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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

ET-344-SP

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Director
Chemicals Notification and Assessment

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Takasago International Corp. of Level 4, 275 Alfred Street NORTH SYDNEY NSW 2060

NOTIFICATION CATEGORY
Standard: Chemical other than polymer.

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: chemical name, CAS number, molecular and structural formulae, molecular weight, spectral data, purity and details of exact import volume.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: manufacturing process, dissociation constant, particle size and inhalation toxicity.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None.

NOTIFICATION IN OTHER COUNTRIES
Not stated.

2. IDENTITY OF CHEMICAL

OTHER NAME(S)
20178810-0

MARKETING NAME(S)
ET-344-SP

METHODS OF DETECTION AND DETERMINATION

ANALYTICAL METHOD	UV/vis, IR, ^{1}H-NMR, ^{13}C-NMR, and MS
TEST FACILITY	Not stated.

3. COMPOSITION

DEGREE OF PURITY
High

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None.

ADDITIVES/ADJUVANTS
None.

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notifier has not yet determined whether the chemical would be imported as a neat substance, as a component in fragrance oil preparations (maximum 1%) or both. The fragrance oil preparation will be reformulated in Australia to produce the final consumer products. In the consumer products, the concentration of the notified chemical will be 0.01%.

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

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

USE
The notified chemical will be used as a component in cosmetic, personal care and household cleaning products. Concentration of the notified chemical in these end use products is estimated to be less than 1% and normally closer to 0.01%.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, transport and storage

PORT OF ENTRY
Not stated.

IDENTITY OF MANUFACTURER/RECIPIENTS
Takasago International Corp.

TRANSPORTATION AND PACKAGING
The neat chemical will be imported in containers varying in size from 1kg to 200kg. While the fragrance preparation will be imported in drums of approximately 200kg. Locally formulated or imported final product will be sold in a variety of containers ranging from approx. 0.1kg to 5kg in size.
If the notified chemical is imported as a neat substance or in blended fragrance oil preparations, the imported packages will be transported from the docks by road to the notifiers warehouse or to formulators. Formulated consumer product containing the notified chemical, both locally formulated or imported, will be transported by road to retail stores for distribution.

5.2. Operation description
The formulation process, mainly involving a blending operation, is likely to be automated and will often occur in a fully enclosed environment. Plant operators will only be involved in opening and closing drums, weighing and charging the chemicals into a mixing vessel, and cleaning and maintenance the equipment.
End-use of consumer products will be widespread and dispersive.

5.3. Occupational exposure

EXPOSURE DETAILS
Transport and Storage
Transport and warehouse workers will be exposed to the notified chemical and the end use products containing the notified chemical only in the event of a spill due to an accident or leaking drum.

Formulation
During formulation into consumer products, the number and category of workers will vary depending on the nature of the customer's business. Occupational exposure is possible during handling of the drums, weighing and transfer of the notified chemical, quality control processes, and cleaning and maintenance of the equipment. Skin and inhalation are likely to be the main routes of exposure. Eye contact due to splashing is also possible.

The formulation process is expected to be in compliance with good manufacturing practices. It is

anticipated that cosmetic and consumer product manufacturers will apply good industrial hygiene practices and use industrial standard personal protective equipment (PPE) at their formulation sites. Typical processes will include the use of local exhaust ventilation, enclosed mixing vessels and automatic filling systems. It is expected that some but not all formulation plant would have fully automated equipment. In addition, industrial standard PPE will be used, and self-contained breathing apparatus are on site for use when required.

Laboratory technicians and maintenance workers may be exposed to the products, and would normally employ PPE and good work practices, in order to minimise exposure to all ingredients of the products.

Once the notified chemical has been incorporated into consumer products, the concentration of the chemical in the products will be approximately 0.01%, and any further occupational exposure as a result of accidental contact with the products would be low.

End Use

Worker exposure to end use products may include professional cleaners (household cleaning products) and beauticians (cosmetics and perfumes). These workers can be expected to use minimal PPE. However, the final concentration of notified chemical in cleaning and cosmetic products will be approximately 0.01%.

5.4. Release

RELEASE OF CHEMICAL AT SITE

The notified chemical will either be imported in end use products, or customers of the notifier may blend the notified chemical into a range of consumer products at their facilities. The waste from the blending process is expected to be limited to traces remaining from the clean-up of spills, residues in empty packaging and discharges to plant effluent systems. At the end of the formulation run, the formulating and packing equipment is washed and it is anticipated that the washings will be included in the next batch. Release during the formulation process is expected to be small as almost closed and automated systems are used.

Less than 10 kg per annum of the notified chemical are expected to remain as residues in import containers. The notifier expects that due to the high unit value of the material and the high cost of removal from plant effluents, residues are minimised before containers are recycled or disposed of to landfill.

RELEASE OF CHEMICAL FROM USE

Since the majority of the products into which the notified chemical will be imported or formulated are expected to be released to the sewer either during or after use, a diffuse environmental release of almost all the notified chemical is expected.

Release due to residues in consumer product containers is expected to be low. These containers, which will vary in size and construction material, will be recycled or disposed of to landfill. Some release of the notified chemical to the atmosphere through evaporation.

5.5. Disposal

The majority of the notified chemical will be disposed of through the sewerage system. A small amount may be disposed of to landfill as residues in containers.

5.6. Public exposure

The main source of public exposure would be through consumer use of household and cosmetic products containing the notified chemical at approximately 0.01%. The range of consumer products in which the notified chemical may be used is varied from cosmetics, perfumery, personal cleaning products, to household and laundry products. Exposure will be mainly by skin contact, with personal products either washed off after use, or left on the skin. Inhalation exposure may also occur, and is expected to be higher through use of spray products, air fresheners or those where the perfume volatilises quickly.

Inadvertent public exposure to the notified chemical could occur in case of accidents in transport.

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa Colourless non-viscous liquid

Melting Point/Freezing Point < -20°C

METHOD EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks Dry-ice bath method.
TEST FACILITY SafePharm Laboratories (1993a).

Boiling Point 228°C at 101.3 kPa

METHOD EC Directive 92/69/EEC A.2 Boiling Temperature - Siwoloboff method.
Remarks Siwoloboff method.
TEST FACILITY SafePharm Laboratories (1993a).

Density 926.4 kg/m^3 at 20°C

METHOD EC Directive 92/69/EEC A.3 Relative Density – Pycnometer method
Remarks Pycnometer method.
TEST FACILITY SafePharm Laboratories (1993a).

Vapour Pressure 0.03 kPa at 25°C

METHOD EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks Isoteniscope method. Calculated data. The results indicate the notified chemical is volatile (Mensink *et al.* 1995).
TEST FACILITY Leeds University (1993).

Water Solubility 31.2 mg/L at 20°C

METHOD EC Directive 92/69/EEC A.6 Water Solubility.
Remarks Shake Flask method.
Double distilled water was shaken with an excess of the test material. The aqueous phase was centrifuged and filtered prior to extraction with dichloromethane. Quantification of levels was achieved using gas chromatography. One deviation in method – test mixtures prepared at approximately 30 times saturation level.
TEST FACILITY SafePharm Laboratories (1993a).

