciences Ltd (1996d).

7.5. Skin sensitisation

TEST SUBSTANCE — Notified chemical.

METHOD — EC Directive 92/69/EEC B.6 Skin Sensitisation – Magnusson and Kligman
OECD Guideline for Testing of Chemicals No. 406, Skin Sensitization

Species/Strain — Guinea pig/Dunkin/Hartley
PRELIMINARY STUDY — Maximum Non-irritating Concentration:
topical: 100%

MAIN STUDY
Number of Animals — Test Group: 10 Control Group: 5
induction phase — Induction Concentration:
intradermal: 7.5%v/v in Alembicol D
topical: 100%
Signs of Irritation — Intradermal injection: Necrosis was recorded at sites receiving Freund's Complete Adjuvant in test and control animals. Slight irritation was seen in test animals at sites receiving Khusinil, 7.5% v/v in Alembicol D and slight irritation was observed in control animals receiving Alembicol D alone.
Topical application: Slight erythema was observed in test and control animals.

CHALLENGE PHASE
1st challenge — topical application: 100%
topical application: 50%v/v in Alembicol D

Remarks – Method

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after challenge:*		
	%	*24 h*	*48 h*	*72 h*
Test Group	100	0/10	0/10	0/10
	50	0/10	0/10	0/10

Control Group	100	0/5	0/5	0/5
	50	0/5	0/5	0/5

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

TEST FACILITY — Huntingdon Life Sciences Ltd (1996e).

7.6. Repeat dose toxicity

TEST SUBSTANCE — Notified chemical.

METHOD — OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
EC Directive 92/69/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).
Joint directive of the Japanese Environmental Protection Agency and the Ministries of Health and Welfare and International Trade and Industry, 5 December 1986.

Species/Strain	Rat, Sprague-Dawley
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28days; Dose regimen: 7 days per week; Post exposure observation period: 14 days
Vehicle	Corn Oil

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	5M, 5F	0	0
II (low dose)	5 M, 5F	15	0
III (mid dose)	5M, 5F	150	0
IV (high dose)	5M, 5F	500	1
V (control recovery)	5M, 5F	0	1
VI (high dose recovery)	5M, 5F	500	0

Mortality and Time of Death

One high-dose female died on day 15 due to a dosing error. One control male was dead on day 44 from an anaesthetic accident during blood sampling procedure.

Clinical Observations

Higher than control water consumption was noted for female rats, and to a lesser extent, for male rats at the high dose level during week 3. Water consumption was still higher than control for high dosage group female rats during the second week of recovery.

There were no other toxicologically important clinical signs noted throughout the study.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

At termination higher globulin levels (and hence higher total protein and lower A/G ratio) and lower alkaline phosphatase levels were recorded for female rats receiving 500 mg/kg/day.

Macroscopic Findings

At termination, enlargement of the liver was noted in 3/5 male and 3/5 female rats receiving 500 mg/kg/day, and 1/5 male receiving 150 mg/kg/day. These findings were not present following a 2-week recovery period.

The liver weights for male and female rats receiving 500 or 150 mg/kg/day were higher than control at the end of the treatment period. Following a 2 week recovery period, liver weights (females) and kidney weights (males) were higher for high dosage group rats than for controls.

Microscopic Findings

Treatment related changes in rats receiving 500 or 150 mg/kg/day included centrilobular hepatocyte enlargement in the liver of male and female rats and renal cortical tubules with eosinophilic inclusions in male rats at the end of treatment. Lower incidences of these changes among rats following a 2 week recovery period showed partial reversibility of these changes. Centrilobular hepatocyte necrosis was also seen in one accidental death female rat receiving 500 mg/kg/day.

Remarks – Results

The target organs in rats treated with Khusinil were liver and kidneys. The findings in the liver indicated an adaptive effect. The effects noted in the kidneys are not considered relevant to man.

