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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Component 2 of Amber Extreme

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

Director
Chemicals Notification and Assessment

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FULL PUBLIC REPORT

Component 2 of Amber Extreme

1. APPLICANT AND NOTIFICATION DETAILS

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

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

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

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

Dissociation Constant
Reactivity

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
US EPA Low Volume (04-251)
EC VIIB (eventually VIIA) (04-38-0014-00)
Environment Canada: Schedule 2 (NSN 13139)

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
Indeno[4,3 a-b] furan decahydro-2,2,7,7,8,9,9-heptamethyl-

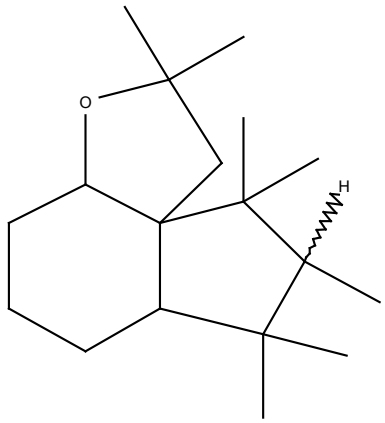
OTHER NAME(S)
Decahydro-2,2,7,7,8,9,9-heptamethyl-indeno[4,3 a-b] furan
3,3,10,10,11,12,12-heptamethyl-4-oxatricyclododecane

MARKETING NAME(S)
Component 2 of Amber Extreme

CAS NUMBER
647828-16-8

MOLECULAR FORMULA
C18H32O

STRUCTURAL FORMULA



MOLECULAR WEIGHT
264

SPECTRAL DATA

METHOD Gas Chromatography/Mass Spectrometry (GC/MS), Nuclear Magnetic Resonance (NMR), Infra Red (IR) and Ultra Violet (UV) spectra.
Remarks
TEST FACILITY IFF Laboratories

METHODS OF DETECTION AND DETERMINATION

METHOD Gas Chromatography (GC)
Remarks
TEST FACILITY IFF Laboratories

3. COMPOSITION

DEGREE OF PURITY
Range 4.5-27%, typically 17%, of Amber Extreme.
The other major component of Amber Extreme is 2H-Indeno[4,5-b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl, which is assessed as LTD/1173, Component 1 of Amber Extreme.

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
All identified impurities were present in the product Amber Extreme that was used for toxicity testing. These tests concluded that Amber Extreme is irritating to the skin and is a skin sensitiser.

Chemical Name 4,4,10,10,11,12,12-heptamethyl-3-oxatricyclo[7,3,0,0(2,6)]dodec-2(6)-ene
CAS No. - *Weight %* 0-8% in Amber Extreme
Hazardous Properties Part of the imported product that is irritating to the skin and a skin sensitiser.

Chemical Name 1,1,2,3,3-pentamethyl octahydro-4H-Inden-4-one
CAS No. 195379-87-4 *Weight %* 0-3% in Amber Extreme
Hazardous Properties Part of the imported product that is irritating to the skin and a skin sensitiser.

Chemical Name 7,7,8,9,9-pentamethyl-3-(2-methylprop-2-enyl)bicyclo[4,3,0]nonan-2-one
CAS No. - *Weight %* 0-8% in Amber Extreme
Hazardous Properties Part of the imported product that is irritating to the skin and a skin sensitiser.

ADDITIVES/ADJUVANTS
None

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
Imported as part of finished fragrance oils or in end-use consumer products

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

Year	*1*	*2*	*3*	*4*	*5*
Kilograms	27 kg	27 kg	54 kg	54 kg	138 kg

USE
The notified chemical is a component of Amber Extreme. The concentration of the notified chemical in Amber Extreme is 4.5-27% (range), typically 17%. The concentration of Amber Extreme in finished fragrance oils is approximately 1%. Fragrance oil containing Amber Extreme will be used as an odorant in alcoholic perfumery, cosmetics, toiletries, household products, soaps and detergents. The final concentration of the notified chemical in end-use consumer products will range from 0.0005% to 0.02%.

Typical concentrations in various product categories are as follows:

Product	% of Fragrance	% Notified Chemical in Final Consumer Product
Body lotion	0.4	0.0011
Creams	0.3	0.0008
Sun creams/lotions	0.4	0.0011
Hairsprays	0.5	0.0013
Shampoos	0.5	0.0013
Dishwashing liquid	0.2	0.0005
Fabric washing liquid	0.8	0.0021
Surface cleaners	0.6	0.0016
Deodorant sprays	1.0	0.0027
Air fresheners (sprays)	5.0	0.0135
Bath products	2.0	0.0054
Shower gels	1.2	0.0032
Toilet waters	8.0	0.0216

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, transport and storage

PORT OF ENTRY
Melbourne

IDENTITY OF MANUFACTURER/RECIPIENTS
Fragrance oils containing the notified chemical will be imported by International Flavours and Fragrances Australia, Ltd. Fragrance oils containing the notified chemical will initially be stored at the notifier's site, and then distributed to manufacturers for reformulation into consumer products.

TRANSPORTATION AND PACKAGING
Amber Extreme will be imported into Australia as a component of finished fragrance oils in sealed, polypropylene lined steel drums (55 gallon). Fragrance oils will be transported from the docks by road to the notifier's warehouse. The fragrance oil will then be transported to customers, typically by road. Finished consumer products have standard packaging requirements and are available for purchase at retail stores. The type and size of packaging vary.

STORAGE FACILITIES & STORAGE REQUIREMENTS
Imported fragrance oil will be stored in the original sealed containers. The drums should be stored in a cool, dry and ventilated area away from heat sources and protected from light.

5.2. Operation description

Amber Extreme is imported as a component of finished fragrance oils. At customer sites, fragrance oils will be blended with other ingredients to make end-use consumer products such as alcoholic perfumes, cosmetics, toiletries, household cleaning products, soaps and detergents. 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.
During formulation, the main activity is blending of the ingredients with the notified chemical. The fragrance oil contained in drums will be transferred to a mixing tank and blended with various ingredients to form the final finished products for consumer use.
The packaging type and size of the final products (maximum 0.02% notified chemical) is expected to vary. The products will be distributed to retail outlets, displayed and sold to the public.

5.3. Occupational exposure

Number and Category of Workers

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

Exposure Details

Import; Transport to and from IFF warehouse

The notified chemical will be imported as a component of fragrance oils, which will be transported by road from the docks to the notifier's warehouse, and then distributed to clients for reformulation. Transport and warehouse workers will only be exposed to the notified chemical, in concentrations of approximately 0.2%, in the event of container breakage and/or accidental spillage.