Fat Solubility Miscible in all preparations with standard fat (HB 307) at 37°C

METHOD Modified version of Standard method A.7 of EC Directive 84/449/EEC.
Remarks Shake Flask method. Test was conducted according to GLP and QA. Concentration of test substance was determined using GC.
TEST FACILITY SafePharm Laboratories (1993a).

Hydrolysis as a Function of pH

METHOD EC Directive 84/449/EEC C.10 Abiotic Degradation: Hydrolysis as a Function of pH.

Remarks Test was done according to GLP and QA.
Less than 10% hydrolysis was observed after 5 days at 50°C in buffer solutions with pH values of 4, 7 and 9. Hence the test substance does not readily hydrolyse.
TEST FACILITY SafePharm Laboratories (1993a)

Partition Coefficient (n-octanol/water) log Pow = 4.51

METHOD EC Directive 84/4499/EEC A.8 Partition Coefficient.
Remarks Shake Flask Method. A stock solution of the test material was prepared in n-octanol saturated water and shaken with varying volumes of water saturated n-octanol for 5 minutes. The organic and aqueous phases were analysed by gas chromatography.
TEST FACILITY SafePharm Laboratories (1993a)

Adsorption/Desorption log K_{oc} = 2.77-2.95
– screening test

METHOD OECD TG 106 Adsorption - Desorption Using a Batch Equilibrium Method.

Soil Type	*Organic Carbon Content (%)*	*pH*	*Koc (mL/g)*
Sandy loam (1)	0.6	4.8	893
Sandy loam (2)	1.8	5.5	596
Sandy loam (3)	0.6	7.3	877

Remarks An aliquot (0.0850 g) of the test material was dissolved in methanol (100 mL) and diluted by a factor of 100 with 0.01 M $CaCl_2$ solution. Duplicates of soil and test solution were equilibrated for each soil type over a 16 h period of shaking. After shaking samples were centrifuged to separate the phases and analysed by gas chromatography. The results of this study were used to determine the above Koc values. The soil sample were then equilibrated to fresh $CaCl_2$ solution in order to measure the rate of desorption. For all soils the amount of test material desorbed was around 34%.
TEST FACILITY SafePharm Laboratories (1996a).

Dissociation Constant Not determined

Remarks There is no mode of dissociation for this chemical.

Surface Tension 69.6 mN/m at 25°C for a 1.61×10^{-2} g/L solution

METHOD EC Directive 92/69/EEC A.5 Surface Tension.
Remarks Test was conducted according to GLP and QA. The test was performed using a surface tensiometer. Concentration of test substance was determined using GC.
One deviation in method – surface tension result not corrected using the Harkins-Sordan correction table.
TEST FACILITY SafePharm Laboratories (1993a).

Particle Size Not determined for a liquid

Flash Point 87.8°C

METHOD EC Directive 92/69/EEC A.9 Flash Point.
Remarks Closed-cup.
TEST FACILITY SafePharm Laboratories (1993b).

Flammability Limits Not determined
Remarks The chemical is not pyrophoric or flammable in contact with water based on its chemical structure and experience in use the chemical.

Autoignition Temperature 300°C

METHOD 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
TEST FACILITY SafePharm Laboratories (1993b).

Explosive Properties Not explosive under influence of flame or shock.

METHOD 92/69/EEC A.14 Explosive Properties.
TEST FACILITY SafePharm Laboratories (1993b).

Reactivity

Remarks The chemical is not expected to have oxidising properties based on its structure and experience in use.

None known any incompatibility with other substances or conditions contributing to instability.

The chemical is considered to be stable. There are no known hazardous decomposition products. However, the chemical is combustible and will burn if involved in a fire, evolving fumes.

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral	LD50>2 000 mg/kg, low toxicity
Rat, acute dermal	LD50>2 000 mg/kg, low toxicity
Rat, acute inhalation	No toxicity data were submitted
Rabbit, skin irritation	Moderately irritating
Rabbit, eye irritation	Slightly irritating
Guinea pig, skin sensitisation – adjuvant test	Limited evidence of sensitisation.
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 15 mg/kg/day based on the effects in blood chemistry, liver and kidney at higher dose levels.
Genotoxicity – bacterial reverse mutation	Non mutagenic
Genotoxicity – in vitro Chromosome Aberration	Non genotoxic
Genotoxicity – in vivo micronucleus test	Non genotoxic
Human volunteers, skin irritation	Non-irritating in human patch test
Guinea pigs, phototoxicity	Non-phototoxicity to the skin

7.1. Acute toxicity – oral

TEST SUBSTANCE Notified chemical

METHOD OECD TG 401 Acute Oral Toxicity – Limit Test.
EC Directive 84/449/EEC B.1 Acute Toxicity (Oral) – Limit Test.
Species/Strain Rat/ Sprague-Dawley
Vehicle None.
Remarks - Method A range-finding study was performed to establish a dosing regime. No deaths were observed and systemic toxicity noted were hunched posture and lethargy with an additional sign of ataxia. Based on these observations, a dose level of 2000 mg/kg bw was selected for the main study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5/sex	2000	None.

LD50 >2000 mg/kg bw
Signs of Toxicity Ataxia, hunched posture and lethargy with additional signs of decreased respiratory rate were seen after dosing. All animals recovered after 24 hours.
Effects in Organs None.
Remarks - Results None.

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

TEST FACILITY SafePharm Laboratories (1993c).

7.2. Acute toxicity - dermal

TEST SUBSTANCE Notified chemical

METHOD OECD TG 402 Acute Dermal Toxicity – Limit Test.
EC Directive 84/449/EEC B.3 Acute Toxicity (Dermal) – Limit Test.

Species/Strain	Rat/Sprague-Dawley
Vehicle	None.
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5/sex	2000	None.

LD50	>2000 mg/kg bw
Signs of Toxicity - Local	None.
Signs of Toxicity - Systemic	None.
Effects in Organs	None.
Remarks - Results	None.

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

TEST FACILITY SafePharm Laboratories (1993d).

7.3. Acute toxicity - inhalation

No inhalation toxicity data were submitted.

7.4. Irritation – skin

7.4.1 Skin Irritation in Rabbits

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Directive 84/449/EEC B.4 Acute Toxicity (Skin Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Vehicle	None.
Observation Period	7 days
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	1.3	2	2	2	72 hours	0
Oedema	2	3	3	4	72 hours	0

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

Remarks - Results	At the 1 and 72-hour observations, well-defined erythema was noted at all treated skin sites. Very slight to well-defined erythema was observed at all treated skin sites at 48 hours. Slight to severe oedema was noted at all treated skin sites 1 and 24-hour after patch removal with slight to moderate oedema at the 48 and 72-hour observations. Oedema extending ventrally below the treatment site was noted at two treated skin sites during this time. The erythema and oedema extended up to 3cm beyond all treated skin sites during the study. Desquamation was observed at day 7.
CONCLUSION	The notified chemical is moderately irritating to the skin.
TEST FACILITY	SafePharm Laboratories (1993e).

