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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

OZOFLEUR

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Director
Chemicals Notification and Assessment

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OZOFLEUR

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT
International Flavours and Fragrances (Australia) Pty Ltd
310 Frankston South Victoria, Australia 3175

NOTIFICATION CATEGORY
Limited: Polymer with NAMW ≥ 1000 (greater than 1 tonne per year).

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT
None

NOTIFICATION IN OTHER COUNTRIES
Spanish Competent Authority (1998); United States (1998); Currently under notification in Canada.

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
Cyclohexane, 1-(1,1-dimethylpropyl)-4-ethoxy-, cis-
Cyclohexane, 1-(1,1-dimethylpropyl)-4-ethoxy-, trans-

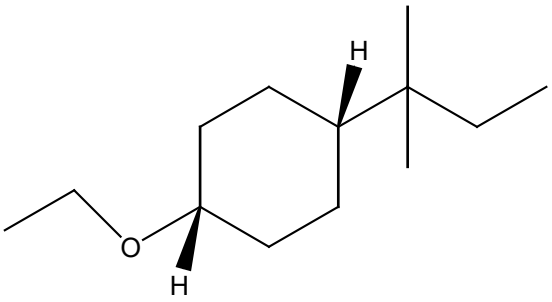
OTHER NAME(S)
Ozofleur

CAS NUMBER
181258-87-7 (cis) and 181258-89-9 (trans)

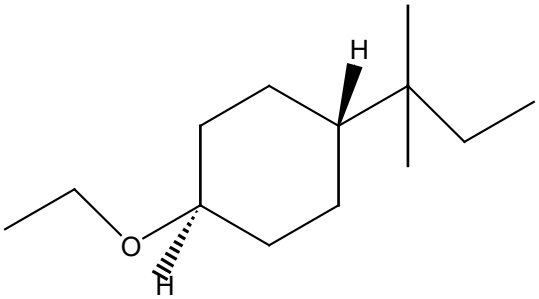
MOLECULAR FORMULA
C_{13} H_{26} O

STRUCTURAL FORMULA

50% cis



50% trans



MOLECULAR WEIGHT 198.198

SPECTRAL DATA

METHOD	UV, GC and IR
Remarks	Wavelengths: 230, 276, 284 and 210 nm Retention times at: 31.938 (cis isomer) and 35.523 (trans isomer) 50.216 (cis isomer) and 48.934 (trans isomer) Peaks at 972.2, 1081.8, 1111.8, 1153, 1374.7, and 1446.3

3. COMPOSITION

DEGREE OF PURITY
99% (a mixture of cis and trans isomers)

HAZARDOUS/NON HAZARDOUS IMPURITIES
Unidentified related isomers

ADDITIVES/ADJUVANTS
p-cresol, 2,6-ditertiary butyl (CAS No 128-37-0) or 2H-1 benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4-8-12-trimethyltridecyl) (CAS No 10191-41-0) : 0.1%

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will only be imported as a component of fragrance oil (up to 5%). Approximately, greater than 97% is a mixture of cis and trans isomers.

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

Year	*1*	*2*	*3*	*4*	*5*
Kg	100				100

USE
The notified chemical will be imported as a component of a fragrance oil at a maximum concentration of 5 %. It will be used in cosmetic and household products (body lotion, creams, sun creams, hairsprays, shampoos, dishwashing liquid, fabric washing liquid, surface cleaners, deodorant sprays, air refresheners, soap bars, foam baths and toilet waters). The maximum weight fraction of the notified chemical in the consumer products is 0.01%.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, Transport and Storage

PORT OF ENTRY
Not provided

IDENTITY OF RECIPIENTS
The notified chemical will be imported by International Flavours and Fragrances (Australia) Pty Ltd (Victoria) and will be reformulated locally. Customers (not specified) will receive the fragrance oil containing the notified chemical for blending into a wide variety of cosmetic and household products.

TRANSPORTATION AND PACKAGING
The notified chemical will be imported in 55 gallon (208.2 L) drums containing approximately 200 kg of finished fragrance oil at 5% i.e, approximately 10 kg notified chemical per drum. After formulation, the final consumer products will be packaged in product specific consumer-sized

containers.

5.2. Operation Description

Detailed information on the formulation process by customers was not provided. However, typical practices by cosmetic and consumer product manufacturers include the use of local exhaust ventilation and open mixing vessels and filling lines, although the processes are often automated.

5.3. Occupational exposure

Exposure Details

Formulation at each customer site may involve several workers (exact number was not provided). Details on the number and category of workers involved in the reformulation of the final products were also not provided.

Worker exposure to the notified chemical may occur during transport and storage of the fragrance oil containing notified chemical at up to 5% if the packing is breached.

Potential exposure exists when opening the drums, weighing and transferring the fragrance oil containing the notified chemical into a mixing vessel, during blending operations and when filling the consumer sized container with the final end use product, containing up to 0.01% notified chemical.

5.4. Release

RELEASE OF CHEMICAL AT SITE

It is expected that the wastage of the notified chemical would be less than 1 kg per annum from what will remain in the empty import containers. It is likely that these would be rinsed and the rinsate either added into the production of the next batch or released into the sewer. The cleaned import containers will either be recycled or disposed of in landfill. Release to the environment during reformulation and cleaning processes are expected to be small as closed, automated systems are used, and will total less than 1 kg per annum of the notified chemical. Wastes from these processes will be disposed of in either landfill or into the sewer.