Formulation of consumer products

Following distribution to customers, import containers of fragrance oil containing the notified chemical will be opened and reformulated into consumer products. The major occupational exposure to the notified chemical will be during weighing and addition to the mixing tank. The consumer products manufacturing sites are typically automated. Workers have potential for exposure during mixing, packaging, cleaning of equipment and sampling for quality control purposes. The main route of exposure is by skin contact; however, inhalation may occur. Coveralls, gloves and safety glasses are expected to be worn by workers at customer's facilities. The concentration of notified chemical in imported fragrance oils that will be reformulated is approximately 0.2%. The final concentration of the notified chemical in end-use consumer products will range from 0.0005% to 0.02%.

End Use

Workers exposed to end use products may include professional cleaners (household cleaning products), beauticians (cosmetics) and hairdressers (hairsprays, shampoos). These workers can be expected to use minimal personal protective equipment (PPE). However, the final concentration of notified chemical in cleaning, cosmetic and hair products will be no more than 0.02%.

5.4. Release

RELEASE OF CHEMICAL AT SITE

Release of the chemical is not expected at the IFF warehouse site. Release from reformulation facilities is anticipated to be extremely low given the concentration of notified chemical in imported fragrance oils (typically 0.2%).

RELEASE OF CHEMICAL FROM USE

Since Amber Extreme will be used in household, laundry and personal cleaning products, almost all (~97%) of Amber Extreme will end up in the sewer. Approximately 1% of the Amber Extreme imported is expected to be lost as residues in consumer containers, which are primarily landfilled. Release to the environment during reformulation would result from residual material in the import container, which would be rinsed and most likely discharged to the sewer. Little material is expected

to be lost during the formulation into the consumer product since the processes are typically automated.

5.5. Disposal

The notified chemical will ultimately be disposed of in either the sewer (major) or landfill. In the event of a spill, the typical practice is to place material and absorbent into sealed container and dispose of in accordance with current applicable laws and regulations.

5.6. Public exposure

End-use products are designed to be sold to consumers. The general public may be frequently exposed to low levels of notified chemical via a number of different consumer products, at concentrations ranging from 0.0005 to 0.02%. Due to its low levels and use patterns, the overall daily exposure to the notified chemical will be very low for a person using one or more consumer products containing Amber Extreme.

Public exposure to the notified chemical as imported as a component of fragrance oils will only occur in the event of transport accident or spillage. Public exposure from the reformulation process is unlikely.

6. PHYSICAL AND CHEMICAL PROPERTIES

GENERAL REMARKS	Physical and chemical properties were determined for Amber Extreme, which contains typically 17% (range 4.5-27%) Component 2.

Appearance at 20ºC and 101.3 kPa Clear, colourless liquid

Melting Point/Freezing Point < -20ºC

METHOD	EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks	The test material became increasingly viscous during cooling.
TEST FACILITY	SafePharm Laboratories, Derby, UK (2003b)

Boiling Point Approximately 255ºC at 101.3 kPa

METHOD	EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks	It was not possible to obtain two determinations within ±1K; this was probably due to the fact that the test material was a mixture of isomers.
TEST FACILITY	SafePharm Laboratories, Derby, UK (2003b)

Density 937 kg/m^3 at 20+/-5ºC

METHOD	EC Directive 92/69/EEC A.3 Relative Density.
Remarks	
TEST FACILITY	SafePharm Laboratories, Derby, UK (2003a)

Vapour Pressure 0.00038 kPa at 25ºC

METHOD	EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks	Vapour pressure balance method. A sequence of runs was started after a sample had been under vacuum for approximately 22 hours. Temperature and pressure readings were taken between 15 and 25ºC with a one hour dwell at 15ºC between runs. The above result indicates that the test material can be classified as moderately volatile according to Mensink *et al.* (1995).
TEST FACILITY	SafePharm Laboratories, Derby, UK (2003c)

Water Solubility <2.02 x 10^{-4} g/L at 20ºC

METHOD	EC Directive 92/69/EEC A.6 Water Solubility.
Remarks	Analytical Method: Gas Chromatography

Flasks containing around 0.013 g in 570 mL of glass double-distilled water were shaken at 30ºC for 3 h and then equilibrated at 20ºC for 1 hour. The short duration was used to minimise losses due to volatilisation. Water solubility was calculated from the sum of all the main isomers in the test sample (Amber Extreme)

TEST FACILITY SafePharm Laboratories, Derby, UK (2003b)

Fat (or n-octanol) Solubility Miscible in all proportions with standard fat HB 307 at 37±0.5ºC

METHOD OECD TG 116 Fat Solubility of Solid and Liquid Substances.

Remarks Analytical Method: Direct Observation

This material showed no upper limit for saturation in standard fat. Up to 19 g was soluble in 1 g of fat when shaken at 37ºC for 5 hours. Solubility was visually assessed.

TEST FACILITY SafePharm Laboratories, Derby, UK (2003a)

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)*	*$t_{½}$ (years)*
4	25	>1
7	25	>1
9	25	>1

Remarks Analytical Method: Gas Chromatography

Sample solutions were prepared in stoppered glass flasks at a nominal concentration of 0.1 mg/L. A 0.1% co-solvent of methanol was used to aid solubility. The buffers of pH 4, 7 and 9 were maintained at 50ºC for 5 days. No degradation was observed during the study. These results are consistent with a lack of hydrolysable functionalities within the notified chemical.

TEST FACILITY SafePharm Laboratories, Derby, UK (2003a)

Partition Coefficient (n-octanol/water) log P_{ow} = 4.42 at 22ºC

METHOD EC Directive 92/69/EEC A.8 Partition Coefficient.

Remarks Analytical Method: Gas Chromatography

TEST FACILITY SafePharm Laboratories, Derby, UK (2003b)

Adsorption/Desorption – screening test log K_{oc} > 5.63 at 30ºC

METHOD EC Directive 2001/59/EC C19

Remarks The method guideline states that the measurement of adsorption coefficient should be carried out on substances in their ionised and unionised forms. However, the test material contains no modes of dissociation, therefore testing was carried out with pH adjustment to the mobile phase. The test material was eluted from the column after the last reference standard, DDT, and occurred after changing the mobile phase to 100% methanol.

TEST FACILITY SafePharm Laboratories, Derby, UK (2003a)

Dissociation Constant Not determined.

METHOD OECD TG 112 Dissociation Constants in Water.

Remarks The notified chemical does not contain acidic or basic functionalities.

TEST FACILITY

Particle Size Not applicable

Remarks The notified chemical is a liquid.

Flash Point 128 +/- 2ºC at 101.3 kPa

METHOD EC Directive 92/69/EEC A.9 Flash Point.
Remarks Closed cup method
TEST FACILITY SafePharm Laboratories, Derby, UK (2003d)

Flammability Limits Not determined.