7.4.2 Skin irritation in human volunteers

TEST SUBSTANCE	Notified chemical
METHOD	
Study Design	Human patch test according to the protocol at the test facility.
Study Group	A study group containing 25 (11 men and 14 women) humans aged 22 to 43 years old.
Vehicle	Petrolatum
Procedure	Blank (vehicle alone) and test material (5% in the vehicle) were put on the upper arms for 23 hours.
Observation Period	1 and 24 hours after removal.
Remarks - Method	The reaction was evaluated on a 5-point scale according to the protocol of the International Contact Dermatitis Research Group.
RESULTS	
Remarks - Results	No reactions were observed in both the test sites and the control sites at 1 and 24 hours after treatment.
CONCLUSION	A human patch test was conducted using the notified chemical diluted with petrolatum to 5%. The notified chemical was non-irritating under the conditions of the test.
TEST FACILITY	Takasago International (1991a).

7.5. Irritation - eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion. EC Directive 84/449/EEC B.5 Acute Toxicity (Eye Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Observation Period	72 hours
Remarks - Method	No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*

	1	2	3			
Conjunctiva: redness	0	0	0	1	1 hour	0
Conjunctiva: chemosis	0	0	0	1	1 hour	0
Conjunctiva: discharge	0	0	0	1	1 hour	0
Corneal opacity	Zero scores were recorded for corneal (opacity and area) and iridial effects in all animals at all time points					
Iridial inflammation						

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

Remarks - Results

No corneal or iridial effects were noted during the study.

Minimal conjunctival irritation was noted in all treated eyes one hour after treatment.

All treated eyes appeared normal 24 hours after treatment.

CONCLUSION

The notified chemical is slightly irritating to the eye.

TEST FACILITY

SafePharm Laboratories (1993f).

7.6. Skin sensitisation

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 406 Skin Sensitisation – adjuvant test.
EC Directive 84/449/EC B.6 Skin Sensitisation

Species/Strain

Guinea pig/ Dunkin-Hartley

PRELIMINARY STUDY

Maximum Non-irritating Concentration:
intradermal: 25%
topical: 75%

MAIN STUDY

Number of Animals

Test Group: 20 Control Group: 10

INDUCTION PHASE

Induction Concentration:
intradermal: 25% notified chemical in arachis oil B.P
topical: 100% notified chemical

Signs of Irritation

Scattered mild redness was elicited by the notified chemical after topical induction.

CHALLENGE PHASE

1st challenge

topical: 50% & 75% notified chemical in arachis oil B.P

Remarks - Method

No signification protocol deviations.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after challenge*	
		24 h	*48 h*
Control Group	50%	0/10	0/10
	75%	0/10	0/10
Test Group	50%	1/20	0/20
	75%	1/20	0/20

Remarks - Results

Positive skin responses (redness grade 1) were observed in two animals at the 24-hour observation. Thus, the positive response to skin sensitisation test is considered to be 10% (2/20).

CONCLUSION

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

TEST FACILITY

SafePharm Laboratories (1993g).

7.7. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Rat/Sprague-Dawley CD.
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days; Dose regimen: 7 days per week; Post-exposure observation period: 2 weeks
Vehicle	Arachis oil B.P.
Remarks - Method	No significant protocol deviations.

RESULTS

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

Mortality and Time to Death
There were no deaths during the study.

Clinical Observations
No clinical signs were detected in mid- and low-dose groups. Animals at high-dose had clinical signs from day 2 onwards including salivation immediately after dosing together with associated wet and stained fur. The high-dose animals also had increased water consumption. These symptoms were not seen in the group VI during the recovery period.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
High-dose males and females had higher gamma-glutamyl transpeptidase levels in their blood samples. High-dose females had increases in plasma total protein and albumin, alanine aminotransferase and bilirubin, and decrease in albumin/globulin (A/G) ratio. While mid-dose females had increased plasma total protein and decreased A/G ratio. Urinalysis results showed that high-dose females had increased reducing substances in the urine probably due to the excretion of the notified chemical or its metabolites.

No treatment related effects were observed in haematology and urinalysis assays in all test groups, or in blood chemistry assays in the mid and low-dose groups.

Macroscopic findings
High-dose animals had dark and/or enlarged livers with higher absolute and relative liver weights. The mid-dose males and high-dose males in the recovery group also had increased absolute and relative liver weights.

High and mid-dose males showed patchy pallor of the kidneys with increased absolute and relative kidney weights.

No treatment related macro-abnormalities were observed in other group animals.

Microscopic findings
Histopathological examination showed hepatocellular enlargement and increased hepatocytoplasmic density in high-dose males. The condition was regressed following an additional 14 days without treatment in the recovery group.

Histopathological examination showed eosinophilic tubular degeneration in high-, mid- and low-dose males.

The condition was regressed following an additional 14 days without treatment in the recovery group.

No treatment related micro-abnormalities were observed in other group animals.

Remarks – Results
The dose levels were selected based on a range-finding study.

The changes in the clinical chemistry parameters suggest that the liver is affected, as evidenced by the macroscopic and microscopic observations in the mid and high dose groups.

Eosinophilic tubular degeneration in kidney is due to hydrocarbon-induced nephropathy, which is typically observed in the renal tubules of male rats. Females were unaffected. This kidney change is peculiar to the male rat and not indicative of a hazard to human health.

CONCLUSION
The NOAEL is determined to be 15 mg/kg bw/day based on the effects in blood chemistry and liver at higher dose levels, and the kidney effects in all male treated animals. However, the effects seen in the kidneys are specific to male rats and not considered relevant to humans.

TEST FACILITY SafePharm Laboratories (1993h).

7.8. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria.
Pre incubation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	Liver fraction (S9 mix) from rats pretreated with phenobarbital and 5,6-benzoflavone.
Concentration Range in Main Test	a) With metabolic activation: 0, 5, 10, 20, 39, 78 156 and 313 μg/plate for *S. typhimurium* strains; 0, 313, 625, 1250, 2500 and 5000 μg/plate for *E. coli* strain. b) Without metabolic activation: 0, 10, 20, 39, 78 156 and 313 μg/plate with *S. typhimurium* strains; 0, 313, 625, 1250, 2500 and 5000 μg/plate with *E. coli* strain
Vehicle	DMSO
Remarks - Method	A summary of the report was provided in English version. A preliminary test was conducted to determine the appropriate concentrations for the main test.

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	≥78			
Test 1		≥78	Not reported	Not observed
Present	≥313			
Test 1		≥313	Not reported	Not observed

Remarks - Results The notified chemical was cytotoxic in all strains of *S. typhimurium* at ≥313μg/plate and ≥78 μg/plate with and without metabolic activation, respectively. However, no toxicity to *E. coli* was observed.

There was no significant increase in revertant colonies observed in any strain tested at any dose.

The positive controls responded appropriately.

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

TEST FACILITY Takasago International (1992).

7.9. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 473 In vitro Mammalian Chromosome Aberration Test.

Cell Type/Cell Line	Chinese Hamster Lung (CHL) Cells
Metabolic Activation System	Liver fraction (S9 mix) from rats pretreated with Aroclor 1254.
Vehicle	Dimethyl Sulphoxide (DMSO)
Remarks - Method	A preliminary study was conducted to determine the appropriate dose level for the main study.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0, 5, 10*, 20* and 40*	6 h	24 h
	0, 5*, 10*, 20* and 40*	12 h	12 h
	0, 5*, 10*, 20* and 40	24 h	24 h
	0, 5, 10*, 20* and 40*	48 h	48 h
Present			
Test 1	0, 25*, 50* 100* and 150	6 h	24 h
	0, 25*, 50*, 100* and 150	4 h	12 h

*Cultures selected for metaphase analysis.