RELEASE OF CHEMICAL FROM USE

Since the notified chemical will be used in household, laundry and personal cleaning products, up to 97 kg per annum will be released to sewer. The main release into air will result from partitioning from water, based on the Simple Treat Model (see Section 9.1.1).

Approximately 1 kg per annum will remain in the end-user container after it has been emptied and will go into domestic rubbish and ultimately landfill.

5.5. Disposal

The notified chemical will ultimately be disposed of in either the sewer (major) or landfill.

5.6. Public exposure

Public exposure to the notified chemical will occur through the use of the cosmetic and domestic products containing a maximum of 0.01% notified chemical.

6. PHYSICAL AND CHE MICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa Colourless liquid with a green, floral odour

Freezing Point <-25ºC

METHOD	EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks	Method used a standard crystallising point apparatus
TEST FACILITY	Huntingdon Life Sciences (1997a)

Boiling Point 241-250 ºC (range)

-

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

Remarks A clear yellow liquid residue was formed from condensed vapour present in the flask.
TEST FACILITY Huntingdon Life Sciences (1997a)

Relative Density 0.872 @ 20ºC

METHOD EC Directive 92/69/EEC A.3 Relative Density.
Remarks Pycnometer method was used.
TEST FACILITY Huntingdon Life Sciences (1997a)

Vapour Pressure 0.0445 kPa at 25ºC (Low volatility)

METHOD Isoteniscope method
Remarks The sample was introduced into the isoteniscope and evacuated to around 0.27 kPa. Nitrogen was introduced to atmospheric pressure and the system was pumped. This was repeated two additional times. The vapour pressure at 25°C was calculated via extrapolation of the vapour pressure value determined at 250°C. Environmentally, the notified chemical is classified as being volatile (Mensink 1995).
TEST FACILITY Taylor (1996)

Water Solubility 5.97 mg/L at 20ºC

METHOD EC Directive 92/69/EEC A.6 Water Solubility.
Remarks The notified chemical (ca. 1000 mg) was added to distilled water (150 mL) and the samples were pre-equilibrated at 30°C for up to 3 days followed by equilibration at 20°C for 24 h. Analysis of these solutions by gas chromatograph indicated that the solubility of the notified chemical is less than 6 mg/L.
TEST FACILITY Huntingdon Life Sciences (1997a)

Hydrolysis as a Function of pH

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

pH	*T (°C)*	$t_{½}$ (at 25°C)
4	50	> 1 year
7	50	> 1 year
9	50	> 1 year

Remarks The notified chemical exhibited less than 10% degradation after 5 days at pH 4, 7 and 9 at 50°C which classifies it as having a half-life of greater than one year at 25°C. As it does not contain any groups capable of hydrolysis, the losses observed during this test could be attributed to experimental error and decomposition.
TEST FACILITY Huntingdon Life Sciences (1997a)

Partition Coefficient (n-octanol/water) log Pow (isomer I) at 19.5ºC = 5.53
log Pow (isomer II) at 19.5ºC = 5.60

METHOD EC Directive 92/69/EEC A.8 Partition Coefficient. (HPLC Method)
Remarks The retention times were between that of the phenanthrene and triphenylamine reference standards. The low water solubility is consistent with the high log P_{ow}, indicating a high affinity for the organic component of soils and sediments.
TEST FACILITY Huntingdon Life Sciences (1997a)

Adsorption/Desorption log K_{oc} = 3.3 at 20°C.

METHOD OECD Draft Document TGP/94.75
Remarks A stock solution of the notified chemical (ca. 0.1 g in 100 mL methanol) was injected onto a cyano HPLC column and the retention time of the test substance

determined. A comparison of test substance retention time against known retention times of standard substances was used to determine the soil absorption coefficient. The high log K_{oc} indicates that the notified chemical is classified as being slightly mobile in soil.

TEST FACILITY Huntingdon Life Sciences (1997b)

Dissociation Constant Not determined

The notified chemical does not contain any groups capable of dissociation.

Particle Size Not determined

Flash Point 97°C (closed cup)

METHOD Method was based on Pensky-Martens closed cup EC Directive 92/69/EEC A.9 Flash Point.
Remarks A blue halo around the test flame was observed from 85°C in both tests.
TEST FACILITY Huntingdon Life Sciences (1997a)

Flammability Limits Not flammable

Autoignition Temperature 271°C

METHOD 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks The observed duplicate ignition delay times of test chemical were 2 sec and 7 sec.
TEST FACILITY Huntingdon Life Sciences (1997a)

Explosive Properties No explosive properties

METHOD EC Directive 92/69/EEC A.14 Explosive Properties.
TEST FACILITY Huntingdon Life Sciences (1997a)

Reactivity

Remarks The notified chemical is a stable, non reactive compound. It has no oxidising properties.