METHOD
Remarks The notified chemical is a combustible liquid.
TEST FACILITY

Autoignition Temperature 296 +/-5ºC

METHOD 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks
TEST FACILITY SafePharm Laboratories, Derby, UK (2003c)

Explosive Properties Not explosive.

METHOD EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks There are no chemical groups in the notified chemical that would imply explosive properties; therefore, the results are predicted negative.
TEST FACILITY SafePharm Laboratories, Derby, UK (2003c)

Reactivity

Remarks Amber Extreme is expected to be stable in water and air under normal conditions of temperature and pressure.

Surface Tension Not determined.

METHOD EC Directive 92/69/EEC A.5 Surface Tension.
Remarks Directive states that surface tension test is not required if water solubility is less than 1 mg/L.
TEST FACILITY SafePharm Laboratories, Derby, UK (2003a)

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint	*Assessment Conclusion*
Rat, acute oral	low toxicity LD50 > 425 mg/kg bw
Rat, acute dermal	low toxicity LD50 > 340 mg/kg bw
Rabbit, skin irritation	moderately irritating
Rabbit, eye irritation	slightly irritating
Skin sensitisation – mouse local lymph node assay	evidence indicative of skin sensitisation
Skin sensitisation – HRIPT	non-irritating and non-sensitising
Rat, repeat dose oral toxicity – 28 days.	NOEL not established NOAEL 3 mg/kg bw/day
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration	non genotoxic
Genotoxicity – in vivo mouse micronucleus	non genotoxic

Note: All toxicity studies were conducted using samples of Amber Extreme, the component of imported fragrance oils that contains 17% (range 4.5-27%) notified chemical.

7.1. Acute toxicity – oral

TEST SUBSTANCE	Amber Extreme, containing 17% (range 4.5-27%) notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/Crl: CD (SD)
Vehicle	Amber Extreme
Remarks - Method	Test material was 2000 mg/kg bw Amber Extreme, which equates to approximately 340 mg/kg bw notified chemical.

RESULTS

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

LD50	>2500 mg/kg bw Amber Extreme (i.e. >425 mg/kg bw notified chemical)
Signs of Toxicity	None reported
Effects in Organs	No abnormalities observed at necropsy
Remarks - Results	
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	SafePharm Laboratories, Derby, UK (2003e)

7.2. Acute toxicity - dermal

TEST SUBSTANCE	Amber Extreme, containing 17% (range 4.5-27%) notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test.
Species/Strain	Rat/Crl: CD (SD)
Vehicle	Amber Extreme
Type of dressing	Semi-occlusive.
Remarks - Method	Test material was 2000 mg/kg bw Amber Extreme, which equates to approximately 340 mg/kg bw notified chemical.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 female + 5 male	2000	0/10

LD50 >2000 mg/kg bw Amber Extreme, which equates to 340 mg/kg bw notified chemical
Signs of Toxicity - Local No signs of dermal irritation observed
Signs of Toxicity - Systemic No signs of systemic toxicity observed
Effects in Organs No abnormalities observed at necropsy
Remarks - Results

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

TEST FACILITY SafePharm Laboratories, Derby, UK (2003f)

7.4. Irritation – skin

TEST SUBSTANCE Amber Extreme, containing 17% (range 4.5-27%) notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain Rabbit/New Zealand White
Number of Animals 3
Vehicle Amber Extreme
Observation Period 72 hours
Type of Dressing Semi-occlusive.
Remarks - Method Additional observations made on days 7 and 14 to assess the reversibility of observed skin reactions.

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	7 days	2 (at 72 hours)
Oedema	2	2	2	2	72 hours	2 (at 72 hours)

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

Remarks - Results Light brown discoloration of the epidermis was noted at all treated skin sites at the 48 and 72 hour observations with an isolated incident of loss of skin elasticity at the 72-hour observation. Severe desquamation was noted at all treated skin sites at the 7-day observation. All treated skin sites appeared normal at the 14-day observation.

CONCLUSION The notified chemical is moderately irritating to the skin.

TEST FACILITY SafePharm Laboratories, Derby, UK (2003g)

7.5. Irritation - eye

TEST SUBSTANCE Amber Extreme, containing 17% (range 4.5-27%) notified chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain Rabbit/New Zealand White
Number of Animals 3
Observation Period 72 hours
Remarks - Method

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	0.33	0.33	1	24 hours	0
Conjunctiva: chemosis	0	0	0	0	-	0
Conjunctiva: discharge	0.33	0.33	0.33	1	24 hours	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	-	0

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

Remarks - Results

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY SafePharm Laboratories, Derby, UK (2003h)

7.6.1. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE Amber Extreme, containing 17% (range 4.5-27%) notified chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain Mouse/CBA/Ca
Vehicle 4:1 acetone/olive oil.
Remarks - Method

RESULTS

Concentration (% v/v Amber Extreme)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance	Mean +/- SD of 5 animals	
0 (vehicle control)	1766 +/- 347	1
25	2378 +/- 1294	1.35
50	5623 +/- 1163*	3.18
100	11158 +/- 3228*	6.32
Positive Control – alpha-hexylcinnamaldehyde		
5		2.0
10		1.9
25		6.8

* Significantly different to vehicle control group, $p<0.05$

Remarks - Results A stimulation index of greater than 3, regarded as a positive result for sensitisation, was recorded for undiluted and 50% v/v Amber Extreme.

CONCLUSION There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY SafePharm Laboratories, Derby, UK (2003i)

7.6.2. Skin sensitisation – Repeated Insult Patch Test

TEST SUBSTANCE 4% Amber Extreme, which equates to approximately 0.7% notified chemical

METHOD
Study Design Induction Procedure: The test material was applied under an occlusive

	dressing, to the upper back, to remain in direct skin contact for 24 hours. Patches were applied thrice/week for 3 weeks. Rest Period: Approximately 14 days Challenge Procedure: Patches were applied to previously untreated sites, for 24 hours. Test sites were evaluated 0, 24 and 48 hours after patch removal.
Study Group	101 adult volunteers completed the study.
Vehicle	3:1 ethanol:diethyl phthalate
Remarks - Method	A control test was run concurrently, on the same volunteers, using 4% distilled water in 3:1 ethanol:diethyl phthalate.

RESULTS

Remarks - Results	No signs of dermal irritation or sensitisation were observed with either 4% Amber Extreme or 4% distilled water.

CONCLUSION	The notified chemical was non-irritating and non-sensitising under the conditions of the test.
TEST FACILITY	Clinical Research Laboratories, Inc., Piscataway, NJ, USA (2003a)

7.7. 28-day repeat dose oral toxicity

TEST SUBSTANCE	Amber Extreme, containing 17% (range 4.5-27%) notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Rat/Crl:CD(SD)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days for 2 recovery groups only
Vehicle	Arachis oil
Remarks - Method	

RESULTS

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

Mortality and Time to Death

There were no deaths during the study.