RESULTS No dose-related enhanced structural aberrations in the cell line could be detected at each fixation interval, both with and without S9-mix.

Remarks - Results The preliminary toxicity study showed that metaphases present up to 100 μg/mL in the 6 and 4 hours with S9-mix. In the studies without S-9-mix, the maximum dose level with metaphases present was 40 μg/mL. Therefore, the concentrations available for metaphase analysis were limited due to the high toxicity of the notified chemical.

All the positive controls except cyclophosphamide without S9-mix gave significant increases in the frequency of cells with aberrations, indicating that the metabolic activation system was satisfactory.

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

TEST FACILITY SafePharm Laboratories (1994)

7.10. Genotoxicity – in vivo

TEST SUBSTANCE Notified chemical

METHOD OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
EC Directive 2000/32/EC B.12 Mutagenicity - Mammalian Erythrocyte

	Micronucleus Test.
Species/Strain	Mouse/CD-1
Route of Administration	Intraperitoneal injection
Vehicle	Arachis oil
Remarks - Method	A range-finding toxicity study was conducted to determine the dose level for the main study. Animals dosed with the test material ≥1875 mg/kg died on day 1 during the study. Clinical signs including hunched posture, lethargy, ataxia, diuresis and ptosis were observed in animals dosed ≥1250 mg/kg. The maximum tolerated dose of 1250 mg/kg was selected for the main study.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
1 (vehicle control)	5/sex	0	72
2 (vehicle control)	5/sex	0	48
3 (vehicle control)	5/sex	0	24
4 (positive control)	5/sex	50 (CP)	24
5 (test)	5/sex	1250	72
6 (test)	5/sex	1250	48
7 (test)	5/sex	1250	24

CP=cyclophosphamide.

RESULTS

Doses Producing Toxicity	None.
Genotoxic Effects	There was a significant increase ($p<0.05$) in the frequency of micronucleated PCEs in group 6 when compared to the historical vehicle controls. As it was within the historical range at the test laboratory, this increase was considered to be of no toxicological significance. There was no statistically significant increase in the NCE/PCE ratio in any of the test groups when compared to their concurrent vehicle control groups or the historical ranges at the test laboratory. The positive control group showed appropriate response.
Remarks - Results	One premature death occurred in the group 5.

CONCLUSION	The notified chemical was not clastogenic under the conditions of this in vivo micronucleus test.
TEST FACILITY	SafePharm Laboratories (1996).

7.11. Phototoxicity study in Guinea pigs

TEST SUBSTANCE Notified chemical

METHOD

Species/Strain	Guinea pig/Hartley Dunkin
Study Design	Phototoxicity test according to the protocol at the test facility.
Study Group	5 females per group.
Vehicle	Acetone
Procedure	The notified chemical (5%, 10%, 30% and 50% in acetone) and the positive control (8-methoxy psoralen) were applied on the back area of guinea pigs in duplicates. One set of treated sites was exposed to UV-A radiation (300-400 nm) for 70 minutes and the other side was shielded with aluminium foil.
Observation Period	24 and 48 hours after application
Remarks - Method	Erythema and oedema of each treated site was scored by the Draize system at the observation time. The differences of scores between exposed sites and unexposed sites were calculated.

No vehicle control was included in the test group.

RESULTS

Remarks - Results: Draize scores for erythema and oedema were all zero in the test sites examined 24 and 48 hours after dermal application of the notified chemical with or without UV-A radiation. Thus, the differences of Draize scores between the exposed and the unexposed sites were all zero.

The positive control had strong responses after exposure to UV-A radiation with a mean response difference of 2.0.

CONCLUSION: The notified chemical did not show phototoxicity to the skin of guinea pigs.

TEST FACILITY: Takasago International (1991b).

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 301 D Ready Biodegradability: Closed Bottle Test.

Inoculum: Equal volumes of filtrate of standard activated sludge, effluent from a domestic sewage treatment plant and river surface water.

Exposure Period: 28 days

Auxiliary Solvent: none

Analytical Monitoring: Dissolved oxygen levels were measured electrochemically on days 0, 14, and 28 (in duplicate).

Remarks - Method: Degradation of test material was determined by comparing oxygen depletion to a Theoretical Oxygen Demand (ThOD). Tests included controls (inoculum mixed with water and water), standard substance (aniline 2 g/L) plus inoculum, test substance (3 mg/L) plus water, and test substance (2 mg/L) plus inoculum. Test temperature was 20°C.

RESULTS

Test substance			*Aniline*	
Day	*% degradation*		*Day*	*% degradation*
	Dissolved O_2	*Residual test material*		*Dissolved O_2*
14	-1	3	14	57
28	-0.5	3.5	28	67

CONCLUSION: The notified chemical is not readily biodegradable as only 3.5% was eliminated after 28 days.

TEST FACILITY: Mitsubishi-kasei (1993)

8.1.2. Bioaccumulation

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 305C Bioconcentration: Flow-through Fish Test.

Species	Common Carp (*Cyprinus carpio*)
Exposure Period	Exposure: 56 days Depuration: 0 days
Auxiliary Solvent	Tetrahydrofuran (THF)
Concentration Range	
Nominal	0.0085 and 0.085 mg/L (and solvent control)
Actual	0.00593 and 0.0584 mg/L (mean measured)
Analytical Monitoring	Gas chromatography
Remarks - Method	A continuous flow-through diluter system was used to deliver the test substance and solvent control. A total of 18 fish were distributed to each test chamber. Dilution water consisted of moderately hard (test water hardness range 128-148 mg/L as $CaCO_3$) groundwater (filtered 0.45 µm and aerated). Test water had a total organic carbon (TOC) concentration of 0.7-53.6 mg/L (mean 38.8 mg/L). Test chambers consisted of 106 L stainless steel aquaria containing 80 L of test solution (depth 19.6 cm). Test chambers were siphoned daily to remove excess feed, faecal matter, algae and bacterial growth. Test concentrations (0.0085 and 0.085 mg/L nominal) were prepared from a primary stock solution by dissolving test substance in THF (2.55 mg/mL). An aliquot of the primary stock solution was diluted with THF to prepare an additional stock solution (0.255 mg/mL). The 2 stock solutions and THF control were injected into the diluter mixing chamber (1.6 mL/h) to achieve the nominal test concentrations. Calibration Standards of the test substance were prepared in the range of 0.08-0.8 mg/L. The limit of quantitation (LOQ) was 0.00035 mg/L (water) and 0.00074 mg/kg (tissues). Fish were fed and observed for adverse effects daily during the test. Water temperature: 25.0°C. Water pH range 7.2-7.4. Dissolved oxygen range: 7.2-8.1 mg/L (acceptable). Photoperiod 16 h light: 8 hours dark.

RESULTS

Whole Fish Bioconcentration Factor (BCF)	14 Days	28 Days	42 days	56 Days
Nominal exposure concentration 0.0085 mg/L	439	183	127	134
Nominal exposure concentration 0.085 mg/L	92	90	126	159

Remarks - Results: There were no mortalities or other adverse reactions to exposure observed in any of the fish in the control and test vessels throughout the duration of the study. The marked reduction in the measured test concentrations compared to nominal is attributed to the volatility of the test substance.