CONCLUSION

The No Observed Effect Level (NOEL) for Khusinil was determined to be 15 mg/kg/day, and The No Observed Adverse Effect Level (NOAEL) for Khusinil, 150 mg/kg/day.

TEST FACILITY Huntingdon Life Sciences Ltd (1996f).

7.7. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 471/472 Bacterial Reverse Mutation Test.
EEC Directive 92/69/EEC B.13 Mutagenicity – Reverse Mutation Assay Using E. coli
EEC Directive 92/69/EEC B.14 Mutagenicity – Reverse Mutation Test using Salmonella typhimurium

Species/Strain *S. typhimurium* TA1535, TA1537, TA 1538, TA98 and TA100
Escherichia coli WP2 uvr A

Metabolic Activation System S-9 mix from liver homogenate of Arochlor 1254 induced rats

Concentration Range in Main Test a) With metabolic activation: 156.25-5000 µg/plate.
b) Without metabolic activation: 156.25-5000 µg/plate.

Vehicle Dimethylsulfoxide

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Present	5000			
Test 1		2500	Not observed	Not observed
Test 2		2500	Not observed	Not observed
Absent	5000			
Test 1		2500	Not observed	Not observed
Test 2		2500	Not observed	Not observed

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

TEST FACILITY Huntingdon Life Sciences Ltd (1996g).

7.8. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 473 In vitro Mammalian Chromosomal Aberration Test.
EEC Directive 92/69/EEC, Annex V, Method B10

Cell Type/Cell Line Human lymphocytes

Metabolic Activation System Liver Homogenates (S-9mix) from Arochlor 1254 induced rats

Vehicle Dimethylsulfoxide

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Present			
Test 1	1000, 500, 250*, 125*, 62.5, 31.25*, 15.6, 7.8, 3.9, 2.0	3 hr	18 hr
Test 2 -trial 1	500, 400, 300, 250, 200, 150*, 125*, 62.5, 31.25*, 15.6	3 hr	18 hr
-trail 2	1000, 750, 500, 375, 250*, 187.5, 125*, 62.5, 31.25*, 15.6	3 hr	32 hr
Absent			
Test 1	1000, 500, 250, 125*, 62.5*, 31.25, 15.6*, 7.8, 3.9, 2.0	3 hr	18 hr
Test 2 -trial 1	300, 250, 200, 150, 125*, 100, 62.5*, 31.25, 15.6*, 7.8	3 hr	18 hr
-trail 2	1000, 500, 250, 125*, 62.5*, 31.25, 15.6*, 7.8, 3.9, 2.0	3 hr	32 hr

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Present	> 250			
Test 1	-	-	>250	Not observed
Test 2-trial 1	-	> 150	>150	Not observed
-trial 2	-	> 250	>187.5	Not observed
Absent	> 125			
Test 1	-	-	>250	Not observed
Test 2-trial 1	-	> 125	>250	Not observed
-trial 2	-	> 125	>250	Not observed

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

TEST FACILITY — Huntingdon Life Sciences Ltd (1996h).

7.9. Skin sensitisation – human volunteers

TEST SUBSTANCE — Khusinil 3% in Alcohol SD 39C:diethylphthalate (DEP) (75:25)

METHOD

Study Design	Human Repeated Insult Patch Test
Study Group	Fifty-three panelists
Vehicle	Alcohol SD39C:diethylphthalate
Induction Procedure	Ten 24-hour occlusive applications of sample to the same site on the skin at 3 times per week. An alternative site was used if samples evoked irritation under conditions of the test.
Rest Period	Following the induction period the subjects did not receive any application of sample for approximately two weeks.
Challenge Procedure	Applications of sample to the original site and to naïve site to test for reaction indicative of contact sensitization. Each site was evaluated at 24, 48 and 72 hours after challenge.

RESULTS

Remarks – Results	No irritation was observed during induction periods. After challenge, observations of both sites treated with test substance remained negative. At the 48 hour challenge observation, one subject exhibited a mild erythema to the negative control.