Clinical Observations

Transient episodes of post-dose increased salivation were detected in either sex treated with 1000 mg/kg/day from Day 14 onwards, regressing in recovery 1000 mg/kg/day animals following cessation of treatment. Associated isolated findings included increased salivation observed in 1000 mg/kg/day females up to an hour after dosing and wet stained fur in one 1000 mg/kg/day male. One female treated with 150 mg/kg/day also showed excessive salivation after dosing on Day 23 only.

All female treatment groups showed a significant reduction in bodyweight gain, as well as slightly impaired food consumption and food efficiency, compared to controls, during Week 4 of the study. Females treated with 1000 mg/kg/day also showed a reduction in bodyweight gain compared to controls during Week 2 of the study. No adverse effect on food consumption or bodyweight was detected in male treatment groups. Further inter-group statistically significant differences were not considered of toxicological importance (i.e. slight increase in bodyweight gain in recovery high dose males during Week 5, and also in high dose females in Week 1).

Functional Observations

No treatment-related changes were detected in functional performance tests, sensory reactivity or behavioural assessments. There were no significant inter-group differences in functional performance tests or sensory reactivity. Inter-group differences in urination, defecation, transfer arousal and tail elevation were considered to be within the range of normal variation for rats of the species and strain used, and therefore to be of no toxicological significance.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

A statistically significant increase in prothrombin time was detected in males treated with 1000 mg/kg/day. A statistically significant increase in plasma cholesterol levels was observed in males and females treated with 1000 mg/kg/day, and in females treated with 150 mg/kg/day. In females treated with 1000 mg/kg/day this was accompanied by an increase in gamma glutamyl transpeptidase. No treatment-related changes were detected in urinalysis.

PATHOLOGY

1. Effects in Organs

Increased liver weight was detected in both sexes treated with 1000 or 150 mg/kg/day. Similar findings, to a lesser degree, were detected in recovery group 1000 mg/kg/day animals following 14 days without treatment.

2. Macroscopic Findings

Upon necropsy, abnormalities were observed in one male (red/brown staining of fur near left eye) and one female (caudal lobe of the liver firm with mottled appearance; ovaries enveloped in fluid filled sac) treated with 1000 mg/kg/day. These were considered incidental findings of no toxicological importance.

3. Histopathology

Centrilobular hepatocyte enlargement was observed in rats of either sex dosed at 1000 mg/kg/day or 150 mg/kg/day. Two male rats receiving 15 mg/kg/day were also affected. Thyroid follicular cell hypertrophy was observed with higher grades of severity for rats of either sex dosed at 1000 mg/kg/day. A similarly higher prevalence of the condition was observed for male rats dosed at 150 mg/kg/day but probably not at the low dose level. There were no differences in incidence or grades of severity for follicular cell hypertrophy between recovery control and recovery 1000 mg/kg/day animals indicating regression of the condition following completion of the recovery period.

Remarks – Results

Excessive salivation of short duration and associated findings are often reported following the oral administration of test material and the daily occurrence of these findings around the time of dosing is considered attributable to an unpleasant tasting or locally irritant formulation rather than an indication of systemic toxicity.

Liver weight changes can often be adaptive. However, in view of associated changes in haematological and clinical chemistry parameters, histopathological observations and thyroid changes, the NOAEL is 15 mg/kg bw/day.

CONCLUSION

A clear No Observed Effect Level (NOEL) was not established, due to adaptive liver changes in 2 of 5 males and reduced bodyweight gain in females treated with the lowest dose of 15 mg/kg bw/day.

The No Observed Adverse Effect Level (NOAEL) was established as 15 mg/kg bw/day in this study, based on liver weight changes in association with changes in haematological and clinical chemistry parameters, histopathological observations and thyroid changes. Noting that the test material was Amber Extreme, which contains 17% notified chemical, this equates to a NO(A)EL of 3 mg/kg bw/day.

TEST FACILITY	SafePharm Laboratories, Derby, UK (2004d)

7.8. Genotoxicity – bacteria

TEST SUBSTANCE	Amber Extreme, containing 17% (range 4.5-27%) notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100.

	E. coli: WP2uvrA$^-$.
Metabolic Activation System	S9 mix from liver homogenate of phenobarbitone/beta-naphthoflavone induced rats
Concentration Range in Main Test	a) With metabolic activation: 50 to 5000 µg/plate µg/plate. b) Without metabolic activation: 50 to 5000 µg/plate µg/plate.
Vehicle	Dimethyl sulfoxide
Remarks - Method	

RESULTS

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

Remarks - Results

CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	SafePharm Laboratories, Derby, UK (2003j)

7.9. Genotoxicity – in vitro

TEST SUBSTANCE	Amber Extreme, containing 17% (range 4.5-27%) notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Cell Type/Cell Line	Chinese Hamster Lung
Metabolic Activation System	S9 mix from liver homogenate of phenobarbitone/beta-naphthoflavone induced rats
Vehicle	Acetone
Remarks - Method	

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 0.63, 1.25*, 2.5*, 5.0*, 7.5*, 10	6 hours	24 hours
Test 2	0*, 0.63, 1.25*, 2.5*, 5.0*, 7.5*, 10	24 hours	24 hours
Present			
Test 1	0*, 5.0, 10*, 20*, 40*, 60, 80	6 hours	24 hours
Test 2	0*, 2.5, 5.0*, 10*, 20*, 40, 60	6 hours	24 hours

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				

Test 1	0.08 µg/mL	1.25 µg/mL	Not observed up to 10 µg/mL	Not observed up to 10 µg/mL
Test 2		1.25 µg/mL	Not observed up to 10 µg/mL	Not observed up to 10 µg/mL
Present				
Test 1	0.31 µg/mL	10 µg/mL	Not observed up to 80 µg/mL	Not observed up to 80 µg/mL
Test 2		5.0 µg/mL	Not observed up to 60 µg/mL	Not observed up to 60 µg/mL

Remarks - Results: No statistically significant rises were observed in the frequency of cells with aberrations, or in the number of polyploid cells, in any exposure group. The positive controls tested accordingly.

CONCLUSION: The notified chemical was not clastogenic to Chinese hamster lung cells treated in vitro under the conditions of the test.

TEST FACILITY: SafePharm Laboratories, Derby, UK (2003k)

7.10. Genotoxicity – in vivo

TEST SUBSTANCE: Amber Extreme, containing 17% (range 4.5-27%) notified chemical

METHOD: OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain: Mouse/Crl:CD-1
Route of Administration: Range finding test – oral gavage and intra-peritoneal injection
Micronucleus test – intra-peritoneal injection
Vehicle: Arachis oil
Remarks - Method

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	14 male	0	24 (n=7) and 48 (n=7)
II (low dose)			
III (mid dose)			
IV (high dose)	14 male	2000	24 (n=7) and 48 (n=7)
V (positive control, CP)	5	50	24

CP=cyclophosphamide.