CONCLUSION: The determined bioconcentration factors indicate that the notified chemical was moderately bioaccumulating under the conditions of the study.

TEST FACILITY: SafePharm Laboratories (1994b)

8.2. Ecotoxicological investigations

8.2.1.a Acute toxicity to fish

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 203 Fish, Acute Toxicity Test – flow through conditions.

Species	Rainbow trout (*Oncorhynchus mykiss*)
Exposure Period	96 hr
Auxiliary Solvent	Tween 80-ethanol 1% v/v
Water Hardness	50 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography
Remarks – Method	Solvent stock solutions (20, 36, 64, 112, and 200 g/L) were prepared fresh daily and fed into a continuous flow dosing apparatus Test

temperature: 21°C. Fish were not fed during the test. Mean length 4.7 cm. Mean weight 0.93 g. The diluent supply (dechlorinated tap water) was continuously aerated during the test. Water pH range 7.2-7.4. Dissolved oxygen range: ≥9.9 mg/L. Photoperiod 16 h light: 8 hours dark.

RESULTS

Concentration mg/L			*Number of Fish*		*Mortality (%)*					
Nominal		*Actual*								
	Initial	*24 h*	*Mean*		*3 h*	*6 h*	*24 h*	*48 h*	*72 h*	*96h*
Control	-	-	-	10	0	0	0	0	0	0
Solvent Control	-	-	-	10	0	0	0	0	0	0
2.0	1.85	0.87	1.36	10	0	0	0	0	0	0
3.6	3.31	3.12	3.22	10	0	0	0	0	0	0
6.4	5.44	6.96	6.20	10	10	10	100	100	100	100
11.2	9.82	9.85	9.835	10	100	100	100	100	100	100
20	25.2	16.9	21.05	10	100	100	100	100	100	100

LC50 3.22 < LC50 < 6.20 mg/L at 24 hours (mean measured concentrations).
3.22 < LC50 < 6.20 mg/L at 48 hours (mean measured concentrations).
3.22 < LC50 < 6.20 mg/L at 72 hours (mean measured concentrations).
3.22 < LC50 < 6.20 mg/L at 96 hours (mean measured concentrations).

NOEC 1.36 mg/L at 96 hours (mean measured concentrations).

Remarks – Results It is not possible to determine an exact value for the LC50 for the test material due to the steepness of the dose response curve, resulting in a lack of intermediate mortality responses required for probit analysis of the data. Observed sublethal effects included swimming at the bottom and loss of equilibrium.

CONCLUSION The notified chemical was acutely toxic to the fish species tested under the conditions of the test (United Nations, 2003; L(E)C50 of 10-100 mg/L).

TEST FACILITY SafePharm Laboratories (1993i)

8.2.1.b Acute toxicity to fish

TEST SUBSTANCE Notified chemical

METHOD Japanese Industrial Standard Method JIS K 0102-1986 Industrial waste water Testing Method 71 "Acute Toxicity Study using Fish" – Semi static

Species Killifish (*Oryzias latipes*).
Exposure Period 48 h
Auxiliary Solvent Tween 80-ethanol 1% v/v
Water Hardness 100 mg/L $CaCO_3$
Analytical Monitoring Gas chromatography

Remarks – Method Test solutions were prepared by addition of 2 mL volumes of stock solutions (20, 36, 64, 112, and 200 g/L) into dechlorinated water to a final volume of 20 L. Test media were renewed after 24 h to overcome losses due to the volatility of the test substance. Test temperature: 21°C. Fish were not fed during the test. Mean length 2.5 cm. Mean weight 0.23 g. Test aquaria were continuously aerated during the test. Photoperiod 16 h light: 8 hours dark.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*	
Nominal	*Actual*		*24 h*	*48 h*
0	-	10	0	0
2.0	-	10	0	0
3.6	-	10	0	0

6.4	-	10	0	10
11.2	-	10	20	100
20	-	10	100	100

LC50 8.5 mg/L at 48 hours (nominal).
NOEC 30 mg/L at 48 hours (nominal).
Remarks – Results No sublethal effects were monitored for or reported.

CONCLUSION The notified chemical was acutely toxic to the fish species tested under the conditions of the test (United Nations, 2003; L(E)C50 of 10-100 mg/L).

TEST FACILITY SafePharm Laboratories (1994b)

8.2.2.a Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static Conditions.
EC Directive 92-69-EEC C.2 Acute Toxicity for Daphnia – Static Conditions.
Species *Daphnia magna*
Exposure Period 48 hours
Auxiliary Solvent Tween 80-ethanol 1% v/v
Water Hardness 50 mg $CaCO_3$/L
Analytical Monitoring Gas chromatography
Remarks - Method Test stock solution was prepared by the addition of 500 µL of the solvent stock solution (200g/L) into aged dechlorinated water and made up to a final volume of 5 L. Test temperature range: 21-22°C. Daphnia were not fed during the test. Water pH range 7.6-7.8. Dissolved oxygen range: 7.3-8.3 mg/L (acceptable). Photoperiod 16 h light: 8 hours dark.

RESULTS

Concentration mg/L				*Number of D. magna*	*Number Immobilised*	
Nominal		*Actual*			*24 h*	*48 h*
	Initial	*48 h*	*Mean*			
Control	-	-	-	20	0	0
Solvent Control	-	-	-	20	0	0
0.20	0.153	0.139	0.15	20	0	0
0.36	0.288	0.245	0.27	20	0	0
0.64	0.526	0.501	0.51	20	0	0
1.12	0.994	0.913	0.95	20	0	0
2.0	1.82	1.77	1.80	20	0	3
3.6	3.30	3.14	3.22	20	0	12
6.4	5.86	5.45	5.66	20	4	18
11.2	10.1	9.46	9.78	20	18	20
20	18.6	17.5	18.1	20	20	20

EC50 7.0 (6.1-8.1 95% CL) mg/L at 24 hours (mean measured concentrations)
2.9 (2.5-3.5 95% CL) mg/L at 48 hours (mean measured concentrations)
NOEC 0.95 mg/L at 48 hours (mean measured concentrations)

CONCLUSION The notified chemical was acutely toxic to the daphnia species tested under the conditions of the test (United Nations, 2003; L(E)C50 of 10-100 mg/L).

TEST FACILITY SafePharm Laboratories (1993j)

8.2.2.b Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE

METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test –Static renewal conditions.
Species	*Daphnia magna*
Exposure Period	21 days
Auxiliary Solvent	Ethanol
Water Hardness	Not specified
Analytical Monitoring	Gas chromatography
Remarks - Method	Serial dilution of the solvent stock solutions (10 and 32 g/L) were made to prepare solvent stock solutions of 320, 1000 and 3200 mg/L. Test stock solution was prepared by the addition of 500 µL of the solvent stock solution into reconstituted water and made up to a final volume of 5 L. Test media was renewed three times per week. Test temperature: 21.0°C. Daphnia were fed unicellular algal culture during the test. Water pH range 7.7-7.8. Dissolved oxygen range: 7.7-8.4 mg/L (acceptable). Photoperiod 16 h light: 8 hours dark.