CONCLUSION — A human repeated insult patch test was conducted using 3% Khusinil in alcohol:DEP under occlusive dressing. The notified chemical was non-irritating and non-sensitizing under the conditions of the test.

TEST FACILITY — Consumer Product Testing Co. (1995).

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test. EEC Directive 92/69/EEC, Annex V, Method C4-E
Inoculum	Activated Sewage Sludge predomiantly of domestic origin
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Dissolved Oxygen Concentrations were determined by means of a Yellow Spring BOD Meter (Model 59)
Remarks – Method	In addition to the test sample, blank sample and samples containing a reference substance were measured. Nitrate and nitrite analyses were done to assess the extent of any nitrification (as the test substance contains a significant amount of nitrogen).

RESULTS

Test substance		*Sodium Benzoate*	
Day	*% degradation*	*Day*	*% degradation*
4	5	4	70
7	5	7	78
11	8	11	81
14	8	14	65
18	14	18	69
21	44	21	77
25	38	25	74
28	46	28	81

Remarks – Results	The total oxygen consumption was corrected for nitrification (0.066 mg O_2/L) to obtain the true oxygen consumption value for carbonaceous biodegradation. The biodegradation of sodium benzoate validated the test conditions. The test substance was not found to be inhibitory to activated sludge bacteria under the test conditions.
CONCLUSION	The notified chemical is not considered to be readily biodegradable according to the OECD ten day window criteria requiring ≥ 60% degradation within 10 days after achieving 10%.
TEST FACILITY	Huntingdon Life Sciences Ltd (1996i).

8.1.2. Ready biodegradability

TEST SUBSTANCE	Notified chemical.
METHOD	EEC Directive 92/62/EEC Method C4-D OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Secondary effluent from a trickling filter plant that predominantly treats domestic sewage.
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Dissolved organic carbon (DOC) and total organic carbon (TOC).
Remarks - Method	A 5 day preliminary bacterial inhibition test was performed under the

conditions of the Closed Bottle test (EC Procedure C.4-E; OECD 301D) to determine whether the notified chemical at a nominal concentration of 100 mg/L inhibited the normal degradation of the inoculum on the reference substance sodium benzoate.

In the main test in addition to the test sample, blank sample and a samples containing a reference substance were measured.

RESULTS

Day	*% degradation*		
	Test substance		*Sodium benzoate*
	Replicate I (Cell 4)	*Replicate II (Cell 5)*	
1	-0.5	-0.8	34.4
4	-1.7	-2.2	66.4
7	-2.2	-3.0	76.4
11	-2.1	7.2	78.3
13	0.6	23.1	80.3
15	24.0	24.5	81.4
18	24.0	24.5	81.4
21	26.4	28.2	85.1
25	28.1	29.7	87.9
28	29.1	29.7	88.8

Remarks - Results

In the preliminary test, the notified chemical at 100 mg/L did not inhibit degradation of the reference material sodium benzoate and showed no evidence of biodegradation.

Biodegradation of sodium benzoate of 89% after 28 days validated the conditions of the main test. The mean levels of biodegradation of the notified chemical were 12% and 29 % after 4 and 28 days, respectively.

CONCLUSION

The notified chemical is not considered to be readily biodegradable according to the OECD ten-day window criteria requiring ≥ 60% degradation within 10 days after achieving 10%.

TEST FACILITY

Huntingdon Life Sciences Ltd (2000).

8.1.3. Bioaccumulation

Data regarding the bioaccumulation potential of the notified chemical were not provided. The moderate water solubility, and high P_{ow} suggest a potential for the notified chemical to cross biological membranes and bioaccumulate (Connell 1990). However, the low import volume and dispersed use suggest exposure will not be significant and limit this potential. Further, an estimated BCF value of 74.44 obtained by using the estimated and measured log K_{ow} values in the BCF Program (v2.14) indicates a low potential for bioconcentration.