ADDITIONAL TESTS

Surface Tension 72.2 mN/m at 19°C

METHOD EC Directive 92/69/EEC A.5 Surface Tension.
Remarks Concentration: 90% saturated aqueous solution. The surface tension was determined using a tensiometer with measurements made at two minute intervals until a constant value was obtained. The notified chemical is not considered to be surface active.
TEST FACILITY Huntingdon Life Sciences (1997a)

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint	*Assessment Conclusion*
Rat, acute oral	Low toxicity LD_{50} >2000 mg/kg bw
Rat, acute dermal	Low toxicity LD_{50} >2000 mg/kg bw

Rat, acute inhalation	Not provided
Rabbit, skin irritation	Moderately irritating
Rabbit, eye irritation	Slightly irritating
Skin sensitisation:	
Guinea pig, Magnusson and kligman	No evidence of skin sensitisation
Human Repeat Insult Patch Test	No evidence of skin sensitisation
Rat, 4-week repeat dose oral toxicity	NOAEL 15 mg/kg/day
Genotoxicity - bacterial reverse mutation	Non mutagenic
Genotoxicity – in vitro [Human lymphocytes]	Not clastogenic

7.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 401 Acute Oral Toxicity
Species/Strain	Rat/ Sprague Dawley (CD)
Vehicle	None (No control animals included in the study)
Remarks – Method	Oral gavage Observation period: 14 days No deviations were noted

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 males	2000	None
2	5 females	2000	None

LD50	>2000 mg/kg bw
Signs of Toxicity	None
Effects in Organs	None
Remarks – Results	Piloerection was observed in all treated animals within 5 minutes of dosing.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Huntingdon Life Sciences (1997c)

7.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity.
Species/Strain	Rats/ Sprague Dawley (CD)
Vehicle	None (No control animals included in the study)
Type of dressing	Occlusive

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 males	2000	None
2	5 females	2000	None

LD50	2000 mg/kg bw
Signs of Toxicity - Local	Transient slight dermal irritation (erythema only) was observed in two animals on Day 3 resolving by Day 4; these animals also showed desquamation on the treatment site from day 3 to 6

Signs of Toxicity - Systemic	No signs of systemic reaction
Effects in Organs	None
Remarks - Results	Effects on body weight was seen in some males and females based on historical data

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

TEST FACILITY Huntingdon Life Sciences (1997d)

7.3. Acute toxicity – inhalation

Remarks Not provided

7.4. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 (2 males and 1 female)
Vehicle	None
Observation Period	Day 14
Type of Dressing	Semi-occlusive.
Remarks - Method	Four hours topical application to intact skin

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	2	2	2	2	> Day 14	1**
Oedema	3.3	2	1	4	Day 12	0

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

Remarks - Results

There were no signs of toxicity or ill health during the observation period.

Moderate to severe erythema was observed in two animals.

The reactions observed resolved gradually and were accompanied by desquamation of the stratum corneum. Very slight erythema accompanied by desquamation of the stratum corneum was observed at day 14 in one animal.

CONCLUSION The notified chemical is moderately irritating to skin.

TEST FACILITY Huntingdon Life Sciences (1997e)

7.5. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.

Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Observation Period	14-15 days
Remarks - Method	Protocol deviation not compromising the study: relative humidity

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	1	0	1	2	Day 4	0
Conjunctiva: chemosis	0	0	0	1	1 hr	0
Cornea: area involved	0	0	0	0		0
Corneal density	0	0	0	0		0
Iridial inflammation	-	-	-			0

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

Remarks - Results: No corneal damage or iridial inflammation was observed. Moderate conjunctival redness and mild conjunctival chemosis was seen in all 3 animals one hour after instillation.

CONCLUSION: The notified chemical is slightly irritating to the eye

TEST FACILITY: Huntingdon Life Sciences (1997f)

7.6. Skin sensitisation

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 406 Skin Sensitisation – Kligman Maximisation Test

Species/Strain: Guinea pig/Duncan Hartley

Vehicle

PRIMARY IRRITATION STUDY: Animals were injected with Freund's complete adjuvant (50:50 with water), approximately 2 weeks prior to the start of the preliminary investigation

MAIN STUDY

Number of Animals: Test Group: 10 males and 10 females; Control Group: Negative (5 males and 5 females), Positive (2 males and 3 females)

INDUCTION PHASE: Induction Concentration:
intradermal: 10 % v/v in Alembicol
topical: 100%

CHALLENGE PHASE (DAY 21)

1st challenge: Topical application: 100% and 50% v/v in Alembicol D

2nd Challenge: Topical application: 50 and 25% v/v in Alembicol D

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after treatment 1st challenge*	
		24 hr	*48 hr*
Test Group			
10 rats	100%	0	0

Remarks – Results: Intradermal injection: necrosis was recorded at sites receiving Freund's Complete Adjuvant in test and control animals

Topical application: slight erythema was observed in test and control animals.

Challenge: No dermal reactions were noted for the test or control animals following the second challenge application.

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 (1997g)

7.6. Skin sensitisation

TEST SUBSTANCE	Notified chemical
METHOD	Repeated Insult Patch Test
Subjects	Preliminary exp (induction): 55 subjects ranging in age from 18 to 70 years (males and females) of which 46 completed the study. Exp: 54 subjects ranging in age from 20 to 69 years (males and females) of which 51 subjects completed the study.
Vehicle	Preliminary exp.: 2% in alcohol:diethylphthalate [75:25] Exp: 5% in alcohol: diethylphthalate [75:25]
MAIN STUDY	
INDUCTION PHASE	The test substance was applied to the skin of the upper back in occluded patches, three times per week for a total of ten applications. The patches were removed 24 hours after application. Rest periods consisted of either 24 hrs (if the day falls during the week) or 48 hrs (during the weekend).
CHALLENGE PHASE	After a rest period of approximately 14 days following the tenth application, a challenge patch was applied to the original site and to a virgin site. Sites were evaluated at 24 and 72 hrs after application
RESULTS	
Remarks – Results	Preliminary induction exp: All treated areas showed a negative response throughout the test interval. Exp: Transient, barely-perceptible non-specific patch test responses were observed on two (2/51) test panellists during the induction and/or challenge phases of the study.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Consumer Product Testing Co. (1996)- 2% in alcohol:diethylphthalate [75:25] Essex Testing Clinic, Inc. (1997)- 5% in alcohol: diethylphthalate [75:25]

7.7. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.