RESULTS

Concentration (mg/L)		*Number of D. magna*	*% Mortality*	*Live young*	*Dead Young*	*Unhatched Eggs*
Nominal	*Actual*[a]					
Control	-	40 (10/rep. × 4 reps.)	0	1900	1	4
Solvent	-	40 (10/rep. × 4 reps.)	0	1919	0	3
0.032	0.032	40 (10/rep. × 4 reps.)	0	1868	2	3
0.10	0.10	40 (10/rep. × 4 reps.)	0	1880	3	1
0.32	0.32	40 (10/rep. × 4 reps.)	0	1895	5	3
1.0	1.0	40 (10/rep. × 4 reps.)	0	1810	0	2
3.2	3.2	40 (10/rep. × 4 reps.)	100[b]	0	11	5

[a]Measured concentrations were ≥ 94% of nominal. [b]All P_1 generation daphnia were immobilised by day 11.

LC50	1.0 < EC50 < 3.2 mg/L at 21 days. (immobilisation) 1.0 < EC50 < 3.2 mg/L at 21 days. (reproduction)
NOEC	1.0 mg/L at 21days (immobilisation and reproduction)
Remarks - Results	The reproduction rate at 1.0 mg/L was not significantly different from the controls.

CONCLUSION Chronically toxic (United Nations, 2003; L(E)C50 of 10-100 mg/L) to Daphnia.

TEST FACILITY SafePharm Laboratories (1996c)

8.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Scenedesmus subspicatus*
Exposure Period	72 hours
Concentration Range	
Nominal	0.20, 0.40, 0.80, 1.6, 3.2 mg/L
Actual	0.106, 0.271, 0.545, 1.06, 2.25 mg/L
Auxiliary Solvent	Tween 80-ethanol 1% v/v
Water Hardness	Not specified
Analytical Monitoring	Gas chromatography
Remarks - Method	Serial dilution of a 32g/L solution was used to prepare the following solvent stock solutions, 16, 8, 4 and 2 mg/L. Test stock solution was prepared by the addition of 100 µL of the solvent stock solution into algal

suspension and made up to a final volume of 1 L. Test temperature range: 21±1°C. Water pH range 8.0-10.3.

RESULTS

Biomass	*Growth*	*NOEC*
E_bC50	*E_rC50*	*mg/L at 72 h*
mg/L at 72 h	*mg/L 0-24 h*	
0.60	0.80	0.271

Remarks - Results: The values in the above table are based on the measured concentration at 72 h. The pH of the solutions generally increased throughout the duration of the study. However, as the concentration of the test substance increased the increase in pH became less marked.

CONCLUSION: Very toxic (L(E)C50 <1 mg/L; United Nations, 2003) to green algae.

TEST FACILITY: SafePharm Laboratories (1996d)

8.2.4. Inhibition of microbial activity

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 209 Activated Sludge, Respiration Inhibition Test.
- Inoculum: Activated sludge from a wastewater treatment plant in Derbyshire UK treating predominantly domestic wastewater.
- Exposure Period: 3 hours
- Concentration Range
- Nominal: 1000 mg/L
- Remarks – Method: The activated sludge study was conducted using sludge obtained from sewage treatment plant in Derbyshire, UK. The reference material used in the study was 3,5-dichlorophenol. The 3-hour EC50 for the notified substance to activated sludge could not be quantified as there was <15% inhibition at the nominal test concentration. Hence, the 3-hour EC50 for the notified substance to activated sludge is expected to be greater than 1000 mg/L. The EC50 of the reference substance was 13.0 mg/L, therefore confirming the suitability of the activated sludge.

RESULTS
- IC50: >1000 mg/L
- NOEC: 1000 mg/L

CONCLUSION: The ecotoxicity data indicates the notified chemical is not inhibitory to activated sludge up to 1000 mg/L suspension.

TEST FACILITY: SafePharm Laboratories (1993k)

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The notified chemical is moderately volatile, therefore it will dissipate into air from the surfaces to which the products containing the notified chemical are applied (eg. skin, aquatic and terrestrial environments). The notified chemical is not expected to hydrolyse in the environmental pH range 4 to 9, and it is not readily biodegradable. Due to its moderate water solubility (31 mg/L) and its adsorption coefficient (est. log K_{oc}=2.77-2.95) the notified chemical is not expected to be highly mobile in soil and sediments.

Relatively minor quantities may potentially be released during formulation, storage, handling and transportation (eg. uncontained spills and leaks), resulting in discharges to land or aquatic environments. A small amount of wastes containing the notified chemical may be generated during the production of end-user products. Generally, these wastes will go into on-site treatment plants where they are likely to be partially adsorbed on to sludge with some released into sewer after treatment. In landfills, the notified chemical may occur in residues in disposed emptied containers from product use, product formulation and drum recycling facilities. Given the low import volume and the low concentration of the notified chemical in the products, container residues will potentially constitute less than 10 kg of the notified chemical per annum. Over time, residues of the notified chemical in containers will adsorb to soil or enter the leachate from the landfill but at very low concentrations and in a diffuse manner.

As a worst case all of the notified chemical in the consumer products will eventually be released into the aquatic environment via the sewerage systems through washing off the skin, hair etc or cleaning activities. The predicted environmental concentration (PEC) in the aquatic environment is estimated, assuming that maximum import volume of 1000 kg of the notified chemical used is discharged into sewerage systems throughout Australia and none is attenuated within these systems.

Amount released	1000 kg
Australian population	20 million people
Average daily water consumption per person	200 L
Days in year	365
$PEC_{(STP)}$	1 000 000 000 / (20 000 000 x 200 x 365) = 6.85×10^{-4} mg/L = 0.68 µg/L
Dilution factor inland	1
Worst case $PEC_{(inland)}$	0.68 µg/L
Dilution factor marine	10
Worst case $PEC_{(marine)}$	0.068 µg/L

The biodegradability test results indicated that the notified chemical was not readily biodegradable. The results obtained using the SIMPLETREAT model (European Commission 1996) for modelling partitioning and losses in sewage treatment plants (STP) using molecular weight (154 g/mole), vapour pressure (10 and 88 Pa) and water solubility (31.2 mg/L), indicated the following partitioning:

- to air 47%
- to water 19%, and
- to sludge 34%.

It also indicated that there would be no degradation in the plant and 81% would be removed from influent/water.

This indicates that 19% of the notified chemical has the potential to remain in the STP effluent when released to the natural water body. Thus the above $PEC_{(inland)}$ and $PEC_{(marine)}$ can be refined to give potential $PEC_{(inland)}$ of 0.13 µg/L and $PEC_{(marine)}$ 0.013 µg/L.

An atmospheric half-life of 12.5 h has been determined for the reaction with hydroxyl radicals using AopWin v1.90 (part of the EPIWIN modelling suite).

While a potential for bioaccumulation is indicated, this is not expected from the proposed low level of import and diffuse use pattern.