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE

Notified chemical.

METHOD

OECD TG 203 Fish, Acute Toxicity Test Rainbow trout, semi-static
EC Directive 92/69/EEC C.1 Acute Toxicity for Fish, Rainbow trout, semi-static

Species	*Oncorhynchus mykiss*
Exposure Period	96 hr
Auxiliary Solvent	None
Water Hardness	159 mg $CaCO_3$/L
Analytical Monitoring	Test concentration verified by GC analysis

Remarks – Method: The test media were renewed daily. The temperature and pH were satisfactorily maintained. The dissolved oxygen levels for the 3 highest concentrations were below 60% of the air saturation value recommended at 24 hours, but were considered not to have a significant effect upon the mortalities.

RESULTS

Concentration mg/L		*Number of Fish*	*Cumulative Mortality*				
Nominal	*Actual*		*3h*	*24h*	*48h*	*72h*	*96h*
Control	Control	10	0	0	0	0	0
1.0	0.86	10	0	0	0	0	0
1.6	1.4	10	0	0	0	0	0
3.2	2.7	10	0	0	0	0	0
5.6	4.9	10	0	6	6	6	6
10	8.4	10	0	8	8	8	8

LC50: 4.6 mg/L at 96 hours.
NOEC (or LOEC): <0.86 mg/L at 96 hours.
Remarks – Results: All results are expressed in terms of measured concentrations. Values ranged from 87-103% of nominal at 0 hours, 40-70% of nominal at 24 hours, 99-112% of nominal at 72 hours and 86-97% of nominal at 96 hours.

Marked reactions to exposure other than mortality were increased pigmentation, lying on the bottom, hyperventilation, loss of equilibrium and moribundity.

CONCLUSION: The notified chemical is toxic to Rainbow trout.

TEST FACILITY: Huntingdon Life Sciences Ltd (1996j).

8.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE: Notified chemical.

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

Species: *Daphnia magna*
Exposure Period: 48 hours
Auxiliary Solvent: None
Water Hardness: Standard medium was used.
Analytical Monitoring: Test concentration verified by GC.
Remarks – Method: Elendt M7 Medium prepared using analytical grade reagents and reverse osmosis purified water was used as test water. Oxygen content, temperature and pH were satisfactorily maintained. The test vessels were sealed to minimise loss of test substance due to volatilisation.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
0.3125	0.700	20	0	0
0.625	0.850	20	0	0
1.25	2.8	20	0	1
2.5	2.6	20	0	0
5.0	4.2	20	0	0
10	7.5	20	6	7
20	19	20	20	20

EC50	12 mg/L
NOEC (or LOEC)	4.2 mg/L at 48 hours
Remarks – Results	All results are expressed in terms of measured concentrations which ranged from 68-229% of nominal at 0 hours and 78-224% of nominal at 48 hours. However, it should be noted that the measured concentrations of the biologically relevant levels (i.e. those concentrations used to generate the EC50 values, 0 and 100% immobilisation concentrations) remained within a much narrower range from 68-102% of nominal at 0 hours and 78-96% of nominal at 48 hours. The highest percentage deviations from the nominal were observed in the lowest test exposure levels (0.3125-1.25 mg/L). This is not expected to affect the validity of the results given that the geometric means for the biologically relevant levels remained within the range 75-96% of nominal.
CONCLUSION	The notified chemical is harmful to *Daphnia magna*.
TEST FACILITY	Huntingdon Life Sciences Ltd (1996k).

8.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	EEC Directive 92/69/EEC, Annex V, Part C, Method C.3, Algal Inhibition test and OECD TG201, Alga, Growth Inhibition Test
Species	*Selenastrum capricornutum*
Exposure period	72 hours
Nominal concentration range	2.3, 5, 11, 23, and 50 mg/L
Actual concentration range	2.6, 4.5, 11, 21 and 40 mg/L
Auxiliary solvent	None
Water hardness	Standard sterile nutrient medium was used.
Analytical monitoring	Test concentration verified by GC analysis
Remarks – Method	The mean pH shift in the control cultures over the study period was recorded as 2.3 units, this was higher than recommended (1.5 units). This was not considered to have affected the integrity of the results given the increase in cell densities was in excess of 40 fold.