Species/Strain	Rats/Sprague Dawley
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days; Dose regimen: 15, 150 or 1000 mg/kg/day 5/7 days per week; Post-exposure observation period:
Vehicle	1% methyl cellulose
Remarks - Method	All rats of Groups II and III (15 and 150 mg/kg/day) were killed following the four-week treatment period. The remaining animals from groups I and IV were retained for a two-week recovery period Deviations not considered compromising the study: Few incidences of high humidity and temperature Recovery group was sacrificed on day 47 instead of 46

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	5 males; 5 females	0	None
II (low dose)	5 males; 5 females	15	None
III (mid dose)	5 males; 5 females	150	None
IV (high dose)	5 males; 5 females	1000	One female
V (control recovery)	5 males; 5 females	0	None
VI (high dose recovery)	5 males; 5 females	1000	None

Mortality and Time to Death

Only one death occurred on day 30 due to an accident during blood sampling.

Clinical Observations

High dose male group showed lower weight gains during the treatment period.

Salivation and associated wet coat following dosing was observed in the high and mid dose group. Lower body weight gains were observed in the high treated male group. In the recovery phase, the gain for this group of males was considered generally comparable with controls.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Haematology:

High dose group- haematology parameters (lower PCV, Hb and RBC values, higher mean platelet values, white blood cell counts and lymphocyte counts) were affected and were statistically significant except for haemoglobin. Total white blood cell and lymphocyte counts were significantly lower in the mid dose groups.

Clinical chemistry:

A dose related decrease in mean glucose values were shown at the mid dose group and significantly at high dosage levels. Other parameters were significantly affected in the high dose group were mean urea nitrogen and creatinine in males, triglyceride values in females and liver enzymes for both sexes including the male recovery group. Lower A/G values were seen for males at the high and mid dose groups.

There was an increase in the total protein for the mid dose (statistically significant) and the high dose groups.

Urinalysis

Lower group mean pH value (statistically significant) and higher total protein value for high dosage group males were seen. In the recovery group, mean total protein value was significantly higher for high dose male groups.

Effects in Organs

The mean liver weights for both sexes at the high dose level were statistically significantly higher. There were no differences in the recovery group after the two-week recovery period.

Macroscopic Pathology

At termination, enlargement of the liver was noted for 3/4 female high dosage level rats compared with controls. Minimal patchy or patchy skin alopecia was evident in 4/4 females from the high dosage level group. No findings were noted in the recovery group.

Microscopic Pathology .

Liver: Centrilobular hypertrophy was seen in 3/5 males and all females receiving 1000 mg/kg/day, in 3/5 males receiving 150 mg/kg/day and in the recovery male group. Centrilobular and midzonal or generalised hepatocyte hypertrophy was seen in the remaining males at the high dose level. In the recovery animals, minimal centrilobular hepatocyte hypertrophy was seen in one animal treated at the high dose. This suggests that recovery was almost complete.

Kidneys: Incidences of eosinophilic droplets in the cortical tubular epithelium were seen in all males at 1000 and 150 mg/kg/day and in the recovery male group. Basophilia and single cell necrosis in the proximal tubules were seen in males receiving 1000 and 150 mg/kg/day.

DISCUSSION

The target organs for the notified chemical are the liver and kidneys (male rats). Macroscopically enlarged liver, higher liver weights and significant changes in blood chemistry were noted in the high dose and medium (males only) dose groups.

The male rat was more sensitive to the effects of treatment than females. The microscopic changes seen in the kidneys of male treated rats were significant and were associated with effects on kidney parameters. These effects however, are not considered relevant to man as they are specific to male rats.

The effects seen on haematology parameters and urinalysis were mild and the values indicated at the medium dose level were within historical values.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 15 mg/kg bw/day based on effects on haematology, clinical chemistry and the liver.

TEST FACILITY	Huntingdon Life Sciences (1997h)

7.8. Genotoxicity – bacteria

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 471 and 472 Bacterial Reverse Mutation Test.
Species/Strain	*S. typhimurium*: TA1538, TA1535, TA1537, TA98, TA100. *E. coli*: WP2 uvrA trp
Metabolic Activation System	Aroclor 1254 activated S9 fraction
Concentration Range in Main Test	a) With metabolic activation: 312.5, 625, 1250, 2500 and 5000 µg/plate. b) Without metabolic activation: 312.5, 625, 1250, 2500 and 5000 µg/plate.
Vehicle	
Remarks – Method	Positive control: With S9: N-ethyl-N'-nitrosoguanidine, 9-aminoacridine and 2-nitrofluorene Without S9: 2-Aminoanthracene

RESULTS

Remarks - Results	No substantial increases in revertant colony numbers of any of the tester strains were observed following treatment with Ozofleur at any dose

level, in the presence or absence of S-9 mix.