9.1.2. Environment – effects assessment

Aquatic ecotoxicity data were available for 4 taxonomic levels of freshwater species (fish, invertebrate, algae and sewage sludge micro-organisms). The notified chemical is acutely toxic to freshwater fish (96 h 3.22 < LC50 < 6.20 mg/L), freshwater cladocerans (*Daphnia* sp.; 48 h EC50 2.9 mg/L) and algae (72 h E_bC50 = 0.6 mg/L); however, sewage sludge micro-organisms were not sensitive (3 h IC50 > 1000 mg/L) to the notified chemical. A chronic NOEC value of 1.0 mg/L was obtained for both mortality and reproduction of daphnia. A predicted no effect

concentration ($PNEC_{aquatic}$) of 6 µg/L has been derived by dividing the lowest L(E)C50 by an assessment factor of 100 used to account for interspecies sensitivity and other adverse factors that may potentially arise in the environment if organisms are exposed to the notified substance.

9.1.3. Environment – risk characterisation

Location	PEC	PNEC	Risk Quotient (RQ)
Australia-wide STPs			
Ocean outfall	0.068 µg/L	6 µg/L	0.012
Inland River	0.68 µg/L	6 µg/L	0.12

The above PECs are the worst case PECs, which account for the likely import volume of the chemical and water entering STPs Australia wide.

The risk quotient values estimated based on the worst-case scenario of discharging the entire import volume of the notified chemical into sewage systems in Australia are less than 1. Therefore, the proposed use of the notified chemical is unlikely to pose an unacceptable risk to the aquatic life, and the risk is further reduced due to partitioning to air and sludge, as shown by the SIMPLETREAT calculations above.

Any material partitioning to the air through evaporation would also rapidly degrade through reaction with hydroxyl radicals.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

Transport and Storage

Transport and warehouse workers will be exposed to the notified chemical (either as a neat substance or as a component in fragrance oil preparations at concentration up to 1%) only when there is an accidental spillage or packaging breach. At the storage site, transport and warehouse workers will wear personal protective equipment (PPE); eye protection, chemical resistant gloves and protective clothing (eg an impervious apron). A vapour mask would also be recommended if exposure could not be prevented or adequately controlled.

Formulation

Worker exposure to the imported notified chemical (as a neat substance, or up to 1%) might occur during the formulation of the consumer products. Dermal and accidental ocular exposure may occur during drum handling, pre weighing, the transfer of the fragrance oil to the batch mixer, mixing, and QC sampling. Exposure may also occur during the cleaning and maintenance of equipment. Worker exposure will be minimised by use of the appropriate PPE. Workers involved the formulation process would wear standard PPE. Local exhaust ventilation will be used and vapour masks will be available if required.

Dermal and inhalation exposure during formulation was estimated using the EASE model (HSE, 1994) for neat chemical (100%) and fragrance preparation containing maximum of 1% notified chemical. Exposure calculations assume year round use for an eight hour day, and more intermittent use will reduce the exposure accordingly.

Formulation using 100% notified chemical

Assuming non-dispersive use and intermittent direct handling, the estimated dermal exposure during formulation is 0.1-1 mg/cm^2/day for the neat notified chemical. Absorption of the notified chemical may be significant, as the substance has a high $LogP_{ow}$ 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 2.8-28 mg/kg bw/day. This exposure would be substantially reduced by the use of protective clothing and gloves.

The estimated atmospheric concentration of notified chemical during formulation is 81-243 mg/m^3 (10-30 ppm) for an open system (non-dispersive use) with aerosol formation and

local exhaust ventilation. If no aerosols are formed, the estimated atmospheric concentration for an open system (non-dispersive use) with local exhaust ventilation is 4-8 mg/m^3. For a closed system, even if aerosols are formed, the estimated atmospheric concentration is 0-0.8 mg/m^3. Therefore for a 70 kg worker, assuming an inhalation rate of 1.3 m^3/hour, an 8 hour exposure time (maximum worker exposure/day) and 100% bioavailability, inhalation exposure is estimated to be 12.1-36.15 mg/kg bw/day for an open system with aerosol formation and local exhaust ventilation; 0.6-1.2 mg/kg bw/day for an open system with local exhaust ventilation and no aerosol formation; 0-0.1 mg/kg bw/day for a closed system with aerosol formation. Inhalation exposure to the notified chemical would be further reduced by the use of personal respiratory equipment.

Formulation using 1% notified chemical

Dermal exposure during formulation (assuming non-dispersive use, intermittent direct handling) is 0.001-0.01 mg/cm^2/day for the fragrance preparations containing up to 1% notified chemical. Systemic exposure is estimated to be 0.028-0.28 mg/kg bw/day.

The estimated atmospheric concentration during formulation is 8.13-16.25 mg/m^3 for an open system of non-dispersive use with aerosol formation and local exhaust ventilation. Without aerosol formation but under the same conditions, the estimated atmospheric concentration is 0.04-0.08 mg/m^3. For a closed system with aerosol formation, the estimated atmospheric concentration is 0-0.008 mg/m^3. Therefore for a 70 kg worker, assuming an inhalation rate of 1.3 m^3/hour, an 8 hour exposure time (maximum worker exposure/day) and 100% bioavailability, inhalation exposure is estimated to be 0.121-0.3615 mg/kg bw/day for an open system with aerosol formation and local exhaust ventilation (LEV); 0.006-0.012 mg/kg bw/day for an open system with LEV and no aerosol formation; 0-0.001 mg/kg bw/day for a closed system with aerosol formation.

End Use

Occupational exposure to end use consumer products containing the notified chemical may occur, for example, with professional cleaners using cleaning products or beauticians using cosmetic products. These workers are less likely to use extensive personal protective equipment (PPE); however, the concentration of the notified chemical in the end use products will be 0.01%. While the products containing the notified chemical are likely to be used regularly, actual applications (eg dermal or aerosol) will only normally occur for very brief periods.

Using the EASE model, assuming wide dispersive use with extensive direct handling and continuous use of the products, the estimated dermal exposure to end use products is 5-15 mg/cm^2/day. This equates to 0.0005-0.0015 mg/cm^2/day of notified chemical at 0.01% in most end use products. For a 70 kg worker with affected area of 1960 cm^2 and assuming 100% absorption, systemic exposure is therefore estimated to be 0.014-0.042 mg/kg bw/day.

The estimated atmospheric concentration of the notified chemical in the end use product is 0.024-0.081 mg/m^3 (0.003-0.01 ppm) for a typical wide dispersive use pattern with aerosol formation and uncontrolled direct handling. Therefore, for a 70 kg worker, assuming inhalation rate of 1.3 m^3/hour, 8-hour exposure time and 100% bioavailability, inhalation exposure is estimated to be 0.0036-0.012 mg/kg bw/day with aerosol formation.

Based on the above results obtained from the modelled worker data, the highest occupational exposure to the notified chemical will be during the reformulation of the neat chemical, but this is likely to be much less regular than exposure through end use products.

9.2.2. Public health – exposure assessment

During import, transport, storage and reformulation of the notified chemical, exposure of the general public will be limited, except in the event of an accidental spill.

The final products containing the notified chemical (such as cosmetics, toiletries, household cleaning products, etc) will be sold in the public domain, thus there is potential for widespread public exposure. Exposure will be via the dermal and inhalation routes. Systemic dermal exposure to the notified chemical in the final consumer product for a 70 kg user is 0.014-0.042

mg/kg bw/day. For inhalation, the end use calculation for occupational exposure of <0.012mg/kg bw/day can be used as the worst case.