RESULTS

Biomass - E_bC50 *mg/L at 72 h*	*Growth - E_rC50* *mg/L at 0-72 h*	*NOEC* *mg/L at 72 h*
11	12	4.5

Remarks – Results	All results are based on measured concentrations. Values ranged from 90-149% of nominal at 0 hours and 71-88% of nominal at 72 hours. No abnormalities were detected at concentrations ≤ 11 mg/L, however, cells were observed to be increasingly pallid at the higher concentrations (21 and 40 mg/L) and cell debris was present.
CONCLUSION	The notified chemical is harmful to *Selenastrum capricornutum*.
TEST FACILITY	Huntingdon Life Sciences Ltd (1996l).

8.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	EEC Directive 87/302/EEC Annex VIII, Part C and OECD TG 209 - Activated Sludge, Respiration Inhibition Test

Inoculum	A mixed population of activated sewage sludge micro-organisms
Exposure period	3 hours
Nominal concentration range	100 mg/L (in duplicate)
Remarks – Method	A positive control (3,5-dichlorophenol) was tested at 3.2, 10 and 32 mg/L. Due to the limited solubility of the test substance it was considered unrealistic to test a concentration higher than 100 mg/L.

RESULTS

EC50	> 100 mg/L
NOEC	100 mg/L (highest concentration tested)
Remarks – Results	The respiration rates of the 2 controls were within 15% of each other and the EC50 value of 3,5-dichlorophenol at 3 hours (10.5 mg/L) was within the acceptable range of 5-30 mg/L, thus validating the test.
CONCLUSION	The notified chemical is not inhibitory to microbial respiration.
TEST FACILITY	Huntingdon Life Sciences Ltd (1996m).

8.2.5 Aquatic toxicity predictions

The following acute aquatic toxicity values predicted based on the structure activity relationships were provided.

ECOSAR Class	*Organism*	*Duration*	*End Point*	*Predicted mg/L*
Neutral organics	Fish	96-h	LC50	7.637
Neutral organics	Fish	96-h	LC50	3.344
Neutral organics	Daphnid	48-h	LC50	8.977
Neutral organics	Green Algae	96-h	EC50	6.062

These estimates were based on a user entered experimentally derived log K_{ow} of 3.34 and a measured water solubility of 109 mg/L, and therefore, may be expected to have moderate to good reliability. The estimates are in reasonable agreement with the measured data.

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

Since the notified chemical is moderately volatile, it will dissipate into air from the surfaces where the products containing the fragrance oil has been applied (eg. skin, aquatic and terrestrial environments). The notified chemical is moderately soluble in water. It will not readily hydrolyse in natural waters at environmental pH values nor will readily biodegrade. However, due to its high P_{ow} the notified chemical has a potential to adsorb to particulate organic material and therefore accumulate in sediments due to sorption and settlement. The notified chemical is expected to be slightly mobile in soils and groundwater due to its estimated Log K_{oc} of 3.38.

Minor quantities may be released during formulation, storage, handling and transportation, (eg. uncontained spills and leaks) resulting in discharges to land or aquatic environments. The majority of the wastes generated is expected to be discharged to sewer or sent to landfills for disposal. In landfills, the notified chemical may present in residues of disposed emptied containers or in sludges derived from wastewater treatment plants, and formulation or drum recycling facilities. Given the low import volume and the low concentration of the notified chemical in the fragrance oil, container residues may potentially constitute up to 10 kg of the notified chemical per annum. Over time, the notified chemical residue in the container and unstabilised sludge may dissolve and mobilise in leachate, although sorption to organic matter is expected to occur.