RESULTS
Doses Producing Toxicity: No premature deaths or clinical signs of toxicity observed at 2000 mg/kg bw. However, there was a non-statistically significant reduction in the ratio of polychromatic to normochromatic erythrocytes in animals dosed with 2000 mg/kg bw Amber Extreme, which may indicate cytotoxicity in the bone marrow. This was taken to indicate that systemic adsorption had occurred.
Genotoxic Effects: There were no statistically significant increases in the frequency of micronucleated polychromatic erythrocytes in animals treated with Amber Extreme.
Remarks - Results

CONCLUSION: The notified chemical was not genotoxic under the conditions of this test.

TEST FACILITY: SafePharm Laboratories, Derby, UK (2003l)

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE	Amber Extreme, containing 17% (range 4.5-27%) notified chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO2 Evolution Test.
Inoculum	Activated Sewage Sludge bacteria
Exposure Period	28 days
Auxiliary Solvent	Granular Silica Gel
Analytical Monitoring	Tekmar-Dohrmann Apollo 9000 TOC analyser and Ionics 1555B TOC Analyzer
Remarks - Method	The test material was sorbed onto granular silica gel prior to the addition to culture media. This was done to increase dispersion of the test material throughout the solution and to increase the surface area available for degradation. A test concentration of 10 mg C/L was used in the study. The inoculum was aerated overnight in culture medium prior to the addition of test materials. Samples were collected from the first CO_2 absorber vessel on Days 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 27, 28 and 29. Samples taken on Days 12 and 18 were not analysed. On day 28 test vessels were treated with 1 mL of concentrated hydrochloric acid to drive off any inorganic carbonates formed. TOC analyses were performed on samples of the control and standard material on Days 0 and 28. DOC analysis was not performed on the test material dispersions due to the insolubility of the test material.

RESULTS

Test substance		*Sodium Benzoate*	
Day	*% degradation*	*Day*	*% degradation*
1	3	1	24
6	0	6	65
10	0	10	84
16	0	16	84
22	0	22	88
28	2	28	95

Remarks - Results	The extent of degradation of the reference material validates the test. A toxicity control containing test material and sodium benzoate reached 35% degradation on day 28 indicating that the notified chemical is not toxic to sewage treatment organisms.
CONCLUSION	The notified chemical cannot be classed as ready biodegradable.
TEST FACILITY	SafePharm Laboratories, Derby, UK (2003m)

8.1.2. Bioaccumulation

The notified chemical has a high proportion of aliphatic carbon carbon bonds, molecular weight > 100, log K_{ow} > 2, low water solubility, is resistant to biodegradation and is not readily ionisable. All these factors indicate that the notified chemical has potential to bioaccumulate (Connell 1989).

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE	Amber Extreme, containing 17% (range 4.5-27%) notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static conditions.
Species	Rainbow Trout (*Oncorhynchus mykiss*)
Exposure Period	96 h
Auxiliary Solvent	Dimethylformamide (DMF)
Water Hardness	190 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	A 2 g/L stock solution of the test material (200 mg) in DMF (100 mL) was prepared. An aliquot (2.2 mL) of the stock solution was diluted to give a final volume of 22 L with dechlorinated water. All test solutions were clear. The test vessels were completely filled with minimal headspace and sealed to minimise losses due to volatilisation. Limit of quantification (LOQ) was 7.8×10^{-4} mg/L. Water quality parameters of pH (7.5-7.6), water temperature (14.3-14.5ºC) and O_2 content (7.8-10.3 mg/L) were within normal limits throughout study. Test solutions were renewed daily.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*					
Nominal	*Actual*		*3h*	*6h*	*24h*	*48h*	*72h*	*96h*
0	0	20	0	0	0	0	0	0
0.2	0.055	20	0	0	0	0	0	0

LC50	>0.055 mg/L at 96 hours.
NOEC	0.055 mg/L at 96 hours.
Remarks – Results	No mortalities or sublethal effects were observed throughout this limit test. The measured concentration reported above is the time weighted average of centrifuged samples of the test solutions prepared throughout the study. The mean measured concentration without centrifugation at the beginning and end of each 24 hour period was found to be 0.145 and 0.0512 mg/L, respectively.
CONCLUSION	The test material was not toxic to fish up to the limit of its water solubility.
TEST FACILITY	SafePharm Laboratories, Derby, UK (2004a)

8.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Amber Extreme, containing 17% (range 4.5-27%) notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – semi-static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	DMF
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks - Method	A 2 g/L stock solution of the test material (200 mg) in DMF (100 mL) was prepared. An aliquot (2.2 mL) of the stock solution was diluted to give a final volume of 20 L with reconstituted water. All test solutions were clear. The test vessels were completely filled with minimal headspace and sealed to minimise losses due to volatilisation. The LOQ was 7.8×10^{-4} mg/L. Water quality parameters of pH (7.6-8.0), water temperature (20.1-21.4ºC) and O_2 content (8.1-8.7 mg/L) were within normal limits throughout study. Test solutions were renewed daily.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0	0	40	0	0
0.2	0.099	40	0	0

LC50	>0.099 mg/L at 48 hours
NOEC	0.099 mg/L at 48 hours
Remarks - Results	No immobilised daphnia or sublethal effects were observed throughout this limit test. The measured concentration reported above is the time weighted average of centrifuged samples of the test solutions prepared throughout the study. The mean measured concentration at the beginning and end of each 24 h period was found to be 0.162 and 0.131 mg/L, respectively.
CONCLUSION	The test material was not toxic to daphnia up to the limit of its water solubility.
TEST FACILITY	SafePharm Laboratories, Derby, UK (2004b)

8.2.3. Algal growth inhibition test

TEST SUBSTANCE	Amber Extreme, containing 17% (range 4.5-27%) notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Scenedesmus subspicatus*
Exposure Period	72 hours
Concentration Range	
Nominal	0-0.2 mg/L
Actual	0.093 mg/L
Auxiliary Solvent	
Water Hardness	Not reported
Analytical Monitoring	HPLC
Remarks - Method	The test vessels were completely filled with minimal headspace and sealed to minimise losses due to volatilisation. Additional sodium bicarbonate was added to the culture medium to provide a source of carbon dioxide for algal growth. The initial cell density in the test media was 10^4 cells per mL. The LOQ was 7.8×10^{-4} mg/L. The initial pH of the test solutions ranged from 7.6-7.7. At the completion of the study the observed pH range in the test media was 9.0-9.3.
RESULTS	Algae were exposed to the notified chemical at a nominal concentration of 0.2 mg/L under constant illumination and aeration. After 72 hours, there was no significant inhibition of algal growth or biomass at the measured concentration of 0.093 mg/L. Therefore, the EC50 > 0.093 mg/L and NOEC = 0.093 mg/L.
CONCLUSION	The test material was not toxic to algae up to the limit of its water solubility.
TEST FACILITY	SafePharm Laboratories, Derby, UK (2004c)

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The notified chemical is considered to be moderately volatile. Therefore, its loss to the atmosphere is likely to be significant from sewers and the aquatic environment. In the atmosphere it is anticipated that the notified chemical will be rapidly degraded through reaction with hydroxyl radicals (Atkinson 1985). It is not readily biodegradable (2% after 28 days in a CO_2 Evolution Test), it has low solubility in water (<0.202 mg/L) and has a hydrolysis half-life of greater than 1 year at pH 4, 7 and 9.