Exposure to the notified chemical is considered minimal given the small concentrations at which the notified chemical is present in the final consumer products (approximately 0.01%), the small quantities of the products used, and the intermittent nature of use.

9.2.3. Human health - effects assessment

The notified chemical was of low acute oral and dermal toxicity in rats. It was a moderate skin irritant and a slight eye irritant in rabbits. There was limited evidence of reactions indicative of skin sensitisation to the notified chemical in an adjuvant test in guinea pigs. A human patch test was conducted using the notified chemical diluted with petrolatum to 5%. The notified chemical was non-irritating under the conditions of the test. The notified chemical did not show phototoxicity to the skin of guinea pigs.

The NOAEL from a 28-days repeat dose gavage study in rats was determined to be 15 mg/kg bw/day based on the changes in blood chemistry, liver and kidney at higher dose levels. Renal histopathological changes, namely, eosinophilic tubular degeneration were noticed in male animals at all three dose levels. This finding was consistent with well-documented changes that are peculiar to the male rat in response to treatment with some hydrocarbons (Alden, 1986), and is therefore not considered relevant to human health.

In genotoxicity studies, the notified chemical was non-mutagenic in bacteria, and non-genotoxic either in an in vitro study in CHL cells or in an in vivo study of micronucleus assay.

Based on the provided toxicological data, the notified chemical is classified as a hazardous substance with R38 (Irritating to skin) and R48/22 (Harmful: danger of serious damage to health by prolonged exposure if swallowed) according to the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999).

9.2.4. Occupational health and safety – risk characterisation

It should be noted that there is no inhalation study available, hence the following margin of exposure (MOE) calculations are based on the NOAEL (15 mg/kg bw/day) from the repeat dose oral study. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. For the reformulation of the neat chemical, the MOE for inhalation exposure is calculated to be 0.415-1.24 for an open system with aerosol formation, 12.5-25 for an open system with no aerosol formation, greater than 150 for a closed system with aerosol formation. The latter scenario of a closed system is the most relevant to the reformulation processes as described for the notified chemical. Nevertheless, the MOE calculated for the neat chemical indicates that the risk to workers handling the neat chemical in the absence of PPE and engineering controls is unacceptable.

The MOE for inhalation exposure during formulation of the fragrance preparation containing 1% notified chemical is calculated to be 41.5-124 for an open system with aerosol formation and LEV; 1250-2500 for an open system with LEV but no aerosol formation; >15000 for a closed system with aerosol formation. Similarly, due to reformulation methods described by the notifier, the scenario of the closed system is most relevant. The modelled worker data indicates that the risk is acceptable for workers handling the notified chemical if aerosols are formed in a closed system or if no aerosols are formed in an open system. Occupational risks as a result of inhalation exposure will be further limited by the use of respiratory PPE, local exhaust ventilation and enclosed/automated equipment.

Due to the likely end use scenarios, aerosol formation is more relevant and should be used as the worst case inhalation exposure. Therefore, the MOE for inhalation exposure calculated for a wide dispersive use pattern with aerosol formation and uncontrolled direct handling of the end use product is 1250-4167. Thus the risk to workers handling the end use product without the use of PPE and engineering controls is acceptable.

During formulation, systemic dermal exposure to the notified chemical was estimated to be 2.8-28 mg/kg bw/day for the neat chemical (worst case scenario). Using the same toxicity data (NOAEL 15 mg/kg bw/day), the MOE is calculated to be greater than 0.54 for dermal exposure. Therefore, the risk to chronic systemic toxicity using modelled worker data is not acceptable for non-dispersive use and intermittent direct handling of the chemical. Nevertheless, the use of personal protective equipment (PPE) and the engineering controls in place will limit dermal exposure when handling the notified chemical during formulation.

The systemic dermal exposure to fragrance preparations containing 1% notified chemical is estimated to be 0.028-0.28 mg/kg bw/day. The MOE equates to 54-536. Hence, the use of PPE and appropriate engineering controls for workers handling the fragrance preparation is highly recommended.

Systemic dermal exposure to end use products containing approximately 0.01% notified chemical is estimated to be 0.014-0.042 mg/kg bw/day. This equates to an MOE of 357-1071. Therefore, the risk to workers handling end use products in the absence of PPE is acceptable.

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

9.2.5. Public health – risk characterisation

Public exposure to the neat chemical and the fragrance mixture (containing up to 1% notified chemical) will be minimal except in the rare event of an accidental spill. However, there will be exposure, through the dermal, inhalation, oral and ocular routes, to products ranging from cosmetics to air fresheners. These products will contain approximately 0.01% of the notified chemical. Due to the low concentration, the low quantities of product used, and the low frequency of use, public exposure will be further reduced compared with the worst case occupational exposures predicted for the end use product. Hence, the public risk from exposure to the notified chemical through all phases of its life cycle is considered to be low.

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

10.1. Hazard classification

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

R38 – Irritating to skin.
R48/22 – Harmful: danger of serious damage to health by prolonged exposure if swallowed.

and

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

For health hazard, the notified chemical is classified as an Irritant Category 2 (causes skin irritation) and a Target Organ-Systemic Toxicant Category 2 (may cause damage to organs (liver) through prolonged or repeated oral exposure).

According to the GHS criteria, the notified chemical is classified as Chronic Category 1 (very toxic to aquatic life with long lasting effects).

10.2. Environmental risk assessment

On the basis of the PEC/PNEC ratio:

The chemical is not considered to pose a risk to the environment based on its reported use pattern.

10.3. Human health risk assessment

10.3.1. Occupational health and safety

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

10.3.2. Public health

There is Negligible Concern to public health when used as described in the notification.

11. MATERIAL SAFETY DATA SHEET

11.1. Material Safety Data Sheet

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

11.2. Label

The label for the notified chemical provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994). The accuracy of the information on the label remains the responsibility of the applicant.

12. RECOMMENDATIONS

REGULATORY CONTROLS
Hazard Classification and Labelling

- The NOHSC Chemicals Standards Sub-committee should consider the following health and environmental hazard classification for the notified chemical:
  R38 – Irritating to skin.
  R48/22 – Harmful: Danger of serious damage to health by prolonged exposure if swallowed.
  R50/53 – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

- The following safety phrases should be used for the notified chemical as introduced:
  – S24/25 Avoid contact with skin and eyes
  – S36/37/39 Wear suitable protective clothing, gloves, and eye/face protection.

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical as introduced:
  – Enclosed and automated systems, no aerosol formation and local exhaust ventilation (particularly when handling the neat chemical)

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:

- Eye protection
- Coveralls
- Impervious gloves
- Enclosed footwear
- Vapour masks, where control measures do not sufficiently reduce exposure to satisfactory levels.

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

- The following concentration limits should be implemented by reformulator to minimise environmental exposure during product formulation of the notified chemical:
  - Bunding and catch drains to prevent end material entering stormwater drains or adjacent natural waterways.

Disposal

- The notified chemical should be disposed of to on-site effluent treatment plants or to approved landfills.

Emergency procedures

- Spills/release of the notified chemical should be contained and adsorbed by using sand or inert powder and earth. The collected material should be placed in labelled, sealable drums and disposed of to landfill.

12.1. Secondary notification

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

(1) Under Section 64(2) of the Act:
  - 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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