Nearly all of the notified chemical in the cosmetic and household products will eventually be released into the aquatic environment via the sewerage systems through washing of the skin, hair etc or cleaning activities. The predicted environmental concentration (PEC) in the aquatic environment is estimated using a worst-case scenario, assuming that all 1000 kg of the notified chemical used is discharged into sewerage systems

throughout Australia and none is attenuated within these systems. Australia has a population of ~19.5 million people, and an average value for water consumption of 200 L/person/day has been adopted for this national-level assessment (3900 ML/day for total population). Therefore, the concentration of notified chemical in the Australian sewerage network may approximate 0.7 μg/L (ie. $1000x10^6$ mg ÷ 365 days/year ÷ $3900x10^6$ L). Based on dilution factors of 1 and 10 for inland and ocean discharges of sewage treatment plants (STP)-treated effluents, outfalls, PECs of the notified chemical in freshwater and marine surface waters may approximate 0.7 μg/L and 0.07 μg/L, respectively.

The results obtained using the SIMPLETREAT model (European Commission 1996) for modelling partitioning and losses in sewage treatment plants indicate that when the chemical is released into the aqueous phase of a STP, about 1% released to air through volatilisation, about 80% partitioned to water, 19% partitioned to biosolids and 20% degraded. The results obtained from a STP Fugacity Model provided by the notifier predicts that 89.5% of the notified chemical will partition to water.

Assuming 80% of the notified chemical (800 kg) may potentially remain in solution, the following PECwater and PECsoil values were obtained (Environment Australia 2003). The worst-case scenario daily predicted environmental concentration (PEC) for the aquatic environment resulting from the nationwide release of the notified chemical into the sewage systems is reduced to 0.56 μg/L prior to any dilution.

Partitioning to biosolids in STPs Australia-wide may result in an average biosolids dry concentration of 1.33 mg/kg. Effluent re-use concentration may potentially approximate $5.6x10^{-4}$ mg/L. 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 0.01 mg/kg in applied soil. This assumes that 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 0.067 mg/kg and 0.133 mg/kg, respectively.

Concentration in effluent		0.56 μg/L	
Concentration in biosolids		1.33 mg/L	
PECwater (μg/L) with 100% release to:			
		Ocean	River
100% population		0.06	0.56
PECsoil (mg/kg) (assumes no degradation)			
		Recycled water	Application of biosolids
Soil concentration	1 year	0.0056	0.0133
	5 years	0.028	0.067
	10 years	0.056	0.133

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 $5.6x10^{-4}$ mg/L may potentially result in a soil concentration of approximately 0.0056 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 0.028 mg/kg and 0.056 mg/kg, respectively.

Bioaccumulation is not expected from the proposed low level of import and diffuse use pattern, although the largely hydrocarbon structure, moderate water solubility and high log P_{ow} indicate a potential to bioaccumulate. However, the low import volume and dispersed use pattern is expected to limit its bioaccumulation potential as supported by modelling.

9.1.2. Environment – effects assessment

Using the lowest end point (ie. the LC50 value of 4.6 mg/L for fish), a predicted no effect concentration (PNEC-aquatic ecosystems) of 4.6 x 10^{-2} mg/L (46 μg/L) has been derived by dividing the EC50 value by a worst-case scenario uncertainty (safety) factor of 100.

Organism	*Duration*	*End Point*	*mg/L*
Fish	96-h	LC50	4.6
Daphnia	48-h	EC50	12
Algae	72-h	E_bC50	11
		E_rC50	12

9.1.3. Environment – risk characterisation

Location	PEC	PNEC	Risk Quotient (RQ)
Australia-wide STPs			
Ocean outfall	7×10^{-5} mg/L	4.6×10^{-2} mg/L	1.52×10^{-3}
	(5.62×10^{-5} mg/L) #		(1.22×10^{-3}) #
Inland River	7×10^{-4} mg/L	4.6×10^{-2} mg/L	1.52×10^{-2}
	(5.62×10^{-4} mg/L) #		(1.22×10^{-2}) #

PEC and RQ values calculated assuming 19% of the notified chemical partitioned into biosolids and 80% partitioned into water during the STP process based on SIMPLETREAT model.