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

TEST FACILITY Huntingdon Life Sciemces (1997i)

7.9. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD OECD TG 473 In vitro Mammalian Cytogenetic Test.
Cell Type Human lymphocytes
Metabolic Activation System Arochlor-induced S9 activation system
Vehicle Ethanol
Remarks - Method Positive controls: Mitomycin C and cyclophosphamide

Metabolic Activation	*Exposure Period*	*Harvest Time*	*Mitotic index*
Absent			
Test 1 (repeat)	3 hr	21 hr	47% at 117.2 μg/mL
Test 2	3 hr	21 or 45 hr	13 % at 78.1 μg/mL
Present			
Test 1	3 hr	21 hr	9% at 2500 μg.mL
Test 2	3 hr	21 or 45 hr	49% at 117.2 μg/mL

RESULTS

Remarks - Results

Test 1:
With S9: 156.3, 78.1 and 39.1 μg/mL were selected for metaphase analyses
Without S9 (repeat): 78.1, 39.1 and 19.5 μg/mL were selected as the highest dose for metaphase analysis

The notified chemical did not cause any statistically significant increases in the proportion of metaphase figures with chromosomal aberrations with or without S9.

Test 2: (21 hour harvest)
With S9: 117.2, 78.1 and 39.1 μg/mL were selected as the highest concentration for metaphase analysis.
Without S9: 78.1, 39.1 and 19.5 were selected as the highest concentration for metaphase analysis.

No statistically significant increases in the proportion of aberrant metaphase figures occurred in cultures treated with the notified chemical with or without S9.

Test 2: (45 hour harvest)
Without S9: 78.1, 39.1 and 19.5 μg/mL were the selected concentrations selected for metaphase analysis.
With S9: 117.2 μg/mL was the highest concentration selected.

The notified chemical did not cause any significant increases in the proportion of metaphase figures with chromosomal aberrations in either

the absence or presence of S9 mix.

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

TEST FACILITY Huntingdon Life Sciences (1997k)

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE Ozofleur

METHOD OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.

Inoculum Activated sludge

Exposure Period 28 days

Remarks - Method The notified chemical was incubated for 28 days at a nominal test substance concentration of 100 mg/L.

RESULTS

Test substance		*Sodium Benzoate*	
Day	*% degradation*	*Day*	*% degradation*
14	0	14	82.5
28	0	28	85.3

Remarks - Results The biodegration of the reference substance, sodium benzoate was 85.3% after 28 days, indicating the test conditions were valid. After 28 days at between 20-24°C, the test substance did not under go any biodegradation which indicates the notified chemical is not readily biodegradable in aerobic environments. The test substance was also found to be non-inhibitory to micro-organisms. It should be noted that the test substance is a poorly water soluble low density liquid and that this may lead to an underestimation of the notified chemical's potential for biodegradation.

CONCLUSION The notified chemical in not readily biodegradable.

TEST FACILITY Huntingdon Life Sciences (1998a)

8.1.2. Bioaccumulation

TEST SUBSTANCE Data regarding the bioaccumulation potential of the notified chemical were not provided. The chemical structure, molecular weight (197), water solubility, and Pow suggest a potential for the notified chemical to cross biological membranes and bioaccumulate (Connell 1990). The low import volume and dispersed use suggest exposure will not be significant and limit this potential.

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE Ozofleur

METHOD OECD TG 203 Fish, Acute Toxicity Test

Species	Rainbow trout (*Oncorhynchus mykiss*)
Exposure Period	96 h
Auxiliary Solvent	Acetone
Water Hardness	130 mg $CaCO_3$/L
Analytical Monitoring	GC

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*					
Nominal	*Actual*		*3 h*	*6 h*	*24 h*	*48 h*	*72 h*	*96 h*
SC*	ND#	10	0	0	0	0	0	0
0	ND							
0.22	0.19	10	0	0	0	0	0	0
0.46	0.40	10	0	0	0	0	0	0
1.0	0.87	10	0	0	1	4	5	6
2.2	1.9	10	0	1	10	10	10	10
4.6	4.5	10	10	10	10	10	10	10

* Solvent control, # Not detected

LC50	0.84 mg/L at 96 hours (95% confidence level of 0.66-1.0 mg/L).
NOEC	0.19 mg/L at 96 hours.
Remarks – Results	The results of the definitive study showed that no mortality was observed in the test vessels with a measured test substance concentration of less than 0.4 mg/L. Above a measured test substance concentration of 0.4 mg/L, fish exhibited sub-lethal effects such as discolouration, lying on the bottom of the test vessel and moribundity. After 96 h, 60, 100 and 100% mortality was observed at measured test concentrations of 0.87, 1.9 and 4.5 mg/L of the notified substance, respectively. The 96-hour EC_{50} for the notified chemical to *Oncorhynchus mykiss* is 0.84 mg/L as determined by the method of Payne et al. in the Genstat 5.1.3 Reference Manual.
CONCLUSION	The ecotoxicity data indicate that the notified chemical is very toxic to fish.
TEST FACILITY	Huntingdon Life Sciences (1997k).