The measured log K_{oc} of >5.63 indicates that the notified chemical is of low mobility in soil. Thus leaching in landfill is unlikely to occur with further possibility of abiotic or slow biotic processes largely responsible for the degradation of the notified chemical disposed of to landfill.

Following its use in Australia, practically all the notified chemical will eventually be released into the aquatic environment. A calculated worst-case scenario daily predicted environmental concentration (PEC) in the sewer effluent is 0.30 µg/L. In calculating the PEC, the following were assumed: (1) usage of the maximum import volume (138 kg) is evenly distributed over a 365 day period; (2) usage is nationwide, with a population of 20.1 million contributing 200 L of water per person per day to the sewer; and (3) there is no adsorption or degradation in the sewer prior to release. However, data provided by the notifier indicates that the notified chemical has some affinity to organic matter (measured log K_{oc} > 5.63); some losses may also occur through adsorption to suspended solids in the sewer, thereby decreasing the PEC.

Using the SIMPLETREAT model for modelling partitioning and losses in sewage treatment plants (European Communities, 2003), the percentage removal from solution by sewage treatment plant (STP) approximates 65% through volatilisation, 28% adsorption in sludge, and 0% biodegraded. This is based on the Henry's Law Constant Log H of 2.7, log K_{ow} of 4.42 and lack of biodegradability. Hence, approximately 7% of the inflow concentration of the notified chemical may potentially remain in solution, passing through the STP. The resulting PEC concentrations in treated effluents will be reduced to 0094 µg/L × 0.0066 = 0.021 µg/L.

Based on the respective dilution factors of 1 and 10 for rural areas and coastal discharges of effluents, the PEC of the notified chemical in rural areas and coastal water may approximate 0.021 and 0.0021 µg/L, respectively.

Partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 0.084 mg/kg (dry weight), assuming 28% attenuation in sludge during the STP process. This is based on the assumption that 0.1 tonne of biosolids is generated for each ML of STP effluent and the consumption of 4020 ML/day for total population per year. Biosolids are applied to agricultural soils, with an assumed average rate of 10 t/ha/year. Assuming a soil bulk density of 1000 kg/m^3 and a soil mixing zone of 0.1 m, the concentration of the notified chemical may approximate 0.084 mg/kg in the applied soil, assuming accumulation of the notified chemical in soil for 10 years under repeated biosolids application.

The effluent re-use (eg. irrigation purposes) concentration of the notified chemical may potentially approximate 0.021 µg/L, assuming 7% remains in solution during the STP process. STP effluent re-use for irrigation in Australia occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 0.1 m of soil (density 1000 kg/m^3). Using these assumptions, irrigation with a concentration of 0.021 µg/L may potentially result in a soil concentration of approximately 2.1 µg/kg assuming accumulation of the notified chemical in soil for 10 years under repeated irrigation with no degradation or losses.

The worst-case PEC values are summarised below:

Sewage effluent/ocean outfall = 0.30 µg/L
Sewage effluent/river discharge = 0.030 µg/L.

The mitigated PEC values are summarised below after taking into account the SIMPLETREAT model
Sewage effluent/ocean outfall = 0.021 µg/L
Sewage effluent/river discharge = 0.0021 µg/L.
Soil concentrations after 10 years application of biosolids = 84 µg/kg
Soil concentrations following 10 years irrigation with effluent = 2.1 µg/kg.

The notified chemical has a high proportion of aliphatic carbon-carbon bonds, molecular weight > 100, log K_{ow} > 2, low water solubility, is resistant to biodegradation and is not readily ionisable. All these factors would indicate that the notified chemical has potential to bioaccumulate (Connell 1989). However, given the volatility of the chemical, low level and diffuse release bioaccumulation is not expected.

9.1.2. Environment – effects assessment

Using the lowest EC50 of >0.055 mg/L for rainbow trout, a predicted no effect concentration (PNEC) of >0.55 µg/L has been derived by dividing the LC50 value by a safety factor of 100 since toxicity data are available for three trophic levels. It should be noted that the endpoints for fish is a limit value and the true LC50 is greater.

9.1.3. Environment – risk characterisation

Location	PEC (µg/L)	PNEC (µg/L)	PEC/PNEC ratio
Australia-wide STPs (worst case)			
Ocean outfall	0.0094	>0.55	<0.017
River discharge	0.094	>0.55	<0.17
After mitigation using SIMPLETREAT model (7% remains in solution)			
Ocean outfall	0.00066	>0.55	<0.0012
River discharge	0.0066	>0.55	<0.012

The values of the PEC/PNEC ratio for the aquatic environment are significantly less than 1, for both marine and fresh water organisms, indicating no immediate concern to the aquatic compartment. The low import volumes (ie. 138 kg/year) and the anticipated nationwide use of the notified chemical indicate that the levels of release of the chemical to the environment will be low and hence the notified chemical is unlikely to pose an unacceptable risk to the environment.

Simple calculations indicate that over 45 tonnes would need to be released before an unacceptable risk was reached. These take into account the mitigation and that only 25% would be to fresh water. It is unlikely that this level of importation will be achieved for this product.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

Transport & Storage

Occupational exposure to the notified chemical during transport and storage of imported fragrance oils containing the notified chemical is only likely in the event of accidental container breakage and/or spillage. Exposure in these circumstances is expected to be infrequent and acute, and can be limited by use of gloves, goggles, masks and protective clothing during clean-up operations.