The risk quotient values estimated based on the worst-case scenario of discharging the entire amount of the notified chemical imported into sewage systems in Australia are less than 1. Therefore, the proposed use of the notified chemical is unlikely to pose an unacceptable risk to the aquatic life.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

The notified chemical will be imported as a component of fragrance oils at 3%, and a maximum concentration of 0.2% of the notified chemical will be contained in the final product.

Formulation of the household or cosmetic products containing the notified chemical will occur at a number of sites in Australia. Dermal, ocular and/or inhalation exposure may occur during formulation processes, particularly during weighing and transfer of fragrance oil to a mixing vessel. However, exposure to significant amounts of the notified chemical is limited as the process is largely enclosed and automated, and engineering controls such as local exhaust ventilation are in place. In addition, adequate personal protective equipment is expected to be worn by workers.

Exposure to the notified chemical during use of the imported products containing the notified chemical would be low due to the low concentration of the chemical in the products.

During transport, storage, and retailing, workers are unlikely to be exposed to the notified chemical except when packaging is accidentally breached.

Occupational exposure is also estimated by the EASE (Estimation and Assessment of Substance Exposure) program developed by the Health and Safety Executive, UK (1997). The results showed that dermal exposure would be lower if a closed system is used and the contact is controlled at intermittent level.

EASE Prediction	
Physical state	Liquid
Temperature	25°C

Vapour pressure	0.00075 kPa	
The volatility of the substance	Very low	
The ability-airborne-vapour of the substance	Very low	
Inhalation exposure		
The control level	Without ventilation	Local exhaust ventilation
The predicted gas/vapour/liquid aerosol exposure	0-0.1 ppm	0-0.1 ppm
Dermal exposure		
The use-pattern	- Wide dispersive use - Direct manual sampling	- Closed system - Non-dispersive use - Directly manual sampling
The contact-level	Extensive	Intermittent
The predicted dermal exposure (product)	5-15 mg/cm2/day	0.1-1 mg/cm2/day
The predicted dermal exposure (notified chemical)	0.15-0.45 mg/cm2/day	0.003-0.03 mg/cm2/day

9.2.2. Public health – exposure assessment

As the notified chemical is an ingredient of various cosmetic and household products, including soaps, shampoos, body lotions, sun creams, hairsprays, washing liquids, surface cleaners, deodorants and air fresheners, to be sold throughout Australia, public exposure is expected to be widespread.

Consumers will be exposed to cosmetic products containing the notified chemical, as they will be applied directly to the body. The consumers may also be exposed to the notified chemical in household products during application of the products or from residual product on the packaging component. Dermal and some ocular contact are the likely routes of exposure. Inhalation exposure in the case of aerosol products such as air fresheners and hair spray may also occur.

The maximum concentration of the notified chemical in the products is 0.23%. Based on the use levels of cosmetic products, typical amount of daily application is approximately 7.5 g/application for body lotion, 10 g/application for hairspray and 3 to 6g /day for soaps with exposure to the notified chemical per product less than 0.069 mg/kg bw/day.

	Body lotion	Hairspray	Soap
Amount per application	7.5 g	10 g	3 g
Exposure frequency	Daily	Daily	6 time/day
Amount of notified chemical	17.25 mg	23 mg	41.4 mg
Body weight	60 kg		
Estimated dose	0.29 mg/kg/day	0.38 mg/kg/day	0.69 mg/kg/day
Dermal absorption	10 %		
Systemic dose	0.029 mg/kg/day	0.038 mg/kg/day	0.069 mg/kg/day

Allowing for the presence of the notified chemical in several products used in the course of the day, exposure is likely to be low, with the majority rinsed-off with water.