8.2.2. Acute/chronic toxicity to aquatic invertebrates

TEST SUBSTANCE	Ozofleur
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Acetone
Analytical Monitoring	GC

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
SC*	ND#	20	0	0
0	ND	20	0	0
0.1	0.086	20	0	0
0.22	0.19	20	0	1
0.46	0.41	20	0	4
1.0	0.87	20	0	4
2.2	1.8	20	4	16
4.6	3.6	20	20	20
10	8.4	20	20	20

* Solvent control, # Not detected

LC50	1.0 mg/L at 48 hours (95% confidence level of 0.8-1.3 mg/L).
NOEC	0.086 mg/L at 48 hours
Remarks - Results	The immobilisation tests with *Daphnia* were performed in quadruplicate using 5 daphnids per flask with observations performed at 24 and 48 hours. The tests were conducted using measured test substance concentrations of 0.086, 0.19, 0.41, 0.87, 1.8, 3.6 and 8.4 mg/L. After 48 h, no immobilised daphnids were observed in the test vessels with 0.086 mg/L, while 5, 20, 20, 80, 100 and 100% mortality was observed at test concentrations of 0.19, 0.41, 0.87, 1.8, 3.6 and 8.4 mg/L, respectively. The 48-hour EC_{50} for the notified chemical to *Daphnia magna* is 1.0 mg/L as determined by the method of Payne et al. in the Genstat 5.1.3 Reference Manual.
CONCLUSION	The ecotoxicity data indicate that the notified chemical is very toxic to aquatic invertebrates.
TEST FACILITY	Huntingdon Life Sciences (1997l).

8.2.3. Algal growth inhibition test

TEST SUBSTANCE	Ozofleur
METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	*Selenastrum capricornutum*
Exposure Period	72 hours
Concentration Range Nominal	0.46, 1.0, 2.2, 4.6 and 10 mg/L
Concentration Range Actual	0.29, 0.61, 1.4, 2.9 and 6.8 mg/L
Auxiliary Solvent	Acetone
Analytical Monitoring	GC

RESULTS

Biomass	*Growth*	*NOEC*
E_bC50 *mg/L at 72 h*	*E_rC50* *mg/L at 72 h*	*mg/L at 72 h*
1.7	> 6.8	0.29

Remarks - Results	Algae were exposed to the test substance at the nominal concentrations of 0.46, 1.0, 2.2, 4.6 and 10 mg/L for 72 h at 22˚C under constant illumination and shaking. Analysis of the test substance concentrations after 72 h showed measured concentrations to range from 0.29-6.8 mg/L. No abnormalities were detected in any of the replicate test samples. The biomass of *Selenastrum capricornutum* was adversely affected by the test substance.
CONCLUSION	The ecotoxicity data indicates the notified chemical is toxic to algae.
TEST FACILITY	Huntingdon Life Sciences (1998b).

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

Exposure

The new chemical will eventually be released into the environment with the majority expected to be discharged into sewerage systems through washing etc. or to volatilise in the air from the skin. For that proportion of the chemical which reaches sewage treatment plants (ie is not volatilised or otherwise destroyed during passage to the plant), the proportions of the chemical which partition into the different environmental compartments may be estimated using the Simple Treat Model (EEC Technical Guidance Document, 1996). These estimates, based on the chemical having a calculated Henry's constant of 1477.4 Pa/m^3/mole based on measured vapour pressure and water solubility, a Log Pow of 5.6 and not being biodegradable, indicate that the chemical would be expected to partition into the air, water and sewer sludge compartments as follows –

Air

13.5%

Water

6%

Sewage Sludge

80.5%

Accordingly, at equilibrium most of the notified chemical will remain associated with soil and sediment.

Fate

The notified chemical associated with soil and sediment will slowly degraded through biological and abiotic processes to water and oxides of carbon. Residual chemical disposed of into landfill with empty containers or with residual solids derived from water treatment at the production facilities is also expected to remain adsorbed to soil/sediment particles, and in this situation would be expected to be slowly destroyed by similar mechanisms to those operating in sediments. Incineration of the material would produce water vapour and oxides of carbon.

Based on annual imports of 100 kg per annum, and assuming the majority 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 0.27 kg/day. Assuming a national population of 19,500,000 and that each person contributes an average 150 L/day to overall sewage flows, the predicted concentration in sewage effluent on a nationwide basis is estimated as 0.093 μg/L.

Amount of chemical entering sewer annually	100 kg
Population of Australia	19.5 million
Amount of water used per person per day	150 L
Number of days in a year	365
Estimated PEC	0.093 μg/L (0.093 ppb)

When released to receiving waters the concentration is reduced by a further factor of at least 10, so the Predicted Environmental Concentration (PEC) is around 0.0093 μg/L. Removal processes such as adsorption to sludge would reduce this value further.

9.1.2. Environment – effects assessment

The results of the ecotoxicological data indicate the notified chemical is very toxic to toxic to aquatic life. The most sensitive species are fish, where the 96 hour EC50 is 0.84 mg/L and the NOEC was 0.19 mg/L.

A predicted no effects concentration (PNEC) can be determined when at least one acute EC50 for each of the three trophic levels is available (ie. fish, *Daphnia*, algae). The PNEC is calculated by taking the EC50 value of the most sensitive species, and dividing this value by an assessment safety factor of either 100 (OECD) or 1000 (EU). Using a worst case scenario safety factor of 100, the PNEC is 8.4 μg/L.