Formulation

During reformulation of fragrance preparations containing the notified chemical into lotions, toiletries and household products, dermal exposure is the most likely route. Ocular exposure may occur due to accidental splashes. Exposure may occur when workers open the drums of fragrance oil containing imported notified chemical at approximately 0.2%, when weighing and transferring the imported fragrance preparations into mixing vessels, during blending operations and when cleaning up spills and equipment.
Exposure to the notified chemical during filling of consumer product containers is expected to be minimal, as the filling of consumer containers is typically automated.
Dermal and inhalation exposure during formulation was estimated using the EASE model (HSE,

1994). Assuming non-dispersive use and intermittent direct handling, the estimated dermal exposure during formulation is 0.1-1 mg/cm^2/day of fragrance oils containing approximately 0.2% of the notified chemical. This equates to 0.0002-0.002 mg/cm^2/day of the notified chemical. Absorption of the notified chemical may be significant, as the substance has a high Log P_{ow} and fat solubility so ready diffusion across membranes would be expected. Therefore, for a 70 kg worker with surface area for hands at 820 cm^2 and forearms at 1140 cm^2, and assuming 100% absorption, systemic exposure is estimated to be 0.006-0.06 mg/kg bw/day of the notified chemical. This exposure would be substantially reduced by the use of protective clothing and gloves.
The estimated atmospheric concentration of Amber Extreme during formulation, assuming non-dispersive use and direct handling (i.e. open systems), is 0-1.1 mg/m^3 in the absence of aerosols, and greater than 11,000 mg/m^3 if aerosols are formed. Use of local exhaust ventilation (LEV) reduces exposure from aerosols to 1,100-2,200 mg/m^3, while use of a closed system reduces exposure to 0-1.1 mg/m^3, even in the presence of aerosols. Amber Extreme contains approximately 0.2% notified chemical, so this equates to 0-0.22 mg/m^3 in the absence of aerosols, greater than 2,200 mg/m^3 in an open system with aerosol formation, 220-440 mg/m^3 if LEV only is used to reduce exposure in the presence of aerosols, and 0-0.22 mg/m^3 for a closed system. Therefore for a 70 kg worker, assuming an inhalation rate of 1.3 m^3/hour, a 4 hour exposure time and 100% bioavailability, inhalation exposure is estimated to be 0-0.02 mg/kg bw/day in the absence of aerosols, greater than 200 mg/kg bw/day in an open system with aerosol formation, 20-40 mg/kg bw/day if LEV is the only control used to reduce exposure in the presence of aerosols, and 0-0.02 mg/kg bw/day for a closed system.
Inhalation exposure to the notified chemical would be further reduced by the use of personal respiratory equipment.

Exposure during formulation will be further limited by the low frequency of formulating days (2/year).

End Use
Occupational exposure to end use consumer products may occur, for example, with professional cleaners using cleaning products, beauticians using cosmetic products, or hairdressers using hair products. These workers are less likely to use extensive PPE; however, the concentration of notified chemical in end use products will be 0.0005-0.02%.
Using the EASE model, and assuming wide dispersive use with extensive, direct handling, estimated dermal exposure to end use products is 5-15 mg/cm^2/day of end use products. This equates to a maximum of 0.000075-0.003 mg/cm^2/day of notified chemical at 0.0005-0.02% in most end use products. For a 70kg worker with 1960 cm^2 surface area and assuming 100% absorption (as above), systemic exposure is therefore estimated to be 0.0021-0.084 mg/kg bw/day of the notified chemical for end use products.

9.2.2. Public health – exposure assessment

It is expected that during import, transport, storage and reformulation of fragrance oils containing the notified chemical, exposure of the general public will be limited, except in the event of an accidental spill.
Consumer products containing the notified chemical (body creams, hair products, deodorant sprays, bath and shower products, dishwashing and fabric washing products) will be sold to the general public; consequently there is likely to be widespread public exposure. Exposure will be principally by the dermal route, with the potential for occasional accidental ocular exposure. Exposure to the notified chemical is considered minimal based on the small amount of notified chemical in final consumer products (ranging from 0.0005% to 0.02%).
Consumer exposure to the notified chemical in different types of product, estimated using algorithms developed by HSE (1994), is summarised in the following table:

Product	Route of exposure	Estimated exposure
Creams and lotions	Dermal	0.0024 mg/kg bw/day
Hairspray	Inhalation	3 x 10^{-5} mg/kg bw/day
Bath products	Dermal	3 x 10^{-5} mg/kg bw/day
Air freshener	Inhalation	0.0003 mg/kg bw/day
Surface cleaner	Dermal	3 x 10^{-6} mg/kg bw/day

9.2.3. Human health – effects assessment

Amber Extreme, the proprietary mixture containing the notified chemical at 4.5-27% (typically 17%) is of low acute oral and dermal toxicity in rats. Acute inhalation toxicity data were not provided. Amber Extreme has very low volatility and is not expected to cause significant adverse effects by inhalation.

Amber Extreme, containing 17% notified chemical, is not mutagenic in a bacteriological test and not clastogenic to Chinese hamster lung cells. No genotoxic effects of Amber Extreme were observed *in vivo* in a mouse erythrocyte micronucleus study.

Amber Extreme, containing 17% notified chemical, was found to be moderately irritating to rabbit skin, slightly irritating to rabbit eye, and produced evidence of skin sensitisation *in vivo* in a mouse local lymph node assay. However, no responses indicative of skin irritation or sensitisation were seen in 101 adult human volunteers exposed repeatedly to 4% Amber Extreme (0.7% notified chemical) over 3 weeks.

In rats, a 4-week repeat dose oral toxicity study did not establish a NOEL, but the NOAEL was 15 mg/kg bw/day of Amber Extreme, which equates to 3 mg/kg bw/day of notified chemical. This was based on liver weight changes in association with changes in haematological and clinical chemistry parameters, histopathological observations and thyroid changes at the next highest dose of 150 mg/kg bw/day Amber Extreme. Treatment-related effects at the NOAEL of 15 mg/kg bw/day Amber Extreme were considered minor, and comprised adaptive changes to the liver and reduced bodyweight gain in some animals.
The observation of adverse effects at the dose level of 150 mg/kg bw/day Amber Extreme, which equates to 30 mg/kg bw/day notified chemical, in a 28 day toxicity test, reaches the relevant cut-off for consideration of the risk classification R48 Danger of serious damage to health by prolonged exposure. However, this classification is not considered appropriate, due to the limited extent of the adverse effects observed, along with evidence of reversibility of adverse effects during the recovery period.

Based on the available data, the notified chemical is classified as a hazardous substance and is assigned R38 (irritating to skin) and R43 (may cause sensitisation by skin contact) in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2002).

9.2.4. Occupational health and safety – risk characterisation

The notified chemical is of low acute toxicity (LD50 >425 mg/kg for oral route and >340 mg/kg for dermal route). Therefore the risk of acute toxic effects in workers is low. The notified chemical is moderately irritating to skin, slightly irritating to eye, and may cause sensitisation by skin contact. However, there was no evidence of skin irritation or sensitisation in humans exposed to 4% Amber Extreme, and imported fragrance oils will contain up to 1% Amber Extreme.
If there are accidental spills during transport or storage of the imported fragrance oils containing approximately 0.2% notified chemical, workers can limit exposure by using skin and eye protection, including gloves, protective clothing and safety glasses or goggles. 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 and sensitisation effects in workers, although this is limited by the low concentration of notified chemical in fragrance oils. Workers can further limit this risk by using protective clothing, gloves and safety glasses when opening the drums, transferring the fragrance oil into mixing vessels and cleaning up spills and equipment.