Skin exposure to the residue remaining on the fibres after application of detergents and softeners is negligible. Given the small amounts used per application and the low concentration of the chemical in the products, public exposure to the notified chemical is determined to be low.

The likelihood of consumers being exposed to the notified chemical as it occurs in consumer products during shopping/purchasing is considered low.

9.2.3. Human health - effects assessment

The notified chemical is harmful via oral route (LD_{50}=1693 mg/kg). It is of low acute dermal toxicity (LD_{50} > 2000 mg/kg). The notified chemical is not a skin irritant or skin sensitiser, but is

slightly irritating to eyes. The NOEL from a 28-day study is established as 15 mg/kg/day based on the changes in livers and kidneys at higher dose levels. It was found to be non-mutagenic in an Ames test and non-clastogenic in an in-vitro study in human lymphocytes.

A human repeated insult patch test showed that the notified chemical was non-irritating and non-sensitising at 3% in humans.

9.2.4. Occupational health and safety – risk characterisation

The notified chemical is harmful via oral route. However workers will not receive exposure to the chemical at concentrations above 3%, and they are unlikely to ingest the notified chemical or the products containing the notified chemical. The most likely route of exposure is expected to be via the dermal route.

Due to the highly automated nature of the formulation and production process, there is not expected to be any significant worker exposure during these processes. Workers responsible for the connection and disconnection of pumps and hoses for transferring the fragrance oil and the rinsing of empty fragrance oil drums, may be exposed to small quantities of the fragrance oil containing <3% notified chemical. Worker exposure is minimized during these processes by wearing industrial coveralls, safety goggles and protective gloves.

On the basis of low exposure of workers to the notified chemical, low concentration of notified chemical in the fragrance oil, the risk to occupational health and safety is considered low.

Workers involved in the use of products containing the notified chemical are not considered to be at significant health risk due to the low concentration of notified chemical in the products. (≤0.23%).

9.2.5. Public health – risk characterisation

The notified chemical has some potential to cross biological membranes. However, as only small amounts of product are generally used in cosmetic and household applications together with the presence of low concentration of the notified chemical in the finished products, the risk to public health is determined to be low.

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

10.1. Hazard classification

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

R22 Harmful if swallowed

According to the Globally Harmonised System for the Classification and Labelling of Chemicals (UN, 2003), the notified chemical is categorised as:

	Hazard category	*Hazard statement*
Acute toxicity	4	Warning: Harmful if swallowed
Chronic hazards to the aquatic environment	2	Toxic to aquatic life with long lasting effects

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 use pattern.

10.3. Human health risk assessment

10.3.1. Occupational health and safety

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

10.3.2. Public health

There is Low Concern to public health when the notified chemical is used based on its reported use pattern.

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, 1994a). 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, 1994b). The accuracy of the information on the label remains the responsibility of the applicant.

12. RECOMMENDATIONS

REGULATORY CONTROLS
Hazard Classification and Labelling

- The NOHSC Chemicals Standards Sub-committee should consider the following health hazard classification for the notified chemical:
  - R22: Harmful if swallowed

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - [≥ 25%]: R22: Harmful if swallowed

CONTROL MEASURES
Occupational Health and Safety

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical in the imported fragrance oils:
  - Protective clothing
  - Gloves
  - Goggles or safety glasses

  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

Disposal

- The notified chemical should be disposed of to landfill according to local regulations.
- Avoid disposing into drains and waterways.

Emergency procedures

- When spilled can contaminate soil and ground and surface water. Gross spillages should be contained using sand or inert powder and earth.
- Collect and seal in properly labelled drums for disposal in accordance with relevant Government regulations.
- Report spill to appropriate authorities if required.
- Prevent runoff into drains and waterways.

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 over 1 tonne per annum of the notified chemical is introduced in Australia, a test report on adsorption/desorption is required to be submitted for the 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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