9.1.3. Environment – risk characterisation

The notified chemical will be used as a fragrance ingredient of domestic cleaning and personal care formulations, and most will eventually be released into domestic sewage systems as a consequence of product use. The compound is not readily biodegradable (0% over 28 days), and has a high partition coefficient of 5.6, a moderate Log Koc of 3.3 and a low water solubility (6 mg/L), all indicating that most of the material would eventually partition to sediment. Here it is expected to slowly degrade to water and oxides of carbon through biological processes.

Although the notified chemical exhibits all the characteristics of a molecule with potential for bioaccumulation (Connell, 1990), release to the aquatic compartment will be low and dispersed.

The PEC/PNEC ratio for the aquatic environment, assuming nationwide use, is 0.001. This value is significantly less than 1, indicating no immediate concern to the aquatic compartment.

The above considerations indicate minimal hazard to the environment when the notified chemical is used as a component of domestic products in the manner and levels indicated by the notifier.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

During reformulation into cosmetics and domestic cleaning products, dermal exposure is the most likely route. Ocular exposure may occur due to accidental splashes. Exposure may occur when workers open the drums containing imported notified chemical at 5%, when weighing and transferring the imported fragrance oil into a mixing vessel, during blending operations and when cleaning up spills and equipment. It is expected that the blending operations are open or closed systems, however, the process is often automated and local exhaust ventilation is usually employed.

Exposure to the notified chemical is minimal during the filling of containers and end use of the formulated products as the concentration is less than 0.01%.

Exposure to the notified chemical (imported in products at 5 % or in consumer products at 0.01%) during transport and storage can only occur in the event of a packaging breach or spills.

Modelled Worker Exposure:

Dermal and inhalation worker exposure were estimated during formulation using the software 'Estimation and Assessment of Substance Exposure' (EASE). The scenarios and assumptions are tabulated below:

Scenario	Assumptions	Dermal Exposure ($mg/cm^2/day$)
Scenario 1 Formulation: Blending is enclosed Imported fragrance oil containing 5% notified chemical	Enclosed process (sampling may occur) Non dispersive use (formulators) Direct handling-Intermittent	0.1-1 (imported formulation) 0.005-0.05 (Ozofleur)
Scenario 2: Formulation/packing Blending is open Imported fragrance oil (containing 5% notified chemical)	Wide dispersive use Direct handling Intermittent	1-5 (final end use product) 0.05-0.25 (Ozofleur)
Scenario 3: Packing and end use Final product containing 0.01% notified chemical	Wide dispersive use Direct handling Intermittent	1-5 (final end use product) 0.0001-0.0005 (Ozofleur)

9.2.2. Public health – exposure assessment

The consumers will be handling the household and cosmetic products. Exposure to the notified chemical is considered minimal given the small amount of notified chemical in the final products (maximum of 0.01%).

Exposure to the notified chemical during transport is limited unless there is an accidental spill.

9.2.3. Human health - effects assessment

The notified chemical is of low acute oral and dermal toxicity in rats. Acute inhalation toxicity data were not provided. The notified chemical is of low volatility and is not expected to cause significant adverse effects by inhalation.

Toxicity studies on the notified chemical showed that it is a moderate skin irritant and slight eye irritant in rabbits, but not a skin sensitiser in guinea pigs or humans.

The notified chemical is classified as a skin irritant and is assigned R38 (Irritating to skin) in accordance with the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999a).

In a 4-week repeat dose oral toxicity rats, the NOAEL was established as 15 mg/kg/day, based on effects on clinical chemistry, haematology and the liver, the effects being observed principally in male rats. A NOEL was not established in the study. Additional effects seen on the kidney, also specific to male rats, were not considered relevant in humans. Based on the guidelines in the NOHSC Approved Criteria, the effects observed in the study were not sufficient to warrant classification for prolonged exposure effects.

The notified chemical was not genotoxic or clastogenic in the *in vitro* tests conducted.

9.2.4. Occupational health and safety – risk characterisation

Acute Toxic potential

The notified chemical is of low acute toxicity (LD_{50} >2000 mg/kg). So the risk of acute toxic effects in workers is low. The notified chemical is a skin and eye irritant and, given the possible dermal exposure to fragrance oil during formulation of end use products, particularly in open mixing processes, there is a risk of skin and eye irritant effects in workers. Therefore, workers will need protective clothing, gloves and safety glasses when opening the drums, weighing and transferring the fragrance oil into the mixing vessel and cleaning up spills and equipment. If the blending process is open, workers will need goggles and gloves.

Inhalation risk is not considered significant as the notified chemical is not volatile and exhaust ventilation is expected to be utilised during formulation.

Repeat dose toxic potential

The NOAEL established from a repeat dose oral study was 15 mg/kg bw/day. For a 70 kg bw worker and assuming a dermal absorption factor of 100% (water solubility and partition coefficient are high indicating that lipid absorption is significant), the equivalent amount of notified chemical is 1.05 g notified chemical or 21 mL product containing 5% notified chemical. Dermal exposure to these amounts will reach the NOAEL. However, it is unlikely that workers will be exposed repeatedly to such large amounts during routine procedures.