During formulation, dermal exposure to the notified chemical was estimated to be 0.006–0.06 mg/kg bw/day, based on an exposure of 4 hours/day. Inhalation exposure during formulation was estimated to be 20-40 mg/kg bw/day for an open system with aerosol formation and local exhaust ventilation, 0-0.02 mg/kg bw/day for an open system with local exhaust ventilation and no aerosol formation, and 0-0.02 mg/kg bw/day for a closed system.

The margin of exposure (MOE) for chronic toxicity is based on a NOAEL of 3 mg/kg bw/day. The following table summarises cumulative exposure and corresponding MOE for each different operation scenario.

Scenario	Open system Aerosols	Open system No aerosols	Closed system
Dermal exposure (mg/kg bw/day)	0.006-0.06	0.006-0.06	0.006-0.06
Inhalation exposure (mg/kg bw/day)	20-40	0-0.02	0-0.02
Total exposure (mg/kg bw/day)	20-40 (dermal contribution negligible)	0.006-0.08	0.006-0.08
MOE	0.08-0.15	38-500	38-500

MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. Therefore, the risk of chronic systemic toxicity using modelled worker data is not acceptable for workers handling fragrance preparations containing approximately 0.2% notified chemical in an open system if aerosols are formed. In this scenario, personal respiratory PPE will be required to limit inhalation exposure. If no aerosols are formed, or if a closed system is used, the risk of chronic systemic toxicity is marginally unacceptable. Occupational risk in this situation can be limited by the use of PPE, particularly gloves and protective clothing to limit dermal exposure.
The risks of chronic exposure are also limited by the predicted exposure frequency, which for reformulation workers is up to 2 days/year.

Maximum dermal exposure to end use cosmetic and hair products containing 0.0005-0.001% notified chemical is estimated to be 0.0021-0.0042 mg/kg bw/day. Using the same toxicity data (NOAEL of 3 mg/kg bw/day), the MOE is calculated to be 714-1429. Therefore the risk to beauticians and hairdressers handling end use products in the absence of PPE is acceptable.

Maximum dermal exposure to end use cleaning products containing approximately 0.002% notified chemical is estimated to be 0.084 mg/kg bw/day. Using the same toxicity data, the MOE is calculated to be 36. Therefore, exposure to these products by end use workers such as professional cleaners should be limited by use of protective clothing and gloves.

9.2.5. Public health – risk characterisation

It is expected that public exposure to imported fragrance oils containing approximately 0.2% notified chemical for industrial use will be minimal except in the rare event of an accidental spill. There will be public exposure to the notified chemical from dermal, inhalation, oral and ocular exposure to lotions, toiletries, and household products containing a maximum of 0.07% notified chemical.
The MOE for consumer exposure to the notified chemical in different types of product, based on a NOAEL of 3 mg/kg bw/day, is summarised in the following table:

Product	Route of exposure	MOE
Creams and lotions	Dermal	1500
Hairspray	Inhalation	$>10^5$
Bath products	Dermal	$>10^5$
Air freshener	Inhalation	$>10^4$
Surface cleaner	Dermal	$>10^5$

Consequently the public risk from exposure to the notified chemical through all phases of its life cycle is considered to be low.

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

10.1. Hazard classification

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:
R38 Irritating to skin
R43 May cause sensitisation by skin contact

As a comparison only, the classification of notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2003) is presented below. This system is not mandated in Australia and carries no legal status but is presented for information purposes.

	Hazard category	*Hazard statement*
Skin corrosion/irritation	3	Causes mild skin irritation
Skin sensitiser	1	May cause allergic skin reaction

It is not possible to assign an aquatic environmental hazard category according to the GHS classification as only limit toxicity data is available.

10.2. Environmental risk assessment

On the basis of the PEC/PNEC ratio, the chemical is not considered to pose a risk to the environment based on its reported use pattern.

10.3. Human health risk assessment

10.3.1. Occupational health and safety

There is Moderate Concern for formulation workers and professional cleaners, and Low Concern for all other workers, regarding occupational health and safety, under the conditions of the occupational settings described.

10.3.2. Public health

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

11. MATERIAL SAFETY DATA SHEET

11.1. Material Safety Data Sheet

The MSDS of Amber Extreme, the component of imported fragrance oils containing approximately 20% notified chemical, provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC 2003). It is published here as a matter of public record. The accuracy of the information on the MSDS remains the responsibility of the applicant.

11.2. Label

The label for Amber Extreme, the component of imported fragrance oils containing approximately 20% notified chemical, provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC 1994). The accuracy of the information on the label remains the responsibility of the applicant.

12. RECOMMENDATIONS

REGULATORY CONTROLS
Hazard Classification and Labelling

- The NOHSC Chemicals Standards Sub-committee should consider the following hazard classification for the notified chemical, and for Amber Extreme, the mixture containing the notified chemical that was used for all toxicological testing and hazard classification:
  - R38 Irritating to skin
  - R43 May cause sensitisation by skin contact
  - S24 Avoid contact with skin

- S37 Wear suitable gloves

- Use the following risk phrases for products/mixtures containing the notified chemical and/or Amber Extreme:
  - 1-20%:
    - R43 May cause sensitisation by skin contact
  - >= 20%:
    - R43 May cause sensitisation by skin contact
    - R38 Irritating to skin

CONTROL MEASURES

Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical:
  - Closed system during mixing of ingredients with fragrance oils containing the notified chemical or the mixture Amber Extreme, particularly if aerosol formation is likely.
  - LEV during weighing and addition to mixing vessel.

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical:
  - Prevent splashes and spills.
  - Prevent aerosol formation during handling, particularly if mixing in an open tank.

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical during formulation of fragrance preparations containing it into consumer products:
  - Chemical resistant gloves, protective overalls and goggles/faceshield.
  - Personal respiratory equipment if aerosols are produced in an open system.

  Guidance in selection of personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

- A copy of the MSDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances*, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Environment

- Do not allow fragrance oils or packaging contaminated with fragrance oils to enter drain, sewers or water course.

Disposal

- The notified chemical should be disposed of by placing material and absorbent into sealed container and dispose of to landfill.

Emergency procedures

- Spills/release of the notified chemical should be contained as described in the MSDS (i.e. by sand or inert powder) and collected in labelled sealable containers for disposal in accordance with Government regulations.

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 subsection 64(1) of the Act; if
- the importation volume exceeds one tonne per annum notified chemical; or
- the notified chemical is itself manufactured locally or imported

or

(2) 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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