The Margins of Exposure (MOE) were calculated for the predicted dermal exposure using EASE:

Scenario	Dermal Absorbed Dose* (mg/kg/day)	MOE (Dermal)**

Scenario 1: Formulation: Blending is closed Imported product (0.05% notified chemical)	0.058-0.58	258-25.86
Scenario 2: Formulation: Blending is open Imported product (0.05% notified chemical	0.58-2.92	25.86-5.14
Scenario 3: Packing and end use: Final product containing 0.01% notified chemical	0.0012-0.0058	12500-2586

* Based on 70 kg body weight, surface area for hands 820 cm^2, default dermal absorption 100% (lipid and water soluble).
** Based on NOAEL of 15 mg/kg/day (4 week repeat oral toxicity study in rats)

MOE greater than 100 (to account for inter- and intra- species differences) are considered acceptable as the NOAEL was based on an animal study. MOE for all the scenarios are adequate during formulation and packing except when the blending operation is open.

The following uncertainties and conservative assumptions are noted:

- Workers were not using personal protective equipment
- Exposure estimates were based on model calculations as no measured data are available
- EASE assumes 8 hr exposure/day

When handling the imported product during formulation, the risk is acceptable provided that the formulation process is enclosed and automated. However, when mixing openly the imported formulation with other ingredients, the risk was not adequate and workers should wear protective clothing, gloves and goggles.
When packing the final end use product and using it, the risk is considered acceptable due to the low concentration of the notified chemical in the products. During packing, it is anticipated that the filling line is automated and workers have adequate local exhaust ventilation.

During transport and storage, the risk is low because of packaging and the small amount of notified chemical in the final product (0.01%). If there are accidental spills during transport or storage of the drums containing 5% notified chemical, workers will need skin and eye protection.

9.2.5. Public health – risk characterisation

Exposure to the notified chemical when using the cosmetic and household products varies. In cosmetic products, the typical amount of consumer product per application ranges between 0.8 g for one time/day (as a face cream) to 12 g/day for 2-7 times/week (in shampoos). The highest amount of notified chemical in cosmetic products is 0.01% (Toilet water) and in household products, it is 0.00025%.

Assuming 0.8 g of Toilet water is applied per day for up to 5 times/day, a dermal absorption factor of 100%, a 60 kg person will have systemic exposure of 0.067 g notified chemical. Considering that the repeat dose NOAEL is 15 mg/kg/day, the MOE is 225. The notified chemical is a moderate skin irritant and slight eye irritant. However, it is present in the consumer products at a maximum of 0.01% and is unlikely to pose a significant risk to public health when used in the proposed manner.

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* (NOHSC, 1999), with the following risk phrase:

R38 Irritating to skin

There are no regulatory requirements in Australia with regard to environmental classification. However, if this chemical were to be classified according to the Globally Harmonised System of Classification and Labelling (GHS), the following would apply:

Category: Acute I 'hazardous to the aquatic environment'

Ozofleur is classified as dangerous for the environment in accordance with the EU with the following risk phrases:

R50 Very toxic to aquatic organisms
R53 May cause long term adverse effects

The notifier classified Ozofleur as a Class 9 Dangerous Goods- Miscellaneous Dangerous Goods and Articles.

10.2. Environmental risk assessment

The chemical is not considered to pose a risk to the environment based on its reported use pattern and PEC/PNEC ratio of <<1.

10.3. Human health risk assessment

10.3.1. Occupational health and safety

There is medium Concern to occupational health and safety under the conditions of the occupational settings described during reformulation if blending processes are open. However during end use the concern to workers is considered to be low.

10.3.2. Public health

There is Low Concern to public health when used in the proposed manner at a maximum of 0.01%.

11. MATERIAL SAFETY DATA SHEET

11.1. Material Safety Data Sheet

The MSDS of the notified chemical and the product containing the notified chemical provided by the notifier were in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994a). They are 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 and products containing the notified chemical provided by the notifier were 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:

R38 Irritating to skin
S36 Wear suitable protective clothing
S37 wear suitable gloves
S39 wear eye/face protection

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

o There are no regulatory requirements in Australia with regard to environmental classification. However, if this chemical were to be classified according to the Globally Harmonised System of Classification and Labelling (GHS), the following would apply:

Category: Acute I 'hazardous to the aquatic environment'

- The National Drugs and Poisons Standing Committee (NDPSC) should consider the notified chemical for listing on the SUSDP.

- The notified chemical should be classified as follows under the ADG Code:
  – Class 9-Miscellaneous Dangerous Goods and Articles.

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 the ingredients with the notified chemical.
  – Local exhaust ventilation if the mixing vessel is open

- 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 the fragrance concentrate and consumer products:
  – Chemical resistant gloves, protective overalls, and goggles/faceshield.

  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 into the sewer or landfill.

Emergency procedures

- Spills/release of the notified chemical should be contained as described in the MSDS (ie. covered with inert material and transfer to a sealable waste container) and the resulting waste disposed of in landfill.

Secondary notification

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

Under subsection 64(1) of the Act; if

(a) The notified chemical itself is manufactured locally or imported;
(b) Additional information becomes available on adverse environmental effects of this chemical; or,
(c) Annual import levels of the notified chemical exceed one tonne.

Under subsection 64(2) of the Act:

if any of the circumstances listed in the subsection arise.

The Director will then decide whether secondary notification is required.

No additional secondary notification conditions are stipulated.

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